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PHARMACOLOGICAL REVIEWS

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I. Introduction

The normal adult pulmonary circulation
The normal adult pulmonary circulation is a low-present that accommodates I. Introduction performance circuit that accommodates the sure, low-resistance circuit that accommodates the state of the right ventricle to the gas exchanging I. Introduction
The normal adult pulmonary circulation is a low-pres-
sure, low-resistance circuit that accommodates the
whole output of the right ventricle to the gas exchanging
surface at less than 20% of the systemic pr surface at less than 20% of the systemic is a low-pre
surface at less than 20% of the systemic pressure. Vaso-
dilators normally have little or no effect on pulmonan The normal adult pulmonary circulation is a low-pres-
sure, low-resistance circuit that accommodates the
whole output of the right ventricle to the gas exchanging
surface at less than 20% of the systemic pressure. Vaso-
d sure, low-resistance circuit that accommodates the
whole output of the right ventricle to the gas exchanging
surface at less than 20% of the systemic pressure. Vaso-
dilators normally have little or no effect on pulmonary whole output of the right ventricle to the gas exchanging
surface at less than 20% of the systemic pressure. Vaso
dilators normally have little or no effect on pulmonary
vascular pressures, indicating that there is little dilators normally have little or no effect on pulmonary
vascular pressures, indicating that there is little or no
resting tone. In contrast to the systemic circulation,
where neural and humoral mechanisms predominate,
the dilators normally have little or no effect on pulmonary
vascular pressures, indicating that there is little or no
resting tone. In contrast to the systemic circulation,
where neural and humoral mechanisms predominate,
the vascular pressures, indicating that there is little or no
resting tone. In contrast to the systemic circulation,
where neural and humoral mechanisms predominate,
the pulmonary circulation is under the control of both
acti resting tone. In contrast to the systemic circulation, from
where neural and humoral mechanisms predominate,
the pulmonary circulation is under the control of both
active and passive factors (Daly and Hebb, 1966). Active
 where neural and humoral mechanisms predominate,
the pulmonary circulation is under the control of both
active and passive factors (Daly and Hebb, 1966). Active
factors alter pulmonary vascular resistance and tone by
causi the pulmonary circulation is under the control of both
active and passive factors (Daly and Hebb, 1966). Active
factors alter pulmonary vascular resistance and tone by
causing contraction or relaxation of vascular smooth
m active and passive factors (Daly and Hebb, 1966). Active infactors alter pulmonary vascular resistance and tone by causing contraction or relaxation of vascular smooth c muscle. These factors include autonomic nerves, hum factors alter pulmonary vascular resistance and tone by
causing contraction or relaxation of vascular smooth
muscle. These factors include autonomic nerves, hu-
moral factors, and gasses. Passive factors include
changes i causing contraction or relaxation of vascular smoomuscle. These factors include autonomic nerves, h
moral factors, and gasses. Passive factors inclu
changes in cardiac output, left atrial pressure, airw
and interstitial pr muscle. These factors include autonomic nerves, humoral factors, and gasses. Passive factors include μ changes in cardiac output, left atrial pressure, airway and interstitial pressure, gravitational force, and vascula moral factors, and gasses. Passive factors includ
changes in cardiac output, left atrial pressure, airwa
and interstitial pressure, gravitational force, and vascu
lar obstruction or recruitment. Passive factors chang
pulmo

pendently of the changes in vascular tone. Although
passive factors may be important in some circumpendently of the changes in vascular tone. Althous
passive factors may be important in some circustances, the pulmonary circulation is acknowledged pendently of the changes in vascular tone. Although
passive factors may be important in some circum-
stances, the pulmonary circulation is acknowledged to
be under active control, and this may be particularly pendently of the changes in vascular tone. Although passive factors may be important in some circumstances, the pulmonary circulation is acknowledged to be under active control, and this may be particularly relevant in dis passive factors may be important in some circum-
stances, the pulmonary circulation is acknowledged to
be under active control, and this may be particularly
relevant in disease (Barer, 1980).

This review describes the current understanding of stances, the pulmonary circulation is acknowledged to
be under active control, and this may be particularly
relevant in disease (Barer, 1980).
This review describes the current understanding of
the active control of pulmon be under active control, and this may be particularly
relevant in disease (Barer, 1980).
This review describes the current understanding of
the active control of pulmonary circulation. Our knowl-
edge of the control of hum relevant in disease (Barer, 1980).
This review describes the current understanding of
the active control of pulmonary circulation. Our knowl-
edge of the control of human pulmonary vessels is far
from complete, and it is i This review describes the current understanding of
the active control of pulmonary circulation. Our knowl-
edge of the control of human pulmonary vessels is far
from complete, and it is important to recognize that
there ar the active control of pulmonary circulation. Our knowledge of the control of human pulmonary vessels is far from complete, and it is important to recognize that there are marked differences in pulmonary vascular responses edge of the control of human pulmonary vessels is far
from complete, and it is important to recognize that
there are marked differences in pulmonary vascular re-
sponses between species. This may relate to alterations
in s from complete, and it is important to recognize that
there are marked differences in pulmonary vascular re-
sponses between species. This may relate to alterations
in structure, in expression of receptors, and in coupling
 there are marked differences in pulmonary vascular responses between species. This may relate to alterations
in structure, in expression of receptors, and in coupling
of receptor mechanisms to responses. There are also
cha sponses between species. This may relate to alterations
in structure, in expression of receptors, and in coupling
of receptor mechanisms to responses. There are also
changes during development, particularly at birth, as
th in structure, in
of receptor mechanges during
the fetal lungs
Hislop, 1981). of receptor mechanisms to responses. There are also changes during development, particularly at birth, as the fetal lungs adapt to air breathing (Howarth and Hislop, 1981).
A. Structure of Pulmonary Vessels
Pulmonary arter e fetal lungs adapt to air breathing (Howarth and
islop, 1981).
Structure of Pulmonary Vessels
Pulmonary arteries, in contrast to systemic arteries,
we a much thinner smooth muscle layer under normal

Hislop, 1981).
A. *Structure of Pulmonary Vessels*
Pulmonary arteries, in contrast to systemic arteries,
have a much thinner smooth muscle layer under normal

PHARMACOLOGICAL REVIEWS

conditions, consistent with a low-pressure system. Small pulmonary arteries of several hundred μ m internal di-REGULATION OF PULMON
conditions, consistent with a low-pressure system. Small
pulmonary arteries of several hundred μ m internal di-
ameter are the major site of vascular resistance and are REGULATION OF PULMONAF
conditions, consistent with a low-pressure system. Small
pulmonary arteries of several hundred μ m internal di-
ameter are the major site of vascular resistance and are
the site of HPV.[†] The pul conditions, consistent with a low-pressure system. Small
pulmonary arteries of several hundred μ m internal di-
ameter are the major site of vascular resistance and are
the site of HPV.[†] The pulmonary capillary bed re conditions, consistent with a low-pressure system. Small
pulmonary arteries of several hundred μ m internal di-
ameter are the major site of vascular resistance and are
the site of HPV.[†] The pulmonary capillary bed. P pulmonary arteries of several hundred μ m internal diameter are the major site of vascular resistance and are the site of HPV.[†] The pulmonary capillary bed responds differently from the systemic capillary bed. Pulmona ameter are the major site of vascular resistance and a
the site of HPV.[†] The pulmonary capillary bed respon
differently from the systemic capillary bed. Pulmona
veins are similar in structure to pulmonary arteries b
have the site of HPV.[†] The pulmonary capillary bed responds differently from the systemic capillary bed. Pulmonary veins are similar in structure to pulmonary arteries but have less smooth muscle and may be regulated differen differently from the systemic capillary bed. Pulmonary
veins are similar in structure to pulmonary arteries but
have less smooth muscle and may be regulated differ-
ently. Constriction of pulmonary arteries results in eleveins are similar in structure to pulmonary arteries have less smooth muscle and may be regulated diffently. Constriction of pulmonary arteries results in vated pulmonary artery pressure, which increases pressure on the ri have less smooth muscle and may be regulated differently. Constriction of pulmonary arteries results in elevated pulmonary artery pressure, which increases the pressure on the right side of the heart, whereas constriction ently. Constriction of pulmonary arteries results in elvated pulmonary artery pressure, which increases the
pressure on the right side of the heart, whereas constrition of pulmonary veins increases pulmonary capillar
press ted pulmonary artery pressure, which increases the
essure on the right side of the heart, whereas constric-
on of pulmonary veins increases pulmonary capillary
essure, and this could result in pulmonary edema.
With diseas

pressure on the right side of the heart, whereas constriction of pulmonary veins increases pulmonary capillary
pressure, and this could result in pulmonary edema.
With disease, the structure of pulmonary vessels may
change tion of pulmonary veins increases pulmonary capillary

pressure, and this could result in pulmonary edema.

With disease, the structure of pulmonary vessels may

change markedly. With a chronic increase in pulmonary

vascu pressure, and this could result in pulmonary edema.
With disease, the structure of pulmonary vessels may
change markedly. With a chronic increase in pulmonary
vascular pressure, there is a structural remodelling with
fibro With disease, the structure of pulmonary vessels may F
change markedly. With a chronic increase in pulmonary cula
vascular pressure, there is a structural remodelling with
fibrosis, particularly in the intimal layer, and i change markedly. With a chronic increase
vascular pressure, there is a structural re
fibrosis, particularly in the intimal layer,
size of the smooth muscle layer. This m
marked alteration in control mechanism:
 $R_{\text{B}}R_{\text$ France of the smooth muscle is
fibrosis, particularly in the is
size of the smooth muscle linarked alteration in control
B. Role of Endothelium
As in the systemic circulat

Equality the smooth muscle layer. This may result in a be arked alteration in control mechanisms.
 $\begin{array}{c}\n\text{Table of Endothelium} \\
\text{As in the systemic circulation, endothelial cells in the}\\
\text{lmonary circulation have a profound influence on vas-}\n\end{array}$ marked alteration in control mechanisms.

B. Role of Endothelium

As in the systemic circulation, endothelial cells in the

pulmonary circulation have a profound influence on vas-

cular tone. Endothelial cells have the ca B. Role of Endothelium

As in the systemic circulation, endothelial cells in the

pulmonary circulation have a profound influence on vas-

cular tone. Endothelial cells have the capacity to release

several constrictor and Section and the systemic circulation, endothelial cells in the negation are pulmonary circulation have a profound influence on vascular tone. Endothelial cells have the capacity to release on several constrictor and dilat As in the systemic circulation, endothelial cells in the neumonary circulation have a profound influence on vas-
cular tone. Endothelial cells have the capacity to release of
several constrictor and dilator substances, as pulmonary circulation have a profound influence on v
cular tone. Endothelial cells have the capacity to reles
several constrictor and dilator substances, as well
agents that affect the growth and differentiation of co
in t cular tone. Endothelial cells have the capacity to release on several constrictor and dilator substances, as well as in agents that affect the growth and differentiation of cells regin the vessel wall (Liu and Barnes, 199 several constrictor and dilator substances, as well as in a agents that affect the growth and differentiation of cells reguin the vessel wall (Liu and Barnes, 1994). When discussing the actions of drugs on pulmonary vesse agents that affect the growth and differentiation of cells
in the vessel wall (Liu and Barnes, 1994). When discuss-
ing the actions of drugs on pulmonary vessels, it is
important to consider their effects on the endotheli in the vessel wall (Liu and Barnes, 1994). When discuss-
ing the actions of drugs on pulmonary vessels, it is
important to consider their effects on the endothelium
and on pulmonary vascular smooth muscle cells, inas-
much ing the actions of drugs on pulmonary vessels, it is
important to consider their effects on the endothelium
and on pulmonary vascular smooth muscle cells, inas-
much as many agonists influence pulmonary vascular
tone via and on pulmonary vascular smooth muscle cells, inas-
much as many agonists influence pulmonary vascular
tone via the release of endothelial mediators (fig. 1).
II. Neural Mechanisms

The autonomic nervous system may modify pulmotone via the release of endothelial mediators (ng. 1).

II. Neural Mechanisms

The autonomic nervous system may modify pulmo-

nary blood flow under physiological conditions and may

intervalses: HPV, hypoxic pulmonary vas

The autonomic nervous system may modify pulmonary blood flow under physiological conditions and may

† Abbreviations: HPV, hypoxic pulmonary vasoconstriction; NO,

nitric oxide; PPA, pulmonary arterial pressure; AChE, acet nary blood how under physiological conditions and m

† Abbreviations: HPV, hypoxic pulmonary vasoconstriction; N

nitric oxide; PPA, pulmonary arterial pressure; AChE, acetylcholiner

derase; ACh, acetylcholine; NANC, nona [†] Abbreviations: HPV, hypoxic pulmonary vasoconstriction; NO, nitric oxide; PPA, pulmonary arterial pressure; AChE, acetylcholinesterase; ACh, acetylcholine; NANC, nonadrenergic, noncholinergic; EFS, electrical field sti terase; ACh, acetylcholine; NANC, nonadrenergic, noncholinergic;
i-NANC, inhibitory nonadrenergic, noncholinergic; EFS, electrical
field stimulation; ATP, adenosine triphosphate; VIP, vasoactive in-
testinal polypeptide; S i-NANC, inhibitory nonadrenergic, noncholinergic; EFS, electrics
field stimulation; ATP, adenosine triphosphate; VIP, vasoactive in
testinal polypeptide; SP, substance P; CGRP, calcitonin gene-relate
peptide; L-NMMA, N^Grestinal polypeptide; SP, substance P; CGRP, calcitonin gene-relate
peptide; L-NMMA, N^G-monomethyl L-arginine; L-NAME, N^G-L-arginine methyester; cGMP, cyclic guanosine 3', 5' monophosphate
PVR, pulmonary vascular resis peptide; L-NMMA, N^G -monomethyl L-arginine; L-NAME, N^G -L-arginine methyester; cGMP, cyclic guanosine 3', 5' monophosphate; PVR, pulmonary vascular resistance; A-II, angiotensin-II; NPY, neu-ropeptide Y; ANP, atrial n mine methyester; cGMP, cyclic guanosine 3', 5' monophosphate;
PVR, pulmonary vascular resistance; A-II, angiotensin-II; NPY, neu-
ropeptide Y; ANP, atrial natriuretic peptide; BK, bradykinin; AVP,
arginine vasopressin; PAC PVR, pulmonary vascular resistance; A-II, angiotensin-II; NPY, neu-
ropeptide Y; ANP, atrial natriuretic peptide; BK, bradykinin; AVP,
arginine vasopressin; PACAP, pituitary adenylate cyclase activating
peptide; PG, prosta adenosine monophosphate; 11. strial natriuretic peptide; BK, bradykinin; AV
arginine vasopressin; PACAP, pituitary adenylate cyclase activatin
peptide; PG, prostaglandin; ADP, adenosine diphosphate; AM
adenosine monophosph let-activative resources in: PACAP, pituitary adenylate cyclase activative peptide; PG, prostaglandin; ADP, adenosine diphosphate; AM adenosine monophosphate; 5-HT, 5-hydroxytryptamine; PAF, plate-activating factor; DNA, d uretic peptide; PG, prostaglandin; ADP, adenosine diphosphate; AMP
adenosine monophosphate; 5-HT, 5-hydroxytryptamine; PAF, plate
let-activating factor; DNA, deoxyribonucleic acid; BNP, brain natri
uretic peptide; CNP, C-t popularity. The ribonucleic acid; ARDS, adult respiratory distress syndrome; PAF, plate-
let-activating factor; DNA, deoxyribonucleic acid; BNP, brain natri-
uretic peptide; CNP, C-type natriuretic peptide; mRNA, messenger **Exercity in Fig. (2018)**
Let-activating factor; DNA, deoxyribonucleic acid; BNP, brain natr
uretic peptide; CNP, C-type natriuretic peptide; mRNA, messengy
ribonucleic acid; ARDS, adult respiratory distress syndrome; COPI concursually carry contriunedic peptide; InRNA, messenger
intentio peptide; CNP, C-type natriunetic peptide; InRNA, messenger
ribonucleic acid; ARDS, adult respiratory distress syndrome; COPD,
chronic obstructive pulmonary ribonucleic acid; ARDS, adult respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; Ca, calcium; ET, endothelin; cAMP, cyclic adenosine 3', 5' monophosphate; NK, neurokinin; NP, neuropeptide; H, hista chronic obstructive pulmonary disease; Ca, calcium; ET, endothelin; cAMP, cyclic adenosine 3', 5' monophosphate; NK, neurokinin; NP, neuropeptide; H, histamine; LT, leukotriene; Tx, thromboxane; iNOS, inducible nitric oxi cAMP, cyclic adenosine 3', 5' monophosphate; NK, neurokinin; NP, neuropeptide; H, histamine; LT, leukotriene; Tx, thromboxane; iNOS, inducible nitric oxide synthase; TNF- α , tumor necrosis factor- α ; eNOS, endothelial neuropeptide; H, histamine; LT, leukotriene; Tx, thromboxane; iNOS, inducible nitric oxide synthase; TNF- α , tumor necrosis factor- α ; eNOS, endothelial nitric oxide synthase; HPH, hypoxia-induced (secondary) pulmonar derived relaxing factor; EDHF, endothelium-derived relaxing factor- α ; eNOS, endothelial nitric oxide synthase; HPH, hypoxia-in duced (secondary) pulmonary hypertension; EDRF, endothelium derived relaxing factor; EDHF, for-a; eNOS, endothelial nitric oxide synthase; HPH, hypoxia-in-
duced (secondary) pulmonary hypertension; EDRF, endothelium-
derived relaxing factor; EDHF, endothelium-derived hyperpolarizing
factor; L-NA, N^G-nitro-L-ar duced (secondary) pulmonary hypertension; EDRF, endothelium-
derived relaxing factor; EDHF, endothelium-derived hyperpolarizi
factor; L-NA, N^G-nitro-L-arginine; PKC, protein kinase C; PPH, p
mary pulmonary hypertension; derived relaxing factor; EDHF, en
factor; L-NA, N^G-nitro-L-arginine
mary pulmonary hypertension; P
SVR, systemic vascular resistanc

be involved in the pathophysiology of pulmonary vascular diseases. Our understanding of autonomic control cular tone is regulated by autonomic nerves, and mediators from
inflammatory cells and endothelial cells.
be involved in the pathophysiology of pulmonary vascu-
lar diseases. Our understanding of autonomic control
mechanis intiammatory cells and endothelial cells.

be involved in the pathophysiology of pulmonary vascu-

lar diseases. Our understanding of autonomic control

mechanisms has increased greatly in recent years, with

(a) the iden be involved in the pathophysiology of pulmonary vascular diseases. Our understanding of autonomic control
mechanisms has increased greatly in recent years, with
(*a*) the identification of novel neurotransmitters such as
n be involved in the pathophysiology of pulmonary vascular diseases. Our understanding of autonomic control mechanisms has increased greatly in recent years, with (a) the identification of novel neurotransmitters such as ne lar diseases. Our understanding of autonomic control
mechanisms has increased greatly in recent years, with
 (a) the identification of novel neurotransmitters such a
neuropeptides, purines, and *NO*, (b) the recognition mechanisms has increased greatly in recent years, with (a) the identification of novel neurotransmitters such as
neuropeptides, purines, and NO, (b) the recognition of
multiple autonomic receptor subtypes, and (c) the (a) the identification of novel neurotransmitters such as
neuropeptides, purines, and NO, (b) the recognition of
multiple autonomic receptor subtypes, and (c) the dem-
onstration of multiple prejunctional control mech neuropeptides, purines, and NO, (b) the recognition
multiple autonomic receptor subtypes, and (c) the de
onstration of multiple prejunctional control mechanis
in autonomic nerve endings. Pulmonary vascular ton
regulated **CONSTRATION OF MULLIPE PRESCRIM**
 A. Adrenergic Mechanisms
 A. Adrenergic Mechanisms
 1. Adrenergic innervation

After the most increase the pulmonary vascular tone. Pulmonary vas-

inflammatory cells and endothelial cells.

be involved in the pathophysiology of pulmonary vascu-

lar diseases. Our understanding of autonomic control
 autonomic nerve endings. Pulmonary vascular tone is
gulated by many autonomic receptors (table 1).
Adrenergic Mechanisms
1. Adrenergic innervation. Sympathetic nerves sup-
ying the pulmonary vessels arise from nerve cell regulated by many autonomic receptors (table 1).

A. Adrenergic Mechanisms

1. Adrenergic innervation. Sympathetic nerves sup-

plying the pulmonary vessels arise from nerve cell bod-

ies in the first five thoracic gangli A. Adrenergic Mechanisms
1. Adrenergic innervation. Sympathetic nerves sup-
plying the pulmonary vessels arise from nerve cell bod-
ies in the first five thoracic ganglia, the satellite ganglia,
and middle and inferior cer A. Adrenergic innervation. Sympathetic nerves sup-
1. Adrenergic innervation. Sympathetic nerves sup-
plying the pulmonary vessels arise from nerve cell bod-
ies in the first five thoracic ganglia, the satellite ganglia,
a 1. Adrenergic innervation. Sympathetic nerves sup-
plying the pulmonary vessels arise from nerve cell bod-
ies in the first five thoracic ganglia, the satellite ganglia,
and middle and inferior cervical ganglia (Daly and plying the pulmonary vessels arise from nerve cell bod-
ies in the first five thoracic ganglia, the satellite ganglia,
and middle and inferior cervical ganglia (Daly and Hebb,
1966; Richardson, 1979). Postganglionic fibers ies in the first five thoracic ganglia, the satellite ganglia, and middle and inferior cervical ganglia (Daly and Hebb, 1966; Richardson, 1979). Postganglionic fibers from these ganglia intermingle with parasympathetic ner and middle and inferior cervical ganglia (Daly and Hebb,
1966; Richardson, 1979). Postganglionic fibers from
these ganglia intermingle with parasympathetic nerve
fibers to form anterior and posterior plexi at the tracheal
 1966; Richardson, 1979). Postganglionic fibers from
these ganglia intermingle with parasympathetic nerver
fibers to form anterior and posterior plexi at the trachea
bifurcation (Daly and Hebb, 1966). Nerve fibers arising
f these ganglia intermingle with parasympathetic nerve
fibers to form anterior and posterior plexi at the tracheal
bifurcation (Daly and Hebb, 1966). Nerve fibers arising
from these plexi enter the lungs to form a periarteri fibers to form anterior and posterior plexi at the traches
bifurcation (Daly and Hebb, 1966). Nerve fibers arisin
from these plexi enter the lungs to form a periarteria
plexus, which innervates the pulmonary vascular tree
 bifurcation (Daly and Hebb, 1966). Nerve fibers arising
from these plexi enter the lungs to form a periarterial
plexus, which innervates the pulmonary vascular tree,
and a peribronchial plexus, which innervates the bron-
c from these plexi enter the lungs to form a periarterial
plexus, which innervates the pulmonary vascular tree,
and a peribronchial plexus, which innervates the bron-
chial tree. There are extensive connections between
these plexus, which innervates the pulmonary vascular trand a peribronchial plexus, which innervates the brochial tree. There are extensive connections betwe these plexi (Richardson, 1979). The periarterial plex starts as bundle chial tree. There are extensive connections between
these plexi (Richardson, 1979). The periarterial plexus
starts as bundles of large nerve trunks, but these dimin-
ish in size so that at the level of arterioles, there is these plexi (Richardson, 1979). The periarterial plexus Internation of the pathonomic reception of the pathonomic control

relaxation of the pathonomic control of the identification of no control and NO, (b) the recognition of

the identification of noticiple projection and NO,

TABLE **¹** *Autonomic receptors in pulmonary vessels*

Receptors	Subtype	Responses	Endothelium dependency
Adrenergic	α_{1}	contraction	no
	α_{2}	relaxation	yes
	$\boldsymbol{\beta_2}$	relaxation	yes
Muscarinic	M ₃	relaxation	yes
Purinergic	$\mathbf{P_{2x}}$	contraction	no
	${\bf P_{2y}}$	relaxation	yes
Tachykinin	NK,	relaxation	ves
	NK,	contraction	no
VIP	?	relaxation	yes or no
CGRP	າ	relaxation	no

aspet

⁹⁰ **BARNES AND LIIJ** Histochemica! examination reveals that, although the 90
Histochemical examination reveals that, although thextrapulmonary arteries and veins generally have abundant catecholamine-containing nerve fibers in all sp BARNE:
Histochemical examination reveals that, although the
extrapulmonary arteries and veins generally have abun-
dant catecholamine-containing nerve fibers in all spe-
cies examined so far, the extent and density of the Histochemical examination reveals that, although the mextrapulmonary arteries and veins generally have abundant catecholamine-containing nerve fibers in all species examined so far, the extent and density of the nerve fibe Histochemical examination reveals that, although the
extrapulmonary arteries and veins generally have abundant catecholamine-containing nerve fibers in all spe-
cies examined so far, the extent and density of the nerve
fib extrapulmonary arteries and veins generally have abundant catecholamine-containing nerve fibers in all species examined so far, the extent and density of the nerve fiber distribution in the intrapulmonary arteries varies c cies examined so far, the extent and density of the nerve function in the intrapulmonary arteries varies the considerably between species (Richardson, 1979; in McLean, 1986). Catecholamine-containing nerve fibers mare gene fiber distribution in the intrapulmonary arteries varies
considerably between species (Richardson, 1979; i
McLean, 1986). Catecholamine-containing nerve fibers
are generally absent in the intrapulmonary arteries of
rat (Br considerably between species (Richardson, 1979;
McLean, 1986). Catecholamine-containing nerve fibers
are generally absent in the intrapulmonary arteries of
rat (Bradley et al., 1970; El-Bermani, 1978; McLean et
al., 1985), McLean, 1986). Catecholamine-containing nerve fibers
are generally absent in the intrapulmonary arteries of
rat (Bradley et al., 1970; El-Bermani, 1978; McLean et
al., 1985), mouse, hedgehog, and badger (Cech, 1969) but
ar are generally absent in the intrapulmonary arteries of rele
rat (Bradley et al., 1970; El-Bermani, 1978; McLean et syst
al., 1985), mouse, hedgehog, and badger (Cech, 1969) but β_2 -r
are sparsely distributed among intr rat (Bradley et al., 1970; El-Bermani, 1978; McLean et al., 1985), mouse, hedgehog, and badger (Cech, 1969) but
are sparsely distributed among intrapulmonary arteries
of pig and calf, extending to those arteries larger th al., 1985), mouse, hedgehog, and badger (Cech, 1969) but β_2 -
are sparsely distributed among intrapulmonary arteries cies
of pig and calf, extending to those arteries larger than 70 gui
 μ m in diameter (Hebb, 1969). of pig and calf, extending to those arteries larger than 70 μ m in diameter (Hebb, 1969). The intrapulmonary arteries of the guinea pig (Kai, 1969), rabbit (Cech and Dolezel, 1967), sheep, cat (Hebb, 1969), and dog (Fil of pig and calf, extending to those arteries larger than 70 gum in diameter (Hebb, 1969). The intrapulmonary arteries of the guinea pig (Kai, 1969), rabbit (Cech and β , Dolezel, 1967), sheep, cat (Hebb, 1969), and dog μ m in diameter (Hebb, 1969). The intrapulmonary arctries of the guinea pig (Kai, 1969), rabbit (Cech and β_2 -Dolezel, 1967), sheep, cat (Hebb, 1969), and dog (Fillenz, pre 1970; Kadowitz et al., 1981) have an extens Dolezel, 1967), sheep, cat (Hebb, 1969), and dog (Fillenz, predominate with a small number of β_1 -receptors also 1970; Kadowitz et al., 1981) have an extensive and dense present (O'Donnell and Wanstall, 1984; Shaul et 1970; Kadowitz et al., 1981) have an extensive and dense
adrenergic innervation, which extends to the arteries <
70 μ m outer diameter. Human intrapulmonary arteries
are also intensively innervated with adrenergic nerve adrenergic innervation, which extends to the arteries \leq 70 μ m outer diameter. Human intrapulmonary arteries are also intensively innervated with adrenergic nerve fibers extending to arterioles \leq 60 μ m outer 70 μ m outer diameter. Human intrapulmonary arte
are also intensively innervated with adrenergic no
fibers extending to arterioles $< 60 \mu$ m outer diam
(Kai, 1969; McLean, 1986). Human small pulmor
arteries of 100 μ m are also intensively innervated with adrenergic nefibers extending to arterioles $<$ 60 μ m outer diamet(Kai, 1969; McLean, 1986). Human small pulmon arteries of 100 μ m outer diameter still have a surrous ing plexus fibers extending to arterioles $<$ 60 μ m outer diameter [Kai, 1969; McLean, 1986). Human small pulmonary (arteries of 100 μ m outer diameter still have a surrounding plexus of fluorescent nerve bundles at the adventi (Kai, 1969; McLean, 1986). Human small pulmonary
arteries of $100 \mu m$ outer diameter still have a surround-
ing plexus of fluorescent nerve bundles at the adventio-
medial margin (Kai, 1969; Mclean, 1986). Compared
with p arteries of 100 μ m outer diameter still have a surround-
ing plexus of fluorescent nerve bundles at the adventio-
medial margin (Kai, 1969; Mclean, 1986). Compared
with pulmonary arteries, intrapulmonary veins are gening plexus of fluorescen
medial margin (Kai, 1
with pulmonary arterie
erally more sparsely
1969; McLean, 1986).
Ultrastructural studi erally more sparsely innervated (Hebb, 1969; Cech,

erally more sparsely innervated (Hebb, 1969; Cech, 1969; McLean, 1986).
1969; McLean, 1986).
11 Ultrastructural studies have confirmed the presence
10 of adrenergic nerve profiles with small dense core vesi-
1981; Rhodin, 1969; McLean, 1986).

Ultrastructural studies have confirmed the presence

of adrenergic nerve profiles with small dense core vesi-

cles in the intrapulmonary arteries of the cat (Knight et

al., 1981; Rhodin, 1978), dog Ultrastructural studies have confirmed the presen
of adrenergic nerve profiles with small dense core ve
cles in the intrapulmonary arteries of the cat (Knight
al., 1981; Rhodin, 1978), dog (Fillenz, 1970), and rabl
(McLean cles in the intrapulmonary arteries of the cat (Knight et al., 1981; Rhodin, 1978), dog (Fillenz, 1970), and rabbit (McLean, 1986) but not the rat (McLean, 1986). Ultrastructural results correlate well with functional stud al., 1981; Rhodin, 1978), dog (Fillenz, 1970), and rabbit L
(McLean, 1986) but not the rat (McLean, 1986). Ultra- α -a
structural results correlate well with functional studies. ant
In the intact and perfused pulmonary (McLean, 1986) but not the rat (McLean, 1986). Ultra-
structural results correlate well with functional studies. ant
In the intact and perfused pulmonary vascular bed, α_2 -
stimulation of sympathetic nerves to the lung structural results correlate well with functional studies.
In the intact and perfused pulmonary vascular bed,
stimulation of sympathetic nerves to the lung induces a
frequency-dependent increase in perfusion pressure and
 In the intact and perfused pulmonary vascular bed
stimulation of sympathetic nerves to the lung induces
frequency-dependent increase in perfusion pressure an
pulmonary vascular resistance. (Kadowitz and Hyman
1973; Kadowi stimulation of sympathetic nerves to the lung induces a
frequency-dependent increase in perfusion pressure and
pulmonary vascular resistance. (Kadowitz and Hyman,
1973; Kadowitz et al., 1976), which is blocked by α -adfrequency-dependent increase in perfusion pressure and
pulmonary vascular resistance. (Kadowitz and Hyman,
1973; Kadowitz et al., 1976), which is blocked by α -ad-
renoceptor antagonists (Hyman and Kadowitz, 1985)
and ab 1973; Kadowitz et al., 1976), which is blocked by α -ad-
renoceptor antagonists (Hyman and Kadowitz, 1985)
and abolished by the adrenergic neuron blockers
guanethidine and bretylium and by chemical denerva-
tion with 6renoceptor antagonists (Hyman and Kadowitz, 1985)
and abolished by the adrenergic neuron blockers
guanethidine and bretylium and by chemical denerva-
tion with 6-hydroxydopamine (Kadowitz et al., 1975,
1976). Moreover, the renoceptor antagonists (Hyman and Kadowitz, 1985)
and abolished by the adrenergic neuron blockers
guanethidine and bretylium and by chemical denerva-
tion with 6-hydroxydopamine (Kadowitz et al., 1975,
1976). Moreover, the and abolished by the adrenergic neuron blockers sponse guanethidine and bretylium and by chemical denerva- 198
tion with 6-hydroxydopamine (Kadowitz et al., 1975, and
1976). Moreover, the attenuated vasoconstrictor re-
res guanethidine and bretylium and by chemical denerva-
tion with 6-hydroxydopamine (Kadowitz et al., 1975, and
1976). Moreover, the attenuated vasoconstrictor re-
response to sympathetic nerve stimulation induced by both
6-hy tion with 6-hydroxydopamine (Kadowitz et al., 1975, 1976). Moreover, the attenuated vasoconstrictor response to sympathetic nerve stimulation induced by 6-hydroxydopamine treatment is associated with a marked decrease in t 1976). Moreover, the attenuated vasoconstrictor response to sympathetic nerve stimulation induced by both both variant is associated with a armarked decrease in the density of fluorescent adrenergic automated decrease in t sponse to sympathetic nerve stimulation induced by 6-hydroxydopamine treatment is associated with a marked decrease in the density of fluorescent adrenergic nerve fibers and with ultrastructural changes in the appearance o marked decrease in the density of fluorescent adrenergic auto
nerve fibers and with ultrastructural changes in the endi-
appearance of adrenergic terminal profiles in both in-
trapulmonary arteries and veins (Kadowitz et a

nerve fibers and with ultrastructural changes in the appearance of adrenergic terminal profiles in both in-
trapulmonary arteries and veins (Kadowitz et al., 1976).
2. Adrenergic receptors. Norepinephrine released from
sym appearance of adrenergic terminal profiles in both in-
trapulmonary arteries and veins (Kadowitz et al., 1976).
2. Adrenergic receptors. Norepinephrine released from
sympathetic nerves and epinephrine secreted by the ad-
 trapulmonary arteries and veins (Kadowitz et al., 1976). dot
2. Adrenergic receptors. Norepinephrine released from the
sympathetic nerves and epinephrine secreted by the ad-
renal medulla act on multiple adrenoceptor subt 2. Adrenergic receptors. Norepinephrine released fragmentation errors and epinephrine secreted by the areal medulla act on multiple adrenoceptor subtyp Three subtypes of β -receptor $(\beta_1, \beta_2,$ and β_3 -) can disting sympathetic nerves and epinephrine secreted by the adverse renal medulla act on multiple adrenoceptor subtypes. 3
Three subtypes of β -receptor $(\beta_1, \beta_2,$, and β_3 -) can be France distinguished both pharmacological Three subtypes of β -receptor $(\beta_1, \beta_2,$ and β_3 -) can be Fra
distinguished both pharmacologically and at a molecu-
lar level. α -Receptors are classified into α_1 - and α_2 - re-
ceptors, which are further c

ND LIU
molecular level, although these cannot always be disti
guished pharmacologically (Strasser et al., 1992). MD LIU
molecular level, although these cannot always be diguished pharmacologically (Strasser et al., 1992).
Both β_1 - and β_2 -adrenoceptors have been ident

medial margin (Kai, 1969; Mclean, 1986). Compared are heterogeneous on the bovine endothelial cells, with
with pulmonary arteries, intrapulmonary veins are gen-
erally more sparsely innervated (Hebb, 1969; Cech, remaining Both *IIU*
blecular level, although these cannot always be distin-
ished pharmacologically (Strasser et al., 1992).
Both β_1 - and β_2 -adrenoceptors have been identified
nctionally in isolated pulmonary vessel rings molecular level, although these cannot always be distinguished pharmacologically (Strasser et al., 1992).
Both β_1 - and β_2 -adrenoceptors have been identified functionally in isolated pulmonary vessel rings and in t molecular level, although these cannot always be distinguished pharmacologically (Strasser et al., 1992).
Both β_1 - and β_2 -adrenoceptors have been identified functionally in isolated pulmonary vessel rings and in t guished pharmacologically (Strasser et al., 1992).
Both β_1 - and β_2 -adrenoceptors have been identified
functionally in isolated pulmonary vessel rings and in
the pulmonary vascular bed; they mediate vasodilation
in Both β_1 - and β_2 -adrenoceptors have been identified
functionally in isolated pulmonary vessel rings and in
the pulmonary vascular bed; they mediate vasodilation
in response to circulating catecholamines (Boe and Si functionally in isolated pulmonary vessel rings and in
the pulmonary vascular bed; they mediate vasodilation
in response to circulating catecholamines (Boe and Si-
monsson, 1980; Hyman et al., 1981) and to neurally
release the pulmonary vascular bed; they mediate vasodilation
in response to circulating catecholamines (Boe and Si-
monsson, 1980; Hyman et al., 1981) and to neurally
released norepinephrine (Hyman et al., 1990). As in
systemic in response to circulating catecholamines (Boe and Si-monsson, 1980; Hyman et al., 1981) and to neurally released norepinephrine (Hyman et al., 1990). As in systemic vessels, these receptors are generally of the β_2 -re monsson, 1980; Hyman et al., 1981) and to neurally
released norepinephrine (Hyman et al., 1990). As in
systemic vessels, these receptors are generally of the
 β_2 -receptor subtype, although this varies between spe-
cies released norepinephrine (Hyman et al., 1990). As in
systemic vessels, these receptors are generally of the
 β_2 -receptor subtype, although this varies between spe-
cies. Thus, β -adrenoceptors on the pulmonary vessels systemic vessels, these receptors are generally of the β_2 -receptor subtype, although this varies between species. Thus, β -adrenoceptors on the pulmonary vessels of guinea pig, rabbit (O'Donnell and Wanstall, 1985), β_2 -receptor subtype, although this varies between species. Thus, β -adrenoceptors on the pulmonary vessels of guinea pig, rabbit (O'Donnell and Wanstall, 1985), and cat (Hyman et al. 1981, 1990) are exclusively of t cies. Thus, β -adrenoceptors on the pulmonary vessels of
guinea pig, rabbit (O'Donnell and Wanstall, 1985), and
cat (Hyman et al. 1981, 1990) are exclusively of the
 β_2 -receptor subtype, whereas in the rat, β_2 -re guinea pig, rabbit (O'Donnell and Wanstall, 1985), and
cat (Hyman et al. 1981, 1990) are exclusively of the
 β_2 -receptor subtype, whereas in the rat, β_2 -receptors
predominate with a small number of β_1 -receptors cat (Hyman et al. 1981, 1990) are exclusively of the β_2 -receptor subtype, whereas in the rat, β_2 -receptors predominate with a small number of β_1 -receptors also present (O'Donnell and Wanstall, 1984; Shaul et a β_2 -receptor subtype, whereas in the rat, β_2 -receptors predominate with a small number of β_1 -receptors also present (O'Donnell and Wanstall, 1984; Shaul et al., 1990). Binding studies indicate that the β -adr predominate with a small number of β_1 -receptors also
present (O'Donnell and Wanstall, 1984; Shaul et al.,
1990). Binding studies indicate that the β -adrenoceptors
on human pulmonary vessels are β_2 -receptors (Ca present (O'Donnell and Wanstall, 1984; Shaul et al., 1990). Binding studies indicate that the β -adrenoceptors on human pulmonary vessels are β_2 -receptors (Carstairs et al., 1985), but functional studies also sugges 1990). Binding studies indicate that the β -adrenoceptors
on human pulmonary vessels are β_2 -receptors (Carstairs
et al., 1985), but functional studies also suggest the
presence of β_1 -receptors (Boe and Simonsson on human pulmonary vessels are β_2 -receptors (Carstairs
et al., 1985), but functional studies also suggest the
presence of β_1 -receptors (Boe and Simonsson, 1980).
Cultured endothelial cells of bovine (Ahmad et al., et al., 1985), but functional studies also suggest the presence of β_1 -receptors (Boe and Simonsson, 1980).
Cultured endothelial cells of bovine (Ahmad et al., 1990) and human (Grigorian et al., 1989) pulmonary arterie presence of β_1 -receptors (Boe and Simonsson, 1980).
Cultured endothelial cells of bovine (Ahmad et al., 1990)
and human (Grigorian et al., 1989) pulmonary arteries
have a high density of β -adrenoceptors. These rece Cultured endothelial cells of bovine (Ahmad et al., 1990)
and human (Grigorian et al., 1989) pulmonary arteries
have a high density of β -adrenoceptors. These receptors
are heterogeneous on the bovine endothelial cells, and human (Grigorian et al., 1989) pulmonary arteries
have a high density of β -adrenoceptors. These receptors
are heterogeneous on the bovine endothelial cells, with
25% of them being of the β_1 -receptor subtype and have a high density of β -adrenoceptors. These receptors
are heterogeneous on the bovine endothelial cells, with
25% of them being of the β_1 -receptor subtype and the
remaining 75% consisting of β_2 - or atypical are heterogeneous on the bovine endothelial cells, we
25% of them being of the β_1 -receptor subtype and t
remaining 75% consisting of β_2 - or atypical β -recepto
There are also facilitatory β_2 -adrenoceptors on 25% of them being of the β_1 -receptor subtype and the remaining 75% consisting of β_2 - or atypical β -receptors.
There are also facilitatory β_2 -adrenoceptors on the pulmonary sympathetic nerve endings (Costa a There are also facilitatory β_2 -adrenoceptors on the pulmonary sympathetic nerve endings (Costa and Majewski, 1988; Molderings et al., 1988; Starke et al., 1989); these facilitate the release of norepinephrine.
Less in here are also facilitatory β_2 -adrenoceptors on the pul-
onary sympathetic nerve endings (Costa and Majew-
i, 1988; Molderings et al., 1988; Starke et al., 1989);
see facilitate the release of norepinephrine.
Less info predominate with a small number of β_1 -receptors also

1990). Binding studies indicate that the β -adrenoceptors

1990). Binding studies indicate that the β -adrenoceptors

on human pulmonary vessels are β_2 -rec

monary sympathetic nerve endings (Costa and Majewski, 1988; Molderings et al., 1988; Starke et al., 1989);
these facilitate the release of norepinephrine.
Less information is available about the distribution of
 α -adren these facilitate the release of norepine
phrine.
Less information is available about the distribution of
 α -adrenoceptors. Studies using selective agonists and
antagonists have demonstrated the presence of α_1 - and
Less information is available about the distribution of α -adrenoceptors. Studies using selective agonists and antagonists have demonstrated the presence of α_1 - and α_2 -receptors on isolated pulmonary vessel ring α -adrenoceptors. Studies using selective agonists and
antagonists have demonstrated the presence of α_1 - and
 α_2 -receptors on isolated pulmonary vessel rings and in
the pulmonary vascular bed of the rabbit (Doche antagonists have demonstrated the presence of α_1 - and α_2 -receptors on isolated pulmonary vessel rings and in the pulmonary vascular bed of the rabbit (Docherty and Starke, 1981), cat (Hyman and Kadowitz, 1985; Hym α_2 -receptors on isolated pulmonary vessel rings and
the pulmonary vascular bed of the rabbit (Docherty a
Starke, 1981), cat (Hyman and Kadowitz, 1985; Hym
et al., 1986), and dog (Greenberg et al., 1981; Shebu
et al., Starke, 1981), cat (Hyman and Kadowitz, 1985; Hyman
et al., 1986), and dog (Greenberg et al., 1981; Shebuski
et al., 1986). Both receptors mediate vasoconstriction.
Canine pulmonary arteries have been reported to re-
spon Starke, 1981), cat (Hyman and Kadowitz, 1985; Hyman
et al., 1986), and dog (Greenberg et al., 1981; Shebuski
et al., 1986). Both receptors mediate vasoconstriction.
Canine pulmonary arteries have been reported to re-
spon et al., 1986), and dog (Greenberg et al., 1981; Shebuski
et al., 1986). Both receptors mediate vasoconstriction.
Canine pulmonary arteries have been reported to re-
spond only to α_1 -adrenoceptor agonists (Shebuski et et al., 1986). Both receptors mediate vasoconstriction.
Canine pulmonary arteries have been reported to re-
spond only to α_1 -adrenoceptor agonists (Shebuski et al., 1987), whereas pulmonary veins constrict to both α Canine pulmonary arteries have been reported to respond only to α_1 -adrenoceptor agonists (Shebuski et al., 1987), whereas pulmonary veins constrict to both α_1 -
and α_2 -adrenergic agonists (Ohlstein et al., 1989 spond only to α_1 -adrenoceptor agonists (Shebuski et al. 1987), whereas pulmonary veins constrict to both α_1 and α_2 -adrenergic agonists (Ohlstein et al., 1989). These results suggest that α_1 -adrenoceptors a results suggest that α_1 -adrenoceptors are located on both pulmonary artery and vein, but α_2 -adrenoceptors are to be found only on pulmonary vein. There are also autoregulatory α_2 -adrenoceptors on sympathetic n both pulmonary artery and vein, but α_2 -adrenoceptors
are to be found only on pulmonary vein. There are also
autoregulatory α_2 -adrenoceptors on sympathetic nerve
endings that participate in a feedback mechanism to
 are to be found only on pulmonary vein. There are also
autoregulatory α_2 -adrenoceptors on sympathetic nerve
endings that participate in a feedback mechanism to
modulate norepinephrine release (Starke et al., 1989). En autoregulatory α_2 -adrenoceptors on sympathetic nerve
endings that participate in a feedback mechanism to
modulate norepinephrine release (Starke et al., 1989). En-
dothelial α_2 -adrenoceptors mediating vasodilation endings that participate in a feedback mechanis modulate norepinephrine release (Starke et al., 1989) dothelial α_2 -adrenoceptors mediating vasodilation thre release of NO have been demonstrated in pulmo vessels (Liu e α 2. Adrenergine phrima release (Starke et al., 1989). Enthelial α_2 -adrenergics mediating vasodilation through
e release of NO have been demonstrated in pulmonary
ssels (Liu et al., 1991a; Pepke-Zaba et al., 1993).
 dothelial α_2 -adrenoceptors mediating vasodilation through
the release of NO have been demonstrated in pulmonary
vessels (Liu et al., 1991a; Pepke-Zaba et al., 1993).
3. Adrenergic control of pulmonary vascular tone.
F

the release of NO have been demonstrated in pulmonary
vessels (Liu et al., 1991a; Pepke-Zaba et al., 1993).
3. Adrenergic control of pulmonary vascular tone.
Francois-Franck (1896) observed an increase in the pul-
monary a vessels (Liu et al., 1991a; Pepke-Zaba et al., 1993).

3. Adrenergic control of pulmonary vascular tone.

Francois-Franck (1896) observed an increase in the pulmonary artery blood pressure and heart rate in response

to th 3. Adrenergic control of pulmonary vascular tone.
Francois-Franck (1896) observed an increase in the pul-
monary artery blood pressure and heart rate in response
to the stimulation of sympathetic nerves supplying the
lung. Francois-Franck (1896) observed an increase in the pul-
monary artery blood pressure and heart rate in response
to the stimulation of sympathetic nerves supplying the
lung. However, because changes in cardiac output, air-

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REGULATION OF PULMON
eters that occur during sympathetic nerve stimulation
have effects on the PPA and vascular resistance, it was REGULATION OF PULMONA
eters that occur during sympathetic nerve stimulation (M
have effects on the PPA and vascular resistance, it was al
not possible to determine whether the increased pulmo-REGULATION OF PU
have effects on the PPA and vascular resistance, it w
not possible to determine whether the increased pulm
nary arterial pressure was attributable to pulmona eters that occur during sympathetic nerve stimulation (have effects on the PPA and vascular resistance, it was and possible to determine whether the increased pulmonary arterial pressure was attributable to pulmonary (vaso have effects on the PPA and vascular resistance, it was not possible to determine whether the increased pulmonary arterial pressure was attributable to pulmonary vasoconstriction. Daly and colleagues (Daly and Hebb, 1952; have effects on the PPA and vascular resistance, it w
not possible to determine whether the increased pulm
nary arterial pressure was attributable to pulmona
vasoconstriction. Daly and colleagues (Daly and Hel
1952; Daly a not possible to determine whether the increased puln
nary arterial pressure was attributable to pulmona
vasoconstriction. Daly and colleagues (Daly and Hel
1952; Daly and Hebb, 1966; Daly et al., 1970) demo
strated that un nary arterial pressure was attributable to pulmona
vasoconstriction. Daly and colleagues (Daly and Hel
1952; Daly and Hebb, 1966; Daly et al., 1970) demo
strated that under conditions of constant flow, symp
thetic nerve st vasoconstriction. Daly and colleagues (Daly and Hebb, then
1952; Daly and Hebb, 1966; Daly et al., 1970) demon-
strated that under conditions of constant flow, sympa- (Nis
thetic nerve stimulation consistently increases pu 1952; Daly and Hebb, 1966; Daly et al., 1970) demon-protected that under conditions of constant flow, sympa-
thetic nerve stimulation consistently increases pulmo-demary vascular resistance. On the other hand, in an in las strated that under conditions of constant flow, sympa-
thetic nerve stimulation consistently increases pulmo-
nary vascular resistance. On the other hand, in an in
situ perfused dog lung preparation, sympathetic nerve
stim thetic nerve stimulation consistently increases pulm
nary vascular resistance. On the other hand, in an
situ perfused dog lung preparation, sympathetic ner
stimulation has little or no effect on pulmonary vascul
resistance nary vascular resistance. On the other hand, in an in last
itu perfused dog lung preparation, sympathetic nerve the
stimulation has little or no effect on pulmonary vascular
resistance but decreases pulmonary vascular comp situ perfused dog lung preparation, sympathetic nerve
stimulation has little or no effect on pulmonary vascular
resistance but decreases pulmonary vascular compli-
ance (Ingram et al., 1968, 1970). The reason for this
disc stimulation has little or no effect on pulmonary vascular
resistance but decreases pulmonary vascular compli-
ance (Ingram et al., 1968, 1970). The reason for this
discrepancy is unclear but may relate to different basal
c resistance but decreases pulmonary vascular compli-
ance (Ingram et al., 1968, 1970). The reason for this
discrepancy is unclear but may relate to different basal
conditions and surgical manipulations. In a closed-chest
do ance (Ingram et al., 1968, 1970). The reason for thit discrepancy is unclear but may relate to different base conditions and surgical manipulations. In a closed-cheed dog lung lobe perfused at constant flow, there is a fre discrepancy is unclear but may relate to different basal
conditions and surgical manipulations. In a closed-chest
dog lung lobe perfused at constant flow, there is a fre-
quency-related increase in pulmonary vascular resis conditions and surgical manipulations. In a closed-ch
dog lung lobe perfused at constant flow, there is a i
quency-related increase in pulmonary vascular re
tance in response to sympathetic nerve stimulat
(Kadowitz and Hym dog lung lobe perfused at constant flow, there is a fre-
quency-related increase in pulmonary vascular resis-
tance in response to sympathetic nerve stimulation mm
(Kadowitz and Hyman, 1973). This response is indepen-
dent quency-related increase in pulmonary vascular resistance in response to sympathetic nerve stimulation.
(Kadowitz and Hyman, 1973). This response is independent of changes in respiration, bronchomotor tone, and blood flow i tance in response to sympathetic nerve stimulation (Kadowitz and Hyman, 1973). This response is independent of changes in respiration, bronchomotor tone, and blood flow in the bronchial circulation. Sympathetic nerve stimu (Kadowitz and Hyman, 1973). This response is independent of changes in respiration, bronchomotor tone, and colored flow in the bronchial circulation. Sympathetic space of the process pulmonary vascular resistance by up to dent of changes in respiration, bronchomotor tone, and
blood flow in the bronchial circulation. Sympathetic
nerve stimulation may increase pulmonary vascular re-
sistance by up to 70% (Daly and Daly, 1973; Kadowitz et
al., blood flow in the bronchial circulation. Sympathetic
nerve stimulation may increase pulmonary vascular re-
sistance by up to 70% (Daly and Daly, 1973; Kadowitz et
al., 1975). Sympathetic nerve stimulation also increases
pu merve stimulation may increase pulmonary vascular resistance by up to 70% (Daly and Daly, 1973; Kadowitz et al., 1975). Sympathetic nerve stimulation also increases repulmonary input impedance and pulmonary vascular resis sistance by up to 70% (Daly and Daly, 1973; Kadowitz et al., 1975). Sympathetic nerve stimulation also increases pulmonary input impedance and pulmonary vascular resistance (Pace et al., 1971; Piene, 1976), indicating that al., 1975). Sympathetic nerve stimulation also increases nor
pulmonary input impedance and pulmonary vascular
resistance (Pace et al., 1971; Piene, 1976), indicating B .
that both increases in pulmonary vascular resistan pulmonary input impedance and pulmonary vascular
resistance (Pace et al., 1971; Piene, 1976), indicating
that both increases in pulmonary vascular resistance
and decreases in pulmonary vascular compliance can be
induced by resistance (Pace et al., 1971; Piene, 1976), indicating
that both increases in pulmonary vascular resistance
and decreases in pulmonary vascular compliance can be
induced by sympathetic nerve stimulation. Thus, sym-
pathet that both increases in pulmonary vascular resistance
and decreases in pulmonary vascular compliance can be
induced by sympathetic nerve stimulation. Thus, sym-
pathetic activation causes an increase in pulmonary vas-
cular and decreases in pulmonary vascular complianced by sympathetic nerve stimula
pathetic activation causes an increase is
cular resistance and a decrease in pul
compliance, thereby increasing PPA.
Both the increase in pulmona duced by sympathetic nerve stimulation. Thus, sym-
thetic activation causes an increase in pulmonary vas-
lar resistance and a decrease in pulmonary vascular
mpliance, thereby increasing PPA.
Both the increase in pulmonary pathetic activation causes an increase in pulmonary vascular
compliance, thereby increasing PPA.
Both the increase in pulmonary vascular resistance
and the decrease in pulmonary vascular compliance that
occur during sympat

cular resistance and a decrease in pulmonary vasculation
compliance, thereby increasing PPA.
Both the increase in pulmonary vascular resistance and the decrease in pulmonary vascular compliance that
occur during sympathet compliance, thereby increasing PPA.
Both the increase in pulmonary vascular resistance
and the decrease in pulmonary vascular compliance that
occur during sympathetic nerve stimulation are medi-
ated by α -adrenoceptors Both the increase in pulmonary vascular resistance
and the decrease in pulmonary vascular compliance that
occur during sympathetic nerve stimulation are medi-
ated by α -adrenoceptors (Ingram et al., 1968, 1970; Kad-
ow and the decrease in pulmonary vascular compliance that
occur during sympathetic nerve stimulation are medi-
ated by α -adrenoceptors (Ingram et al., 1968, 1970; Kad-
owitz and Hyman, 1973; Kadowitz et al., 1975, 1976),
 occur during sympathetic nerve stimulation are med
ated by α -adrenoceptors (Ingram et al., 1968, 1970; Kao
owitz and Hyman, 1973; Kadowitz et al., 1975, 1976
and primarily by α_1 -adrenoceptors (Hyman, 1986
There als ated by α -adrenoceptors (Ingram et al., 1968, 1970; Kad-
owitz and Hyman, 1973; Kadowitz et al., 1975, 1976), pu
and primarily by α_1 -adrenoceptors (Hyman, 1986). in
There also seems to be a β -adrenoceptor-mediat owitz and Hyman, 1973; Kadowitz et al., 1975, 19
and primarily by α_1 -adrenoceptors (Hyman, 19
There also seems to be a β -adrenoceptor-mediated
monary vasodilation in response to sympathetic r
stimulation inasmuch a and primarily by α_1 -adrenoceptors (Hyman, 1986). ing
There also seems to be a β -adrenoceptor-mediated pul-
monary vasodilation in response to sympathetic nerve mas
stimulation inasmuch as in the presence of α -ad There also seems to be a β -adrenoceptor-mediated pul-
monary vasodilation in response to sympathetic nerve
stimulation inasmuch as in the presence of α -adrenocep-
tor blockade, sympathetic nerve stimulation elicits stimulation inasmuch as in the presence of α -adrenoceptor blockade, sympathetic nerve stimulation elicits a vasodilator response (Hyman et al., 1981), and that β -adrenoceptor blockade enhances the constrictor respon r blockade, sympathetic nerve stimulation elicits
sodilator response (Hyman et al., 1981), and the
adrenoceptor blockade enhances the constrictor r
onse to sympathetic nerve stimulation (Hyman, 1986
Sympathetic nerves may

vasodilator response (Hyman et al., 1981), and that no
 β -adrenoceptor blockade enhances the constrictor response to sympathetic nerve stimulation (Hyman, 1986). sp
Sympathetic nerves may also play a role in the main-
t β -adrenoceptor blockade enhances the constrictor sponse to sympathetic nerve stimulation (Hyman, 198
Sympathetic nerves may also play a role in the matemance of basal pulmonary vascular tone. Removal
the satellite gang sponse to sympathetic nerve stimulation (Hyman, 1986)
Sympathetic nerves may also play a role in the maid tenance of basal pulmonary vascular tone. Removal
the satellite ganglia and the first five thoracic sympethetic gang Sympathetic nerves may also play a role in the main-
tenance of basal pulmonary vascular tone. Removal of
the satellite ganglia and the first five thoracic sympa-
thetic ganglia significantly decrease pulmonary vascu-
lar tenance of basal pulmonary vascular tone. Removal of larticle statellite ganglia and the first five thoracic sympathectic ganglia significantly decrease pulmonary vascu-
thetic ganglia significantly decrease pulmonary vasc the satellite ganglia and the first five thoracic sympa-
thetic ganglia significantly decrease pulmonary vascu-
lar resistance in cats (Duke and Stedeford, 1960). Tho-
not extend to vessels < 70 μ m in diameter (Hebb, 1 lar resistance in cats (Duke and Stedeford, 1960). Thoracic sympathectomy lower PPA and vascular tone in the dogs and lambs (Kabins et al., 1962; Colebatch et al., 1965). Moreover, α -adrenergic antagonists reduce pul-m macic sympathectomy lower PPA and vascular tone in the Puldogs and lambs (Kabins et al., 1962; Colebatch et al., and 1965). Moreover, α -adrenergic antagonists reduce pulmonary vascular resistance in anesthetized cats a 1965). Moreover, α -adrenergic antagonists reduce pulmonary vascular resistance in anesthetized cats and conscious dogs (Barer, 1966; Murray et al., 1986), and β -adrenergic antagonists increase pulmonary vascular res monary vascular resistance in anesthetized cats and bit, these extend down to the vessels of $\lt 100 \mu$ m (Hebb, conscious dogs (Barer, 1966; Murray et al., 1986), and 1969) and even to arterioles (Cech, 1973). Cat and she

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ic nerve stimulation (Malik and Newmark, 1976; Murray et al., 1986; Kane et
ar resistance, it was al., 1994). These results indicate that there is a degree of ary vascular tone
(Malik and Newmark, 1976; Murray et al., 1986; Kane et
al., 1994). These results indicate that there is a degree of
basal sympathetic tone under normal physiological con-91

Malik and Newmark, 1976; Murray et al., 1986; Kane et

al., 1994). These results indicate that there is a degree of

basal sympathetic tone under normal physiological con-

ditions. After left lung autotransplantation (Malik and Newmark, 1976; Murray et al., 1986; Kane et al., 1994). These results indicate that there is a degree of basal sympathetic tone under normal physiological conditions. After left lung autotransplantation in dogs (Malik and Newmark, 1976; Murray et al., 1986; Kane et al., 1994). These results indicate that there is a degree of basal sympathetic tone under normal physiological conditions. After left lung autotransplantation in dogs basal sympathetic tone under normal physiological conditions. After left lung autotransplantation in dog
there is an increased response to α -adrenergic agonist
presumably attributable to denervation supersensitivi
(Nis basal sympathetic tone under normal physiological conditions. After left lung autotransplantation in dogs, there is an increased response to α -adrenergic agonists, presumably attributable to denervation supersensitivit ditions. After left lung autotransplantation in dometers is an increased response to α -adrenergic agonis presumably attributable to denervation supersensitivity.
(Nishiwaki et al., 1993). This provides additional edenc there is an increased response to α -adrenergic agonists,
presumably attributable to denervation supersensitivity
(Nishiwaki et al., 1993). This provides additional evi-
dence of basal adrenergic tone in the pulmonary v presumably attributable to denervation super
(Nishiwaki et al., 1993). This provides addidence of basal adrenergic tone in the pulmon
lar bed under normal physiological conditions
this is lower than in the systemic circula ishiwaki et al., 1993). This provides additional evi-
nce of basal adrenergic tone in the pulmonary vascu-
r bed under normal physiological conditions, although
is is lower than in the systemic circulation.
The segmental d

dence of basal adrenergic tone in the pulmonary vaso
lar bed under normal physiological conditions, althou
this is lower than in the systemic circulation.
The segmental distribution of the vasoconstrictor
sponse to sympath lar bed under normal physiological conditions, although
this is lower than in the systemic circulation.
The segmental distribution of the vasoconstrictor re-
sponse to sympathetic nerve stimulation in the pulmo-
nary circu this is lower than in the systemic circulation.
The segmental distribution of the vasoconstrictor re-
sponse to sympathetic nerve stimulation in the pulmo-
nary circulation is not entirely clear. By comparing the
responses nary circulation is not entirely clear. By comparing the responses during forward and retrograde perfusion,
Daly et al. (1970) concluded that the arteries were the
major site of the increased resistance. Direct measure-
ments of pressure in intrapulmonary veins of 2.5 to 3.5
mm responses during forward and retrograde perfusion,
Daly et al. (1970) concluded that the arteries were the
major site of the increased resistance. Direct measure-
ments of pressure in intrapulmonary veins of 2.5 to 3.5
mm Daly et al. (1970) concluded that the arteries were the major site of the increased resistance. Direct measurements of pressure in intrapulmonary veins of 2.5 to 3.5 mm diameter have indicated that up to 50% of the inc major site of the increased resistance. Direct measurements of pressure in intrapulmonary veins of 2.5 to 3.5
mm diameter have indicated that up to 50% of the increase in total pulmonary vascular vascular resistance
occurs mm diameter have indicated that up to 50% of the in-
crease in total pulmonary vascular vascular resistance
occurs in these vessels (Kadowitz et al., 1975). Using a
stop-flow technique, a venous component in the vasocon-
s mm diameter have indicated that up to 50% of the increase in total pulmonary vascular vascular resistance occurs in these vessels (Kadowitz et al., 1975). Using a stop-flow technique, a venous component in the vasoconstric crease in total pulmonary vascular vascular resistance
occurs in these vessels (Kadowitz et al., 1975). Using a
stop-flow technique, a venous component in the vasocon-
strictor response to satellite ganglion stimulation is occurs in these vessels (Kadowitz et al., 1979).
strictor response to satellite ganglion s
apparent, although these vessels const
norepinephrine (Hakim et al., 1979). *B. Cholinergic Mechanisms*

sponse to sympathetic nerve stimulation in the pulmo-
nary circulation is not entirely clear. By comparing the
responses during forward and retrograde perfusion,
Daly et al. (1970) concluded that the arteries were the
maj parent, although these vessels constrict to exogenous
 1. Cholinergic Mechanisms
 1. Cholinergic innervation. Unlike in the airway,
 1. Cholinergic innervation. Unlike in the airway,
 nere cholinergic innervation p norepinephrine (Hakim et al., 1979).

B. Cholinergic Mechanisms

1. Cholinergic innervation. Unlike in the airway,

where cholinergic innervation predominates (Barnes,

1986), the pulmonary circulation receives less cholin 1986). Cholinergic Mechanisms
1. Cholinergic innervation. Unlike in the airway
where cholinergic innervation predominates (Barne
1986), the pulmonary circulation receives less cholinergic input, compared with adrenergic in E. Cholinergic innervation. Unlike in the airway
where cholinergic innervation. Unlike in the airway
where cholinergic innervation predominates (Barnes
1986), the pulmonary circulation receives less cholinergic input, comp 1. Cholinergic innervation. Unlike in the airway,
where cholinergic innervation predominates (Barnes,
1986), the pulmonary circulation receives less cholin-
ergic input, compared with adrenergic innervation.
Preganglionic where cholinergic innervation predominates (Barnes,
1986), the pulmonary circulation receives less cholin-
ergic input, compared with adrenergic innervation.
Preganglionic cholinergic efferent nerve fibers arise
from the v 1986), the pulmonary circulation receives less cholinergic input, compared with adrenergic innervation.
Preganglionic cholinergic efferent nerve fibers arise
from the vagal nuclei of the brainstem and pass down
the vagus n ergic input, compared with adrenergic innervation.
Preganglionic cholinergic efferent nerve fibers arise
from the vagal nuclei of the brainstem and pass down
the vagus nerves into the lungs (Daly and Hebb, 1966).
These fib Preganglionic cholinergic efferent nerve fibers arise
from the vagal nuclei of the brainstem and pass down
the vagus nerves into the lungs (Daly and Hebb, 1966).
These fibers relay in the pulmonary plexi or with the
postga from the vagal nuclei of the brainstem and pass down
the vagus nerves into the lungs (Daly and Hebb, 1966).
These fibers relay in the pulmonary plexi or with the
postganglionic nerve cell bodies in hilar plexi. The dis-
tr the vagus nerves into the lungs (Daly and Hebb, 1966).
These fibers relay in the pulmonary plexi or with the
postganglionic nerve cell bodies in hilar plexi. The dis-
tribution of these postganglionic nerve fibers along th These fibers relay in the pulmonary plexi or with the postganglionic nerve cell bodies in hilar plexi. The distribution of these postganglionic nerve fibers along the pulmonary vascular tree has been studied in detail usin postganglionic nerve cell bodies in hilar plexi. The distribution of these postganglionic nerve fibers along the pulmonary vascular tree has been studied in detail using histochemical techniques, including AChE staining an tribution of these postganglionic nerve fibers along the
pulmonary vascular tree has been studied in detail us-
ing histochemical techniques, including AChE staining
and choline acetyltransferase staining. There is a
marke pulmonary vascular tree has been studied in detail using histochemical techniques, including AChE staining
and choline acetyltransferase staining. There is a
marked species-dependent variation in the distribution
of cholin ing histochemical techniques, including AChE staining
and choline acetyltransferase staining. There is a
marked species-dependent variation in the distribution and choline acetyltransferase staining. There is
marked species-dependent variation in the distribut
of cholinergic nerve fibers. Intrapulmonary arteries
the guinea pig, mouse, and rat have no AChE-posit
nerve fibers, alth marked species-dependent variation in the distribution
of cholinergic nerve fibers. Intrapulmonary arteries of
the guinea pig, mouse, and rat have no AChE-positive
nerve fibers, although they were found in the extrapul-
mo the guinea pig, mouse, and rat have no AChE-positive
nerve fibers, although they were found in the extrapul-
monary arteries and large pulmonary veins of these
species (Cech, 1969, 1973; Bradley et al., 1970). AChE-
posit nerve fibers, although they were found in the extrapulmonary arteries and large pulmonary veins of these positive nerve fibers are found in pig pulmonary arteries species (Cech, 1969, 1973; Bradley et al., 1970). AChE-
positive nerve fibers are found in pig pulmonary arteries
larger than 200 μ m in diameter and large pulmonary
veins (Hebb, 1969). The pulmonary arteries of calf ha positive nerve fibers are found in pig pulmonary arteries larger than 200 μ m in diameter and large pulmonary veins (Hebb, 1969). The pulmonary arteries of calf have a sparse cholinergic nerve fiber distribution, which larger than 200 μ m in diameter and large pulmonary
veins (Hebb, 1969). The pulmonary arteries of calf have
a sparse cholinergic nerve fiber distribution, which does
not extend to vessels $< 70 \mu$ m in diameter (Hebb, 19 veins (Hebb, 1969). The pulmonary arteries of calf have
a sparse cholinergic nerve fiber distribution, which does
not extend to vessels $< 70 \mu m$ in diameter (Hebb, 1969).
Pulmonary arteries of the rabbit, dog, monkey, sh a sparse cholinergic nerve fiber distribution, which does
not extend to vessels $<$ 70 μ m in diameter (Hebb, 1969).
Pulmonary arteries of the rabbit, dog, monkey, sheep,
and cat (Cech, 1969, 1973; Fillenz, 1970) are ex Pulmonary arteries of the rabbit, dog, monkey, sheep, and cat (Cech, 1969, 1973; Fillenz, 1970) are extensively and cat (Cech, 1969, 1973; Fillenz, 1970) are extensively
innervated with AChE-positive nerve fibers. In the rab-
bit, these extend down to the vessels of $< 100 \mu m$ (Hebb,
1969) and even to arterioles (Cech, 1973). Cat a innervated with AChE-positive nerve fibers. In the rab-
bit, these extend down to the vessels of $< 100 \mu$ m (Hebb,
1969) and even to arterioles (Cech, 1973). Cat and sheep
pulmonary arteries have even more dense cholinerg

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down to vessels of 40 μ m diameter (Hebb, 1969). Posi
tively-stained nerve bundles and ganglionic cells hav 92
down to vessels of 40 μ m diameter (Hebb, 1969). Posi-
tively-stained nerve bundles and ganglionic cells have
been found in the adventitia of the large rabbit and cat BARNES A
down to vessels of 40 μ m diameter (Hebb, 1969). Posi-
tively-stained nerve bundles and ganglionic cells have
been found in the adventitia of the large rabbit and cat
intrapulmonary veins (Hebb, 1969). Large in down to vessels of 40 μ m diameter (Hebb, 1969). lively-stained nerve bundles and ganglionic cells been found in the adventitia of the large rabbit an intrapulmonary veins (Hebb, 1969). Large intrapunary veins are also down to vessels of 40 μ m diameter (Hebb, 1969). Positively-stained nerve bundles and ganglionic cells have
been found in the adventitia of the large rabbit and cat
intrapulmonary veins (Hebb, 1969). Large intrapulmo-
n tively-stained nerve bundles and ganglionic cells habeen found in the adventitia of the large rabbit and contrapulmonary veins (Hebb, 1969). Large intrapulmonary veins are also innervated with AChE-position nerve fibers in been found in the adventitia of the large rabbit and distributionary veins (Hebb, 1969). Large intrapulm
nary veins are also innervated with AChE-positionary veins are also innervated with AChE-positionary fibers in sheep intrapulmonary veins (Hebb, 1969). Large intrapulnary veins are also innervated with AChE-position erve fibers in sheep (Hebb, 1969). Although no ACl positive nerve fibers have been found in human pulnary arteries and vein nerve fibers in sheep (Hebb, 1969). Although no AChE-
positive nerve fibers have been found in human pulmo-
positive nerve fibers have been found in human pulmo-
dothelial muscarinic receptors in the bovine aorta and
nary nerve fibers in sheep (Hebb, 1969). Although no AChE-
positive nerve fibers have been found in human pulmo-
nary arteries and veins (Partanen et al., 1982), cholines-
terase staining has revealed cholinergic innervation of positive nerve fibers have been found in human pulmo-
nary arteries and veins (Partanen et al., 1982), cholines-
terase staining has revealed cholinergic innervation of
intrapulmonary arteries of the developing human fetus nary arteries and veins (Partanen et al., 1982), cholines-
terase staining has revealed cholinergic innervation of et
intrapulmonary arteries of the developing human fetus
(Taylor and Smith, 1971; Pessacq, 1971). Both the terase staining has reveale
intrapulmonary arteries of
(Taylor and Smith, 1971; P.
sity and extent of this inn
(Taylor and Smith, 1971).
Ultrastructural studies h trapulmonary arteries of the developing human fetus
aylor and Smith, 1971; Pessacq, 1971). Both the den-
y and extent of this innervation increase with age
aylor and Smith, 1971).
Ultrastructural studies have confirmed the

(Taylor and Smith, 1971; Pessacq, 1971). Both the density and extent of this innervation increase with age
(Taylor and Smith, 1971).
Ultrastructural studies have confirmed the existence
of cholinergic innervation to the pu sity and extent of this innervation increase with age different (Taylor and Smith, 1971). Mus.

Ultrastructural studies have confirmed the existence relation of cholinergic innervation to the pulmonary vascular arts tree i (Taylor and Smith, 1971).

Ultrastructural studies have confirmed the existence

of cholinergic innervation to the pulmonary vascular

tree in the dog and cat (Cech, 1973; Rhodin, 1978). In

both species, bundles of nonmye Ultrastructural studies have confirmed the existence re
of cholinergic innervation to the pulmonary vascular at
ree in the dog and cat (Cech, 1973; Rhodin, 1978). In
both species, bundles of nonmyelinated nerve fibers enof cholinergic innervation to the pulmonary vascular
tree in the dog and cat (Cech, 1973; Rhodin, 1978). In
both species, bundles of nonmyelinated nerve fibers en-
closed by Schwann cells were found in the adventitia of
s within 150 nm of smooth muscle cells. Most varicosities closed by Schwann cells were found in the adventitia of small arterioles down to $30 \mu m$ (Fillenz, 1970; Rhodin, 1978; Knight et al., 1981). Axons with vesicles are found within 150 nm of smooth muscle cells. Most varicos small arterioles down to 30 μ m (Fillenz, 1970; Rhodin, cept
1978; Knight et al., 1981). Axons with vesicles are found resi
within 150 nm of smooth muscle cells. Most varicosities Kas
are probably adrenergic, inasmuch a 1978; Knight et al., 1981). Axons with vesicles are found rewithin 150 nm of smooth muscle cells. Most varicosities Kare probably adrenergic, inasmuch as they contain small redense-cored vesicles $(40 \text{ to } 60 \text{ nm})$. Some within 150 nm of smooth muscle cells. Most varicosities
are probably adrenergic, inasmuch as they contain small
dense-cored vesicles (40 to 60 nm). Some of them (20 to
40%) are small agranular vesicles (40 to 60 nm), which are probably adrenergic, inasmuch as they contain small
dense-cored vesicles (40 to 60 nm). Some of them (20 to
40%) are small agranular vesicles (40 to 60 nm), which is
a characteristic morphological appearance of periphe dense-cored vesicles (40 to 60 nm). Some of them (20 to be 40%) are small agranular vesicles (40 to 60 nm), which is auded a characteristic morphological appearance of peripheral such olinergic nerve profiles (Fillenz, 197 40%) are small agranular vesicles $(40 \text{ to } 60 \text{ nm})$, which is auded a characteristic morphological appearance of peripheral such olinergic nerve profiles (Fillenz, 1970; Rhodin, 1978; to Kadowitz et al., 1976; Knight et a characteristic morphological appearance of peripheral
cholinergic nerve profiles (Fillenz, 1970; Rhodin, 1978;
Kadowitz et al., 1976; Knight et al., 1981). Moreover, the
histological appearance of this type of vesicle is histological appearance of this type of vesicle is not altered
by 5- or 6-hydroxydopamine treatment (Kadowitz et al.,
1976). Cholinergic vesicles have not been identified in the
intrapulmonary veins of dogs (Fillenz, 1970) *2. Muscarinic receptors.* Studies on the effects of Achievis or 6-hydroxydopamine treatment (Kadowitz et al., on 76). Cholinergic vesicles have not been identified in the spectrapulmonary veins of dogs (Fillenz, 1970).
2.

by 5- or 6-hydroxydopamine treatment (Kadowitz et a 1976). Cholinergic vesicles have not been identified in the intrapulmonary veins of dogs (Fillenz, 1970).
2. *Muscarinic receptors*. Studies on the effects of A on the p 1976). Cholinergic vesicles have not been identified in the intrapulmonary veins of dogs (Fillenz, 1970).
2. Muscarinic receptors. Studies on the effects of ACh
on the pulmonary circulation have proved to be contra-
dictor intrapulmonary veins of dogs (Fillenz, 1970).

2. Muscarinic receptors. Studies on the effects of ACh

on the pulmonary circulation have proved to be contra-

dictory, with both vasoconstrictor (Catravas et al., 1984;

McL 2. Muscarinic receptors. Studies on the effects of ACh
on the pulmonary circulation have proved to be contra-
dictory, with both vasoconstrictor (Catravas et al., 1984;
McLean, 1986; Sada et al., 1987) and vasodilator (Fri on the pulmonary circulation have proved to be contra-
dictory, with both vasoconstrictor (Catravas et al., 1984;
McLean, 1986; Sada et al., 1987) and vasodilator (Fritts
et al., 1958; Nandiwada et al., 1983; Cherry and Gi dictory, with both vasoconstrictor (Catravas et al., 1984;
McLean, 1986; Sada et al., 1987) and vasodilator (Fritts
et al., 1958; Nandiwada et al., 1983; Cherry and Gillis,
1987) responses being reported. Later, it was fou McLean, 1986; Sada et al., 1987) and vasodilator (Fritts
et al., 1958; Nandiwada et al., 1983; Cherry and Gillis,
1987) responses being reported. Later, it was found that
these conflicting results could be explained by the et al., 1958; Nandiwada et al., 1983; Cherry and Gillis, 1987) responses being reported. Later, it was found that these conflicting results could be explained by the level of pre-existing tone. Thus, ACh induces a pressor these conflicting results could be explained by the level basal PPA or vascular resistance (Murray et al., 1986).

of pre-existing tone. Thus, ACh induces a pressor re-

sponse under resting conditions but causes a depress these conflicting results could be explained by the level
of pre-existing tone. Thus, ACh induces a pressor re-
sponse under resting conditions but causes a depressor
response under conditions of elevated tone (Hyman and
K of pre-existing tone. Thus, ACh induces a pressor re-
sponse under resting conditions but causes a depressor
response under conditions of elevated tone (Hyman and
Kadowitz, 1988, 1989). There also seems to be a species
Heb sponse under resting conditions but causes a depressor pull
response under conditions of elevated tone (Hyman and the
Kadowitz, 1988, 1989). There also seems to be a species Heb
variation in the ACh response, as both the m Kadowitz, 1988, 1989). There also seems to be a species Hebb, 1966), vagal stimulation induces pulmonary vavariation in the ACh response, as both the mechanism soconstriction. By contrast, pulmonary vasodilation is and cha variation in the ACh response, as both the mechanism
and characteristics of the vasoconstrictor response in
the rabbit are different from those in the cat pulmonary
circulation (Catravas et al., 1984; Hyman and Kadowitz,
1 variation in the ACh response, as both the mechanism
and characteristics of the vasoconstrictor response in
the rabbit are different from those in the cat pulmonary
circulation (Catravas et al., 1984; Hyman and Kadowitz,
1 and characteristics of the vasoconstrictor response in in
the rabbit are different from those in the cat pulmonary acirculation (Catravas et al., 1984; Hyman and Kadowitz, pi
1988). In humans, ACh induces a clear vasodilat circulation (Catravas et al., 1984; Hyman and Kadowitz, 1988). In humans, ACh induces a clear vasodilator response, both under resting conditions and during acute hypoxic pulmonary vasoconstriction (Fritts et al., 1958). A circulation (Catravas et al., 1984; Hyman and Kadowitz, 1988). In humans, ACh induces a clear vasodilator response, both under resting conditions and during acute hypoxic pulmonary vasoconstriction (Fritts et al., 1958). A 1988). In humans, ACh induces a clear vasodilator re-
sponse, both under resting conditions and during acute
hypoxic pulmonary vasoconstriction (Fritts et al., 1958). chan
Although ACh was the first identified endothelium-

hypoxic pulmonary vasoconstriction (Fritts et al., 1958).
Although ACh was the first identified endothelium-
dependent vasorelaxant, binding studies have failed to
identify the muscarinic receptor binding site on vascular
 hypoxic pulmonary vasoconstriction (Fritts et al., 1958)
Although ACh was the first identified endothelium
dependent vasorelaxant, binding studies have failed to
identify the muscarinic receptor binding site on vascula
end Although ACh was the first identified endothelium-
dependent vasorelaxant, binding studies have failed to
identify the muscarinic receptor binding site on vascular
endothelial cells in several arterial preparations (Ste-
p dependent vasorelaxant, binding studies have failed to
identify the muscarinic receptor binding site on vascular
endothelial cells in several arterial preparations (Ste-
phenson and Summers, 1987; Summers et al., 1987),
in identify the muscarinic receptor binding site on vascular
endothelial cells in several arterial preparations (Ste-
phenson and Summers, 1987; Summers et al., 1987),
including the rabbit and rat pulmonary vasculature
(Steph endothelial cells in several arterial preparations (Ste-
phenson and Summers, 1987; Summers et al., 1987), air
including the rabbit and rat pulmonary vasculature due
(Stephenson et al., 1988; De Michele et al., 1991). Thus

ND LIU
produces vasodilation via an intermediate step involving
vascular smooth muscle (Summers et al., 1987). Using ND LIU
produces vasodilation via an intermediate step involving
vascular smooth muscle (Summers et al., 1987). Using
rabbit aortic endothelial cell membranes, Sim and Man-BARNES AND LIU

. Posi- produces vasodilation via an intermediate step involving

s have vascular smooth muscle (Summers et al., 1987). Using

and cat rabbit aortic endothelial cell membranes, Sim and Man-

pulmo- jeet (19 produces vasodilation via an intermediate step involving
vascular smooth muscle (Summers et al., 1987). Using
rabbit aortic endothelial cell membranes, Sim and Man-
jeet (1990) were able to demonstrate the presence of
musc vascular smooth muscle (Summers et al., 1987). Using
rabbit aortic endothelial cell membranes, Sim and Man
jeet (1990) were able to demonstrate the presence o
muscarinic receptors on endothelial cells. Evidence sub
sequent vascular smooth muscle (Summers et al., 1987). Using
rabbit aortic endothelial cell membranes, Sim and Man-
jeet (1990) were able to demonstrate the presence of
muscarinic receptors on endothelial cells. Evidence sub-
sequ rabbit aortic endothelial cell membranes, Sim and Man-
jeet (1990) were able to demonstrate the presence of
muscarinic receptors on endothelial cells. Evidence sub-
sequently accumulated to indicate the existence of en-
do muscarinic receptors on endothelial cells. Evidence sub-
sequently accumulated to indicate the existence of en-
dothelial muscarinic receptors in the bovine aorta and
coronary artery (Brunner and Kukovetz, 1991; Brunner
et muscarinic receptors on endothelial cells. Evidence a
sequently accumulated to indicate the existence of
dothelial muscarinic receptors in the bovine aorta
coronary artery (Brunner and Kukovetz, 1991; Brun
et al., 1991). quently accumulated to indicate the existence of en-
the ial muscarinic receptors in the bovine aorta and
ronary artery (Brunner and Kukovetz, 1991; Brunner
al., 1991). Muscarinic receptors are heterogeneous.
Five subtype

both species, bundles of nonmyelinated nerve fibers en-
closed by Schwann cells were found in the adventitia of Zwieten, 1989; Mak and Barnes, 1990). Muscarinic re-
small arterioles down to 30 μ m (Fillenz, 1970; Rhodin cholinergic nerve profiles (Fillenz, 1970; Rhodin, 1978; tors predominate, whereas in rabbit lung, M_4 -receptors
Kadowitz et al., 1976; Knight et al., 1981). Moreover, the predominate in pulmonary vessels (Mak and Barne dothelial muscarinic receptors in the bovine aorta and
coronary artery (Brunner and Kukovetz, 1991; Brunner
et al., 1991). Muscarinic receptors are heterogeneous.
Five subtypes (M_1 to M_5) have been identified using
 coronary artery (Brunner and Kukovetz, 1991; Brunner
et al., 1991). Muscarinic receptors are heterogeneous.
Five subtypes $(M_1 \text{ to } M_5)$ have been identified using
molecular biological techniques, and M_1 to M_4 can b et al., 1991). Muscarinic receptors are heterogenec
Five subtypes $(M_1 \text{ to } M_5)$ have been identified molecular biological techniques, and M_1 to M_4 califferentiated pharmacologically (Hulme et al., 1
Muscarinic rece Five subtypes $(M_1 \text{ to } M_5)$ have been identified using
molecular biological techniques, and M_1 to M_4 can be
differentiated pharmacologically (Hulme et al., 1990).
Muscarinic receptors mediating endothelium-dependen molecular biological techniques, and M_1 to M_4 can be differentiated pharmacologically (Hulme et al., 1990).
Muscarinic receptors mediating endothelium-dependent relaxations are classified as M_3 -receptors in pulmo differentiated pharmacologically (Hulme et al., 1990).
Muscarinic receptors mediating endothelium-dependent
relaxations are classified as M_3 -receptors in pulmonary
arteries (McCormack et al., 1988). The muscarinic re-
c Muscarinic receptors mediating endothelium-dependent
relaxations are classified as M_3 -receptors in pulmonary
arteries (McCormack et al., 1988). The muscarinic re-
ceptor subtypes on vascular smooth muscle seem to have
 relaxations are classified as M_3 -receptors in pulmonary
arteries (McCormack et al., 1988). The muscarinic re-
ceptor subtypes on vascular smooth muscle seem to have
a variable regional distribution (van Charldorp and v arteries (McCormack et al., 1988). The muscarinic receptor subtypes on vascular smooth muscle seem to have
a variable regional distribution (van Charldorp and van
Zwieten, 1989; Mak and Barnes, 1990). Muscarinic receptors ceptor subtypes on vascular smooth muscle seem to have
a variable regional distribution (van Charldorp and van
Zwieten, 1989; Mak and Barnes, 1990). Muscarinic receptors mediating the increase in pulmonary vascular
resist a variable regional distribution (van Charldorp and van Zwieten, 1989; Mak and Barnes, 1990). Muscarinic receptors mediating the increase in pulmonary vascular resistance seem to be M_1 -like receptors in rabbit (El-Kash Zwieten, 1989; Mak and Barnes, 1990). Muscarinic receptors mediating the increase in pulmonary vascular resistance seem to be M_1 -like receptors in rabbit (El-
Kashef and Catravas, 1991), whereas both M_1 - and M_2 -
 ceptors mediating the increase in pulmonary vascular
resistance seem to be M_1 -like receptors in rabbit (El-
Kashef and Catravas, 1991), whereas both M_1 - and M_2 -
receptors are involved in canine pulmonary vascular Kashef and Catravas, 1991), whereas both M_1 - and M_2 -
receptors are involved in canine pulmonary vascular
beds (El-Kashef et al., 1991). More recent results from
autoradiographic mapping and in situ hybridization Kashef and Catravas, 1991), whereas both M_1 - and l
receptors are involved in canine pulmonary vascu
beds (El-Kashef et al., 1991). More recent results fr
autoradiographic mapping and in situ hybridizat
suggest that in receptors are involved in canine pulmonary vascular
beds (El-Kashef et al., 1991). More recent results from
autoradiographic mapping and in situ hybridization
suggest that in human and guinea pig lung, M_3 -recep-
tors p beds (El-Kashef et al., 1991). More recent results from
autoradiographic mapping and in situ hybridization
suggest that in human and guinea pig lung, M_3 -recep-
tors predominate, whereas in rabbit lung, M_4 -receptors
 autoradiographic mapping and in situ hybridization
suggest that in human and guinea pig lung, M_3 -recep-
tors predominate, whereas in rabbit lung, M_4 -receptors
predominate in pulmonary vessels (Mak and Barnes,
1990, suggest that in human and guinea pig lung, M_3 -receptors predominate, whereas in rabbit lung, M_4 -receptors predominate in pulmonary vessels (Mak and Barnes, 1990, 1992, 1993). There are also M_1 - and M_2 -receptor tors predominate, whereas in rabbit lung, M_4 -recept
predominate in pulmonary vessels (Mak and Barn
1990, 1992, 1993). There are also M_1 - and M_2 -recept
on sympathetic and parasympathetic nerve endings,
spectively predominate in pulmonary
1990, 1992, 1993). There are
on sympathetic and parasys
spectively (Maclagan et al.
nephrine and ACh release.
3. Cholinergic control of p on sympathetic and parasympathetic nerve endings, re-
spectively (Maclagan et al., 1989), modulating norepi-
nephrine and ACh release.
3. Cholinergic control of pulmonary vascular tone. Al-
though the pulmonary circulation arteries (McCormack et al., 1988). The muscarinic re-
exptor authypes on vascular smooth muscle seem to have
a variable regional distribution (van Charldorp and van
Zwieten, 1989; Mak and Barnes, 1990). Muscarinic re-
exp

on sympathetic and parasympathetic nerve endings, re-
spectively (Maclagan et al., 1989), modulating norepi-
nephrine and ACh release.
3. Cholinergic control of pulmonary vascular tone. Al-
though the pulmonary circulation spectively (Maclagan et al., 1989), modulating norepi-
nephrine and ACh release.
3. Cholinergic control of pulmonary vascular tone. Al-
though the pulmonary circulation of many species is
innervated with cholinergic nerves 3. Cholinergic control of pulmonary vascular tone. μ though the pulmonary circulation of many species innervated with cholinergic nerves, their functional s mificance is less clear. These nerves do not seem to importan though the pulmonary circulation of many species is
innervated with cholinergic nerves, their functional sig-
nificance is less clear. These nerves do not seem to be
important in the maintenance of low pulmonary vascu-
lar innervated with cholinergic nerves, their functional significance is less clear. These nerves do not seem to be important in the maintenance of low pulmonary vascular tone, inasmuch as cholinergic blockade does not alter b mificance is less clear. These nerves do not seem to be
important in the maintenance of low pulmonary vascu-
lar tone, inasmuch as cholinergic blockade does not alter
basal PPA or vascular resistance (Murray et al., 1986). important in the maintenance of low pulmonary vascular tone, inasmuch as cholinergic blockade does not alter
basal PPA or vascular resistance (Murray et al., 1986).
Earlier studies on the effects of vagal stimulation on t basal PPA or vascular resistance (Murray et al., 1986). basal PPA or vascular resistance (Murray et al., 1986).
Earlier studies on the effects of vagal stimulation on the
pulmonary circulation provided conflicting results. In
the perfused lungs of the dog and guinea pig (Daly a Earlier studies on the effects of vagal stimulation on the
pulmonary circulation provided conflicting results. In
the perfused lungs of the dog and guinea pig (Daly and
Hebb, 1966), vagal stimulation induces pulmonary va-
 pulmonary circulation provided conflicting results. In
the perfused lungs of the dog and guinea pig (Daly and
Hebb, 1966), vagal stimulation induces pulmonary va-
soconstriction. By contrast, pulmonary vasodilation is
indu the perfused lungs of the dog and guinea pig (Daly and Hebb, 1966), vagal stimulation induces pulmonary vasoconstriction. By contrast, pulmonary vasodilation is induced by vagal stimulation in adult pig (Mclean, 1986) and Hebb, 1966), vagal stimulation induces pulmonary vasoconstriction. By contrast, pulmonary vasodilation is
induced by vagal stimulation in adult pig (Mclean, 1986)
and fetal lamb lungs (Rudolph, 1979). In the perfused
pulmo soconstriction. By contrast, pulmonary vasodilation is
induced by vagal stimulation in adult pig (Mclean, 1986)
and fetal lamb lungs (Rudolph, 1979). In the perfused
pulmonary vascular bed of dog, Daly and Hebb (1952)
show induced by vagal stimulation in adult pig (Mclean, 1986)
and fetal lamb lungs (Rudolph, 1979). In the perfused
pulmonary vascular bed of dog, Daly and Hebb (1952)
showed that stimulation of the cervical vagosympathetic
ner and fetal lamb lungs (Rudolph, 1979). In the perfused
pulmonary vascular bed of dog, Daly and Hebb (1952)
showed that stimulation of the cervical vagosympathetic
nerve trunk causes increased, decreased, or biphasic
changes pulmonary vascular bed of dog, Daly and Hebb (1952)
showed that stimulation of the cervical vagosympathetic
nerve trunk causes increased, decreased, or biphasic
changes in PPA. This result is not surprising, because
vagal showed that stimulation of the cervical vagosympathetic
nerve trunk causes increased, decreased, or biphasic
changes in PPA. This result is not surprising, because
vagal nerves in the dog contain sympathetic nerve fibers
(nerve trunk causes increased, decreased, or biphasic
changes in PPA. This result is not surprising, because
vagal nerves in the dog contain sympathetic nerve fibers
(Daly and Hebb, 1952). Vagal stimulation is therefore
lik changes in PPA. This result is not surprising, because
vagal nerves in the dog contain sympathetic nerve fibers
(Daly and Hebb, 1952). Vagal stimulation is therefore
likely to cause an adrenergic vasoconstriction as well a vagal nerves in the dog contain sympathetic nerve fibers
(Daly and Hebb, 1952). Vagal stimulation is therefore
likely to cause an adrenergic vasoconstriction as well as
vasodilation. Furthermore, changes in cardiac output, (Daly and Hebb, 1952). Vagal stimulation is therefore likely to cause an adrenergic vasoconstriction as well as vasodilation. Furthermore, changes in cardiac output, airway pressure, and bronchial blood flow that are induc likely to cause an adrenergic vasoconstriction as well as
vasodilation. Furthermore, changes in cardiac output,
airway pressure, and bronchial blood flow that are in-
duced by vagal stimulation may also affect PPA. For
exa vasodilation. Furthermore, changes in cardiac output,
airway pressure, and bronchial blood flow that are in-
duced by vagal stimulation may also affect PPA. For
example, vagal stimulation-induced increases in airway
pressu

aspet

REGULATION **OF PULMONARY VASCULAR TONE** ⁹³

REGULATION OF PULMONARY
and therefore confound the decrease in PPA induced by vess
vagal stimulation (Colebatch and Halmagyi, 1963). In the in p REGULATION OF PULMONAL
and therefore confound the decrease in PPA induced by ver
vagal stimulation (Colebatch and Halmagyi, 1963). In the in
perfused cat lung, vagal stimulation evokes an increase in ies REGULATION OF PULMON.

and therefore confound the decrease in PPA induced by

vagal stimulation (Colebatch and Halmagyi, 1963). In the

inerfused cat lung, vagal stimulation evokes an increase in

julmonary perfusion press and therefore confound the decrease in PPA induced by vagal stimulation (Colebatch and Halmagyi, 1963). In the perfused cat lung, vagal stimulation evokes an increase in pulmonary perfusion pressure under basal conditions, and therefore confound the decrease in PPA induced l
vagal stimulation (Colebatch and Halmagyi, 1963). In the
perfused cat lung, vagal stimulation evokes an increase
pulmonary perfusion pressure under basal condition
where vagal stimulation (Colebatch and Halmagyi, 1963). In the in
perfused cat lung, vagal stimulation evokes an increase in ies
pulmonary perfusion pressure under basal conditions, α)
whereas under conditions of elevated va perfused cat lung, vagal stimulation evokes an increase in
pulmonary perfusion pressure under basal conditions,
whereas under conditions of elevated vascular tone, perfu-
sion pressure decreases (Nandiwada et al., 1983). T pulmonary perfusion pressure under basal conditions,
whereas under conditions of elevated vascular tone, perfu-
sion pressure decreases (Nandiwada et al., 1983). The
pressor and depressor responses are blocked by phenoxy-
 whereas under conditions of elevated vascular tone, per
sion pressure decreases (Nandiwada et al., 1983). T
pressor and depressor responses are blocked by pheno
benzamine and atropine, respectively, confirming th
both adre sion pressure decreases (Nandiwada et al., 1983). Thesesor and depressor responses are blocked by phenox
benzamine and atropine, respectively, confirming the both adrenergic vasoconstriction and cholinergic vasodil
tion ar pressor and depressor responses are blocked by phenoxy
benzamine and atropine, respectively, confirming tha
both adrenergic vasoconstriction and cholinergic vasodila
tion are induced by vagal nerve stimulation. After chemi benzamine and atropine, respectively, confirming that en
both adrenergic vasoconstriction and cholinergic vasodila-
tion are induced by vagal nerve stimulation. After chemi-
cal sympathectomy with 6-hydroxydopamine, vagal both adrenergic vasoconstriction and cholinergic vasodilation are induced by vagal nerve stimulation. After chemical sympathectomy with 6-hydroxydopamine, vagal stimulation induced a frequency-dependent decrease in the neu tion are induced by vagal nerve stimulation. After chemical sympathectomy with 6-hydroxydopamine, vagal stimulation induced a frequency-dependent decrease in the lobar artery pressure under elevated vascular tone induced b cal sympathectomy with 6-hydroxydopamine, vagal stim-
ulation induced a frequency-dependent decrease in the
lobar artery pressure under elevated vascular tone induced tive
by both the thromboxane analog U44169 and hypoxia. ulation induced a frequency-dependent decrease in
lobar artery pressure under elevated vascular tone indu
by both the thromboxane analog U44169 and hypo:
Exogenously administered ACh mimics the response
vagal stimulation. lobar artery pressure under elevated vascular tone induced tive
by both the thromboxane analog U44169 and hypoxia. several
Exogenously administered ACh mimics the response to et a
vagal stimulation. The responses to both v Exogenously administered ACh mimics the response vagal stimulation. The responses to both vagal stimulation and ACh are blocked by atropine and enhanced by physostigmine, a cholinesterase inhibitor. Moreover, this vagally vagal stimulation. The responses to both vagal stimulation and ACh are blocked by atropine and enhanced by physostigmine, a cholinesterase inhibitor. Moreover, this vagally induced vasodilation is not affected by elevating tion and ACh are blocked by atropine and enhanced by CGRP-like immunoreactive substance is released upon physostigmine, a cholinesterase inhibitor. Moreover, electrical stimulation of these vessels (Maggi et al., this vaga tion and ACh are blocked by atropine and enhanced by
physostigmine, a cholinesterase inhibitor. Moreover,
this vagally induced vasodilation is not affected by ele-
vating airway pressure or by reducing systemic blood
press physostigmine, a cholinesterase inhibitor. Moreover, this vagally induced vasodilation is not affected by elevating airway pressure or by reducing systemic blood (pressure. Vagally released ACh acts on the vascular the end this vagally induced vasodilation is not affected by elevating airway pressure or by reducing systemic blood (pressure. Vagally released ACh acts on the vascular endothelium to induce NO release, which then causes (vasodil vating airway pressure or by reducing systemic blood (Lipressure. Vagally released ACh acts on the vascular the endothelium to induce NO release, which then causes tre vasodilation (McMahon et al., 1992). Human pulmonary t pressure. Vagally released ACh acts on the vascular endothelium to induce NO release, which then causes vasodilation (McMahon et al., 1992). Human pulmonary arteries relax in response to ACh, and this response is lost when (Greenberg et al., 1987a).
C. Nonadrenergic, Noncholinergic Mechanisms lost when the endothelium is removed. Under these con-

(Greenberg et al., 1987a).
C. Nonadrenergic, Noncholinergic Mechanisms
1. Nonadrenergic, noncholinergic nerves. In additio
to the classic adrenergic and cholinergic innervation
there are neural mechanisms that are not inhi C. Nonadrenergic, Noncholinergic Mechanisms

1. Nonadrenergic, noncholinergic nerves. In addition

to the classic adrenergic and cholinergic innervation, C

there are neural mechanisms that are not inhibited by bran

adren 1. Nonadrenergic, noncholinergic nerves. In addition
to the classic adrenergic and cholinergic innervation,
there are neural mechanisms that are not inhibited by
adrenergic and cholinergic blockade (Barnes et al.,
1991). N to the classic adrenergic and cholinergic innervation,
there are neural mechanisms that are not inhibited by
adrenergic and cholinergic blockade (Barnes et al., C
1991). NANC nerves may not represent separate neural on
pat there are neural mechanisms that are not inhibited
adrenergic and cholinergic blockade (Barnes et
1991). NANC nerves may not represent separate neu
pathways but are more likely to be manifestations
neurotransmission in sym adrenergic and cholinergic blockade (Barnes et al., CO
1991). NANC nerves may not represent separate neural on
pathways but are more likely to be manifestations of arr
neurotransmission in sympathetic, parasympathetic, are 1991). NANC nerves may not represent separate neural only pathways but are more likely to be manifestations of art neurotransmission in sympathetic, parasympathetic, art and sensory nerves. NANC neural responses that are i pathways but are more likely to be manifestations
neurotransmission in sympathetic, parasympathet
and sensory nerves. NANC neural responses that a
excitatory (excitatory-NANC, vasoconstrictor) a
i-NANC (vasodilator) have b neurotransmission in sympathetic, parasympathet
and sensory nerves. NANC neural responses that a
excitatory (excitatory-NANC, vasoconstrictor) a
i-NANC (vasodilator) have been demonstrated in pulm
nary vessels electrophysi excitatory (excitatory-NANC, vasoconstrictor) and sei-NANC (vasodilator) have been demonstrated in pulmo-
nary vessels electrophysiologically in rat small pulmo-
nary arteries (Inoue and Kannan, 1988) and by EFS of N
preco i-NANC (vasodilator) have been demonstrated in pulmo-
nary vessels electrophysiologically in rat small pulmo-
nary arteries (Inoue and Kannan, 1988) and by EFS of
precontracted pulmonary artery rings of guinea pig or
cat (nary vessels electrophysiologically in rat small pulmo-
nary arteries (Inoue and Kannan, 1988) and by EFS of NAI
precontracted pulmonary artery rings of guinea pig or rece
cat (Kubota et al., 1988; Maggi et al., 1990; Liu nary arteries (Inoue and Kannan, 1988) and by EFS of NA
precontracted pulmonary artery rings of guinea pig or recat (Kubota et al., 1988; Maggi et al., 1990; Liu et al., AT
1992a). In precontracted pulmonary artery rings, precontracted pulmonary artery rings of guinea pig or rece
cat (Kubota et al., 1988; Maggi et al., 1990; Liu et al., ATI
1992a). In precontracted pulmonary artery rings, EFS guin
induces a frequency-dependent relaxation, w cat (Kubota et al., 1988; Maggi et al., 1990; Liu et a
1992a). In precontracted pulmonary artery rings, El
induces a frequency-dependent relaxation, which
abolished by tetrodotoxin but is largely unaffected
treatment with 1992a). In precontracted pulmonary artery rings, EFS guideleast induces a frequency-dependent relaxation, which is mabolished by tetrodotoxin but is largely unaffected by treatment with a combination of adrenergic and cho induces a frequency-dependent relaxation, which is a
abolished by tetrodotoxin but is largely unaffected by
treatment with a combination of adrenergic and cholin-
ergic antagonists, indicating that the main component of
th abolished by tetrodotoxin but is largely unaffected
treatment with a combination of adrenergic and cholergic antagonists, indicating that the main component
this relaxation is mediated via NANC nerves (Maggi
al., 1990, Liu treatment with a combination of adrenergic and cholivergic antagonists, indicating that the main component α this relaxation is mediated via NANC nerves (Maggi ϵ al., 1990, Liu et al., 1992a). EFS also relaxes precor ergic antagonists, indicating that the main component of
this relaxation is mediated via NANC nerves (Maggi et
al., 1990, Liu et al., 1992a). EFS also relaxes precon-
tracted pulmonary arteries of dog, rabbit, and cow. How this relaxation is mediated via NANC nerves (Maggi et al., 1990, Liu et al., 1992a). EFS also relaxes precontracted pulmonary arteries of dog, rabbit, and cow. However, these responses are not of neural origin, inasmuch as al., 1990, Liu et al., 1992a). EFS also relaxes precontracted pulmonary arteries of dog, rabbit, and cow. However, these responses are not of neural origin, inasmuch as they are tetrodotoxin-resistant (Frank and Bevan, 198 acted pulmonary arteries of dog, rabbit, and cow. Her, these responses are not of neural origin, inasm
2. Herefore are tetrodotoxin-resistant (Frank and Bevass)
83, Greenberg et al., 1986; Buga and Ignarro, 199
2. Nonadr

ever, these responses are not of neural origin, inasmuch
as they are tetrodotoxin-resistant (Frank and Bevan,
1983, Greenberg et al., 1986; Buga and Ignarro, 1992).
2. Nonadrenergic, noncholinergic neurotransmitters.
The n as they are tetrodotoxin-resistant (Frank and Bevan, al
1983, Greenberg et al., 1986; Buga and Ignarro, 1992). m
2. Nonadrenergic, noncholinergic neurotransmitters. N
The neurotransmitters of NANC nerves in pulmonary w
ves

vary vascular tone
vessel. ATP may act as an excitatory-NANC transmitter
in pulmonary artery. In rat small intrapulmonary arter-I
I SARY VASCULAR TONE
In pulmonary artery. In rat small intrapulmonary arter-
ies, EFS evokes an excitatory junction potential that 93

vessel. ATP may act as an excitatory-NANC transmitter

in pulmonary artery. In rat small intrapulmonary arter-

ies, EFS evokes an excitatory junction potential that is

(a) insensitive to adrenergic, cholinergic, hist vessel. ATP may act as an excitatory-NANC transmitt
in pulmonary artery. In rat small intrapulmonary arte
ies, EFS evokes an excitatory junction potential that
(*a*) insensitive to adrenergic, cholinergic, histaminerg
and in pulmonary artery. In rat small intrapulmonary arter-
ies, EFS evokes an excitatory junction potential that is
(*a*) insensitive to adrenergic, cholinergic, histaminergic,
and serotonergic blockade, (*b*) unaffected by ies, EFS evokes an excitatory junction potential that is (*a*) insensitive to adrenergic, cholinergic, histaminergic, and serotonergic blockade, (*b*) unaffected by catecholamine depletion or sympathetic denervation, but (a) insensitive to adrenergic, cholinergic, histaminergic, and serotonergic blockade, (b) unaffected by catecholamine depletion or sympathetic denervation, but (c) is abolished by tetrodotoxin and inhibited by α , β -(a) insensitive to adrenergic, cholinerg
and serotonergic blockade, (b) unaffer
amine depletion or sympathetic dene
abolished by tetrodotoxin and inhibite
ene ATP (Inoue and Kannan, 1988).
NO is the most likely i-NANC d serotonergic blockade, (b) unaffected by catechol-
nine depletion or sympathetic denervation, but (c) is
olished by tetrodotoxin and inhibited by α , β -methyl-
e ATP (Inoue and Kannan, 1988).
NO is the most likely

vasodilation (McMahon et al., 1992). Human pulmonary
arteries relax in response to ACh, and this response is 1992a). An SP-like immunoreactive substance is also
lost when the endothelium is removed. Under these con-
dition *L. Nonadrenergic, Noncholinergic Mechanisms*
1. Nonadrenergic, noncholinergic nerves. In addition et al., 1992a).
1. Nonadrenergic, noncholinergic nerves. In addition et al., 1992a).
1. Nonadrenergic and cholinergic inner amine depletion or sympathetic denervation, but (c) is
abolished by tetrodotoxin and inhibited by α , β -methyl-
ene ATP (Inoue and Kannan, 1988).
NO is the most likely i-NANC neurotransmitter in
most organs studied abolished by tetrodotoxin and inhibited by α , β -methyl-
ene ATP (Inoue and Kannan, 1988).
NO is the most likely i-NANC neurotransmitter in
most organs studied (Rand, 1992), but neuropeptides
such as VIP, SP, and CGR ene ATP (Inoue and Kannan, 1988).
NO is the most likely i-NANC neurotransmitt
most organs studied (Rand, 1992), but neuropep
such as VIP, SP, and CGRP may also be involve
neural vasodilator responses. CGRP-like immuno
tive NO is the most likely i-NANC neurotransmitter in
most organs studied (Rand, 1992), but neuropeptides
such as VIP, SP, and CGRP may also be involved in
neural vasodilator responses. CGRP-like immunoreac-
tive nerves are loc most organs studied (Rand, 1992), but neuropeptides
such as VIP, SP, and CGRP may also be involved in
neural vasodilator responses. CGRP-like immunoreac-
tive nerves are located around pulmonary arteries of
several species such as VIP, SP, and CGRP may also be involved in
neural vasodilator responses. CGRP-like immunoreac-
tive nerves are located around pulmonary arteries of
several species. (Lauweryns and Ranst, 1987; Mulderry
et al., 1985) neural vasodilator responses. CGRP-like immunoreactive nerves are located around pulmonary arteries of several species. (Lauweryns and Ranst, 1987; Mulderry et al., 1985). CGRP is likely to mediate the i-NANC response in l several species. (Lauweryns and Ranst, 1987; Mulderry
et al., 1985). CGRP is likely to mediate the i-NANC
response in large pulmonary arteries of guinea pig.
CGRP-like immunoreactive substance is released upon
electrical s et al., 1985). CGRP is likely to mediate the i-NANC response in large pulmonary arteries of guinea pig. CGRP-like immunoreactive substance is released upon electrical stimulation of these vessels (Maggi et al., 1990). CGRP response in large pulmonary arteries of guinea pig. et al., 1985). CGRP is likely to mediate the i-NANC
response in large pulmonary arteries of guinea pig.
CGRP-like immunoreactive substance is released upon
electrical stimulation of these vessels (Maggi et al.,
1990). CGRP electrical stimulation of these vessels (Maggi et al., electrical stimulation of these vessels (Maggi et 1990). CGRP mimics the NANC vasodilator responentially clinically these vessels (Mak and Barnes, 1988). Moreover, interatment with capsaicin to deplete sensory neuroperties 1990). CGRP mimics the NANC vasodilator response (Liu et al., 1992a), and CGRP receptors are localized to these vessels (Mak and Barnes, 1988). Moreover, pretreatment with capsaicin to deplete sensory neuropeptides markedl (Liu et al., 1992a), and CGRP receptors are localized to
these vessels (Mak and Barnes, 1988). Moreover, pre-
treatment with capsaicin to deplete sensory neuropep-
tides markedly inhibits the i-NANC response (Liu et al.,
1 these vessels (Mak and Barnes, 1988). Moreover, pre-
treatment with capsaicin to deplete sensory neuropep-
tides markedly inhibits the i-NANC response (Liu et al.,
1992a). An SP-like immunoreactive substance is also
releas treatment with capsaicin to deplete sensory neuropeptides markedly inhibits the i-NANC response (Liu et al., 1992a). An SP-like immunoreactive substance is also released during electrical stimulation in this vessel.
Howeve tides markedly inhibits the i-NANC response (Li
1992a). An SP-like immunoreactive substance
released during electrical stimulation in this
However, SP is unlikely to be the i-NANC transm
this vessel, inasmuch as SP is an e 1992a). An SP-like immunoreactive substance is a released during electrical stimulation in this vest-
However, SP is unlikely to be the i-NANC transmitte
this vessel, inasmuch as SP is an endothelium-dep
dent relaxant, wh released during electrical stimulation in this vessel.
However, SP is unlikely to be the i-NANC transmitter in
this vessel, inasmuch as SP is an endothelium-depen-
dent relaxant, whereas the i-NANC response is endothe-
liu However, SP is
this vessel, ina
dent relaxant, v
lium-independ
et al., 1992a).
CGRP may ı is vessel, inasmuch as SP is an endothelium-depen-
nt relaxant, whereas the i-NANC response is endothe-
um-independent in this vessel (Maggi et al., 1990; Liu
al., 1992a).
CGRP may not mediate the i-NANC response in the
an

and sensory nerves. NANC neural responses that are is an endothelium-independent vasodilator in this ve-
excitatory (excitatory-NANC, vasoconstrictor) and sel. Moreover, capsaicin treatments in vivo and in vitro
i-NANC (v dent relaxant, whereas the i-NANC response is endothe-

lium-independent in this vessel (Maggi et al., 1990; Liu

et al., 1992a).

CGRP may not mediate the i-NANC response in the

branch pulmonary arteries of guinea pig, h lium-independent in this vessel (Maggi et al., 1990; Liu
et al., 1992a).
CGRP may not mediate the i-NANC response in the
branch pulmonary arteries of guinea pig, however.
CGRP does not mimic the i-NANC relaxation and has
o et al., 1992a).
CGRP may not mediate the i-NANC response in the
branch pulmonary arteries of guinea pig, however.
CGRP does not mimic the i-NANC relaxation and has
only a minimal relaxant effect in branch pulmonary
arterie CGRP may not mediate the i-NANC response in the
branch pulmonary arteries of guinea pig, however.
CGRP does not mimic the i-NANC relaxation and has
only a minimal relaxant effect in branch pulmonary
arteries. The i-NANC re branch pulmonary arteries of guinea pig, however.
CGRP does not mimic the i-NANC relaxation and has
only a minimal relaxant effect in branch pulmonary
arteries. The i-NANC response in the branch pulmonary
arteries is parti CGRP does not mimic the i-NANC relaxation and has
only a minimal relaxant effect in branch pulmonary
arteries. The i-NANC response in the branch pulmonary
arteries is partially endothelium-dependent, but CGRP arteries. The i-NANC response in the branch pulmonary
arteries is partially endothelium-dependent, but CGRP
is an endothelium-independent vasodilator in this ves-
sel. Moreover, capsaicin treatments in vivo and in vitro
ha NANC response is significantly inhibited by the P_{2v} . is an endothelium-independent vasodilator in this vessel. Moreover, capsaicin treatments in vivo and in vitro
have no significant effect on the i-NANC response in
branch pulmonary arteries (Liu et al., 1992a). The i-
NANC sel. Moreover, capsaicin treatments in vivo and in vitro
have no significant effect on the i-NANC response in
branch pulmonary arteries (Liu et al., 1992a). The i-
NANC response is significantly inhibited by the P_{2y}-
rec have no significant effect on the i-NANC response in
branch pulmonary arteries (Liu et al., 1992a). The i-
NANC response is significantly inhibited by the P_{2y} -
receptor antagonist, reactive blue 2, suggesting that
ATP branch pulmonary arteries (Liu et al., 1992a). The i-
NANC response is significantly inhibited by the P_{2y} -
receptor antagonist, reactive blue 2, suggesting that
ATP at least partially mediates the i-NANC response in
g NANC response is significantly inhibited by the
receptor antagonist, reactive blue 2, suggestin
ATP at least partially mediates the i-NANC response
guinea pig branch arteries (Liu et al., 1992a). N
mediates the i-NANC resp *3. Suggesting that*
 PP at least partially mediates the i-NANC response in

inea pig branch arteries (Liu et al., 1992a). NO also

ediates the i-NANC response in these vessels.

3. Nitric oxide as i-nonadrenergic noncho ATP at least partially mediates the i-NANC response in guinea pig branch arteries (Liu et al., 1992a). NO also mediates the i-NANC response in these vessels.
3. Nitric oxide as *i*-nonadrenergic noncholinergic neurotransmi

mediates the i-NANC response in these vessels.

3. Nitric oxide as i-nonadrenergic noncholinergic neu-

rotransmitter. There is convincing evidence of NO action

as an i-NANC neurotransmitter in pulmonary arteries

(Liu et 3. Nitric oxide as i-nonadrenergic noncholinergic notransmitter. There is convincing evidence of NO act as an i-NANC neurotransmitter in pulmonary arter (Liu et al., 1992b). In the presence of adrenergic acholinergic bloc rotransmitter. There is convincing evidence of NO a
as an i-NANC neurotransmitter in pulmonary art
(Liu et al., 1992b). In the presence of adrenergic
cholinergic blockade, EFS induces a transient, free
cy-dependent relaxat as an i-NANC neurotransmitter in pulmonary arteries
(Liu et al., 1992b). In the presence of adrenergic and
cholinergic blockade, EFS induces a transient, frequen-
cy-dependent relaxation of precontracted, endothelium-
denu (Liu et al., 1992b). In the presence of adrenergic and
cholinergic blockade, EFS induces a transient, frequen-
cy-dependent relaxation of precontracted, endothelium-
denuded, guinea pig pulmonary artery rings, which is
abo cholinergic blockade, EFS induces a transient, frequency-dependent relaxation of precontracted, endothelium-denuded, guinea pig pulmonary artery rings, which is abolished by tetrodotoxin. This i-NANC relaxation is markedly denuded, guinea pig pulmonary artery rings, which is
abolished by tetrodotoxin. This i-NANC relaxation is
markedly inhibited by the NO synthase inhibitors, 1
NMMA or L-NAME, in a L-arginine reversible mannes
with D-arginin abolished by tetrodotoxin. This i-NANC relaxation is
markedly inhibited by the NO synthase inhibitors, L-
NMMA or L-NAME, in a L-arginine reversible manner,
with D-arginine being inactive (Liu et al., 1992b). Pyro-
gallol,

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oxide radical generation, also inhibits the i-NANC rela

ation, and the i-NANC relaxation is fully restored **l** BARNES AND 1

oxide radical generation, also inhibits the i-NANC relax-

ation, and the i-NANC relaxation is fully restored by plon

adding superoxide dismutase at the peak of pyrogallol- to E BAI

oxide radical generation, also inhibits the i-NANC re

ation, and the i-NANC relaxation is fully restored

adding superoxide dismutase at the peak of pyroga

evoked inhibition. exide radical genestion, and the i-land
adding superoxide
evoked inhibition.
Inhibition of the

ation, and the i-NANC relaxation is fully restored by
adding superoxide dismutase at the peak of pyrogallol-
evoked inhibition.
Inhibition of the formation of cGMP, the second-mes-
senger of NO action, by methylene blue senger of NO action, by methylene blue $(5 \mu M)$ causes > the inhibition. The inhibition is second-mesured inhibition of the formation of cGMP, the second-mesured senger of NO action, by methylene blue $(5 \mu M)$ causes > ATH 80% inhibition of the i-NANC relaxation. Additionall Inhibition of the formation of cGMP, the second-mes-
senger of NO action, by methylene blue $(5 \mu M)$ causes > ATI
80% inhibition of the i-NANC relaxation. Additionally, (Be
the i-NANC relaxation is significantly potentiat degradation. Furthermore, i-NANC relaxation is accompanied by a marked increase in the tissue concentration 80% inhibition of the i-NANC relaxation. Additionally,
the i-NANC relaxation is significantly potentiated by
zaprinast, a type V PDE inhibitor that prevents cGMP
degradation. Furthermore, i-NANC relaxation is accom-
panied the i-NANC relaxation is significantly potentiated by ges

zaprinast, a type V PDE inhibitor that prevents cGMP tide

degradation. Furthermore, i-NANC relaxation is accom-

panied by a marked increase in the tissue concen zaprinast, a type V PDE inhibitor that prevents cGMP tion
degradation. Furthermore, i-NANC relaxation is accom-
panied by a marked increase in the tissue concentration
of cGMP. The EFS-induced elevation in tissue cGMP D degradation. Furthermore, i-NANC relaxation is accompanied by a marked increase in the tissue concentration of cGMP. The EFS-induced elevation in tissue cGMP concentration is significantly inhibited by L-NMMA. As discussed panied by a marked increase in the tissue concentration
of cGMP. The EFS-induced elevation in tissue cGMP
concentration is significantly inhibited by L-NMMA. As
discussed above, in endothelium-denuded pulmonary ar-
teries, of cGMP. The EFS-induced elevation in tissue cGMP
concentration is significantly inhibited by L-NMMA. As
discussed above, in endothelium-denuded pulmonary ar-
teries, an NO synthase inhibitor significantly augments
adrener concentration is significantly inhibited by L-NMMA.
discussed above, in endothelium-denuded pulmonary
teries, an NO synthase inhibitor significantly augmen
adrenergic contraction, without any effect on basal v:
cular tone discussed above, in endothelium-denuded pulmonary arteries, an NO synthase inhibitor significantly augments adrenergic contraction, without any effect on basal vascular tone or contraction evoked by exogenous norepinephrin teries, an NO synthase inhibitor significantly augments
adrenergic contraction, without any effect on basal vas-
cular tone or contraction evoked by exogenous norepi-
nephrine, suggesting that there is neural release of NO cular tone or contraction evoked by exogenous norepi-
nephrine, suggesting that there is neural release of NO,
which acts as a functional antagonist to the adrenergic ula
neural contractile response elicited by EFS (Liu et nephrine, suggesting that there is neural release of NO, complist which acts as a functional antagonist to the adrenergic ulation neural contractile response elicited by EFS (Liu et al., area, in 1992b). However, it is unl which acts as a functional antagonist to the adrenergient and contractile response elicited by EFS (Liu et 1992b). However, it is unlikely that NO mediating i-NANC vasodilator response to EFS is derived faderenergic nerves neural contractile response elicited by EFS (Liu et al., arc
1992b). However, it is unlikely that NO mediating the
i-NANC vasodilator response to EFS is derived from dil
adrenergic nerves, inasmuch as chemical sympathec-
c 1992b). However, it is unlikely that NO mediating the i-NANC vasodilator response to EFS is derived from adrenergic nerves, inasmuch as chemical sympathectomy with 6-hydroxydopamine has no effect on the NANC vasodilator re i-NANC vasodilator response to EFS is derived
adrenergic nerves, inasmuch as chemical sympa-
tomy with 6-hydroxydopamine has no effect on
NANC vasodilator response to EFS (Liu et al., 19:
The possibility that NO is release adrenergic nerves, inasmuch as chemical sympathectomy with 6-hydroxydopamine has no effect on the NANC vasodilator response to EFS (Liu et al., 1992b). In The possibility that NO is released from parasympathetic nerves as tomy with 6-hydroxydopamine has no effect on the puln
NANC vasodilator response to EFS (Liu et al., 1992b). mor
The possibility that NO is released from parasympa-resp
thetic nerves as a cotransmitter with ACh is a possibi NANC vasodilator response to EFS (Liu et al., 1992b). In The possibility that NO is released from parasympa-
thetic nerves as a cotransmitter with ACh is a possibility chat cannot be further investigated until it is possib The possibility that NO is released from parasympa-
thetic nerves as a cotransmitter with ACh is a possibility
that cannot be further investigated until it is possible to
selectively destroy these nerves. However, it is po

that cannot be further investigated until it is possible to speectively destroy these nerves. However, it is possible m
that NO may also be released by separate NANC nerves. a
Although a large body of evidence supports the selectively destroy these nerves. However, it is possible man, 1
that NO may also be released by separate NANC nerves. a puln
Although a large body of evidence supports the notion (Hessle
that NO mediates the NANC relaxant that NO may also be released by separate NANC nerves.
Although a large body of evidence supports the notion
that NO mediates the NANC relaxant response, its
source remains uncertain. The neuronal form of NO
synthase has be Although a large body of evidence supports the notion (that NO mediates the NANC relaxant response, its lsource remains uncertain. The neuronal form of NO synthase has been localized to nerves innervating is mooth muscle o that NO mediates the NANC relaxant response, its In source remains uncertain. The neuronal form of NO staynthase has been localized to nerves innervating in smooth muscle of pulmonary vessels (Klimaschewski et (Mal., 1992) source remains uncertain. The neuronal form of Naynthase has been localized to nerves innervation
smooth muscle of pulmonary vessels (Klimaschewski
al., 1992), suggesting that NO is released from the
nerve endings. Another synthase has been localized to nerves innervating is
smooth muscle of pulmonary vessels (Klimaschewski et al., 1992), suggesting that NO is released from these
nerve endings. Another possibility is that nerve stimulation i smooth muscle of pulmonary vessels (Klimaschewski et al., 1992), suggesting that NO is released from these nerve endings. Another possibility is that nerve stimulation induces transmitter release, which in turn causes NO r al., 1992), suggesting that NO is released from these Pulmonary vascular tone is also modulated by periph-
nerve endings. Another possibility is that nerve stimu-
lead chemoreceptors and baroreceptors. Depending on
lation lation induces transmitter release, which in turn causes lation induces transmitter release, which in turn causes
NO release from smooth muscle or/and endothelial cells.
NO derived from endothelial cells partially mediates the
realistic vasodilator response in guinea pig pulmona NO release from smooth muscle or/and endothelial cells.
NO derived from endothelial cells partially mediates the
NANC vasodilator response in guinea pig pulmonary
arteries, in contrast to bovine mesenteric and monkey
Fereb NO derived from endothelial cells partially mediates the
NANC vasodilator response in guinea pig pulmonary
arteries, in contrast to bovine mesenteric and monkey
lerebral arteries, where endothelially derived NO plays
no ro NANC vasodilator response in guinea pig pulmonary Dalarteries, in contrast to bovine mesenteric and monkey PV
cerebral arteries, where endothelially derived NO plays cau
no role in mediating the NANC vasodilator response c arteries, in contrast to bovine mesenteric and monkey PVR (cerebral arteries, where endothelially derived NO plays causes
no role in mediating the NANC vasodilator response crease
(Toda and Okamura, 1990; Ahlner et al., 19 cerebral arteries, where endothelially derived NO plays
no role in mediating the NANC vasodilator response
crease
(Toda and Okamura, 1990; Ahlner et al., 1991). It is also
Flint
possible that vascular smooth muscle may rel no role in mediating the NANC vasodilator response creation (Toda and Okamura, 1990; Ahlner et al., 1991). It is also Flipposible that vascular smooth muscle may release NO movem stimulated by transmitter released from NAN (Toda and Okamura, 1990; Ahlner et al., 1991). It is also Frossible that vascular smooth muscle may release NO m
when stimulated by transmitter released from NANC synerves, although there is little evidence to support the possible that vascular smooth muscle may release NO momentum stimulated by transmitter released from NANC symterves, although there is little evidence to support the Flire contention. The time course of NO production from when stimulated by transmitter r
nerves, although there is little evi
contention. The time course of NO p
cells, which depends on inducible
slow to account for neurotransmiss
4. Nonadrenergic, noncholinergi rves, although there is little evidence to support the intention. The time course of NO production from the lls, which depends on inducible NO synthase, is we to account for neurotransmission.
4. *Nonadrenergic, noncholine* results, which depends on inducible NO synthase, is to
cells, which depends on inducible NO synthase, is to
slow to account for neurotransmission.
4. Nonadrenergic, noncholinergic control of pulmo
nary vascular tone. Altho

cells, which depends on inducible NO synthase, is to
slow to account for neurotransmission.
4. Nonadrenergic, noncholinergic control of pulmo
nary vascular tone. Although i-NANC vasodilator
nerve-mediated pulmonary vasodil slow to account for neurotransmission.
4. Nonadrenergic, noncholinergic control of pulmo-
nary vascular tone. Although i-NANC vasodilator,
nerve-mediated pulmonary vasodilation has been dem-
onstrated in vitro (Kubota et a 4. Nonadrenergic, noncholinergic control of pulmonary vascular tone. Although i-NANC vasodilator, nerve-mediated pulmonary vasodilation has been demonstrated in vitro (Kubota et al., 1988; Maggi et al., 1990; Liu et al., 1 mary vascular tone. Although i-NANC vasodilator, in
merve-mediated pulmonary vasodilation has been dem-
onstrated in vitro (Kubota et al., 1988; Maggi et al., ne
1990; Liu et al., 1992a), it has not been described in vivo.

adding superoxide dismutase at the peak of pyrogallol-
evoked inhibition.
evoked inhibition.
Inhibition of the formation of cGMP, the second-mes-
pulmonary vascular tone and pulmonary blood flow.
senger of NO action, by m ND LIU
control of pulmonary vascular tone remain to be ex-
plored. Because the major part of the relaxant response ND LIU
control of pulmonary vascular tone remain to be ex-
plored. Because the major part of the relaxant response
to EFS is mediated through the i-NANC pathway, this ND LIU
control of pulmonary vascular tone remain to be ex-
plored. Because the major part of the relaxant response
to EFS is mediated through the i-NANC pathway, this
neural mechanism may play a role in the regulation of control of pulmonary vascular tone remain to be ex-
plored. Because the major part of the relaxant response
to EFS is mediated through the i-NANC pathway, this
neural mechanism may play a role in the regulation of
pulmonar plored. Because the major part of the relaxant response plored. Because the major part of the relaxant response
to EFS is mediated through the i-NANC pathway, this
neural mechanism may play a role in the regulation of
pulmonary vascular tone and pulmonary blood flow.
ATP modula to EFS is mediated through the i-NANC pathway, this
neural mechanism may play a role in the regulation of
pulmonary vascular tone and pulmonary blood flow.
ATP modulates hypoxic pulmonary vasoconstriction
(Benumof et al., neural mechanism may play a role in the regulatio
pulmonary vascular tone and pulmonary blood f
ATP modulates hypoxic pulmonary vasoconstric
(Benumof et al., 1982). Circumstantial evidence a
gests that vagal sensory nerves pulmonary vascular tone and pulmonary blood flow.
ATP modulates hypoxic pulmonary vasoconstriction
(Benumof et al., 1982). Circumstantial evidence sug-
gests that vagal sensory nerves and sensory neuropep-
tides have a pro (Benumof et al., 1982). Circumstantial evidence suggests that vagal sensory nerves and sensory neuropeptides have a protective action against fibrin-induced neurogenic pulmonary edema (Hashiba et al., 1989).
D. Reflex mech *Filipes* have a protective action against fibrin-induced neurogenic pulmonary edema (Hashiba et al., 1989).
 D. Reflex mechanisms

The pulmonary circulation is also under central and

cular tone or contraction evoked by exogenous norepi-
nephrine, suggesting that there is neural release of NO,
nephrine (Szidon and Fishman, 1981). Electrical stim-
which acts as a functional antagonist to the adrenergic u thetic nerves as a cotransmitter with ACh is a possibility cord, indicating a pathway from forebrain through the
that cannot be further investigated until it is possible to spinal cord that regulates pulmonary vascular ton des have a protective action against fibrin-induced

urogenic pulmonary edema (Hashiba et al., 1989).

Reflex mechanisms

The pulmonary circulation is also under central and

cal reflex controls. Stimulation of the hypotha neurogenic pulmonary edema (Hashiba et al., 1989).

D. Reflex mechanisms

The pulmonary circulation is also under central and

local reflex controls. Stimulation of the hypothalamic

integrative area for the defense reacti D. Reflex mechanisms
The pulmonary circulation is also under central and
local reflex controls. Stimulation of the hypothalamic
integrative area for the defense reaction causes a small
increase in pulmonary vascular resist D. Reflex mechanisms
The pulmonary circulation is also under central and
local reflex controls. Stimulation of the hypothalamic
integrative area for the defense reaction causes a small
increase in pulmonary vascular resist The pulmonary circulation is also under central and
local reflex controls. Stimulation of the hypothalamic
integrative area for the defense reaction causes a small
increase in pulmonary vascular resistance (Anderson
and Br local reflex controls. Stimulation of the hypothalami
integrative area for the defense reaction causes a smal
increase in pulmonary vascular resistance (Anderso
and Brown, 1967) or a decrease in pulmonary vascula
complianc integrative area for the defense reaction causes a small
increase in pulmonary vascular resistance (Anderson
and Brown, 1967) or a decrease in pulmonary vascular
compliance (Szidon and Fishman, 1981). Electrical stim-
ulat and Brown, 1967) or a decrease in pulmonary vascular and Brown, 1967) or a decrease in pulmonary vascula
compliance (Szidon and Fishman, 1981). Electrical stin
ulation of the medulla near the vascular regulatory C-
area, in most experiments, induces sympathetically me
diated compliance (Szidon and Fishman, 1981). Electrical stimulation of the medulla near the vascular regulatory C-1 area, in most experiments, induces sympathetically mediated pulmonary vasoconstriction, followed by a vaso-
dila ulation of the medulla near the vascular regulatory C-1
area, in most experiments, induces sympathetically me-
diated pulmonary vasoconstriction, followed by a vaso-
dilator response (Hyman, 1986). Stimulation of a dis-
cr area, in most experiments, induces sympathetically mediated pulmonary vasoconstriction, followed by a vaso-
dilator response (Hyman, 1986). Stimulation of a discrete area in the forebrain also causes an abrupt
pulmonary va diated pulmonary vasoconstriction, followed by a vaso-
dilator response (Hyman, 1986). Stimulation of a dis-
crete area in the forebrain also causes an abrupt
pulmonary vasoconstriction followed by a prolonged pul-
monary dilator response (Hyman, 1986). Stimulation of a discrete area in the forebrain also causes an abrupt pulmonary vasoconstriction followed by a prolonged pulmonary vasodilation. Both the constrictor and dilator responses ar crete area in the forebrain also causes an abrupt
pulmonary vasoconstriction followed by a prolonged pul-
monary vasodilation. Both the constrictor and dilator
responses are blocked by freezing or severing the spinal
cord, pulmonary vasoconstriction followed by a prolonged pulmonary vasodilation. Both the constrictor and dilator
responses are blocked by freezing or severing the spinal
cord, indicating a pathway from forebrain through the
spi monary vasodilation. Both the constrictor and dilator
responses are blocked by freezing or severing the spinal
cord, indicating a pathway from forebrain through the
spinal cord that regulates pulmonary vascular tone (Hy-
m responses are blocked by freezing or severing the spinal
cord, indicating a pathway from forebrain through the
spinal cord that regulates pulmonary vascular tone (Hy-
man, 1986). Elevation of intracranial pressure produces cord, indicating a pathway from forebrain through the
spinal cord that regulates pulmonary vascular tone (Hy-
man, 1986). Elevation of intracranial pressure produces
a pulmonary vasoconstriction via the Cushing reflex
(Hes man, 1986). Elevation of intracranial pressure produced a pulmonary vasoconstriction via the Cushing ref (Hessler and Cassin, 1977; Maron and Dawson, 1971). Intracranial hypertension-induced pulmonary vasoc striction is li a pulmonary vasoconstriction via the Cushing reflex
(Hessler and Cassin, 1977; Maron and Dawson, 1979).
Intracranial hypertension-induced pulmonary vasocon-
striction is likely to be the result of increasing circulat-
ing (Hessler and Cassin, 1977; M
Intracranial hypertension-ind
striction is likely to be the rearing catecholamines released
(Maron and Dawson, 1979).
Pulmonary vascular tone is Intracranial hypertension-induced pulmonary vasoconstriction is likely to be the result of increasing circulating catecholamines released from the adrenal medulla (Maron and Dawson, 1979). integrative area for the defense reaction causes a small
increase in pulmonary vascular resistance (Andersor
and Brown, 1967) or a decrease in pulmonary vascular
compliance (Szidon and Fishman, 1981). Electrical stim-
ula

ing catecholamines released from the adrenal medulla
(Maron and Dawson, 1979).
Pulmonary vascular tone is also modulated by periph-
eral chemoreceptors and baroreceptors. Depending on
the experimental conditions, the stimu (Maron and Dawson, 1979).

Pulmonary vascular tone is also modulated by peripheral chemoreceptors and baroreceptors. Depending on

the experimental conditions, the stimuli, and the pre-

existing tone, stimulation of chemo Pulmonary vascular tone is also modulated by peripheral chemoreceptors and baroreceptors. Depending on the experimental conditions, the stimuli, and the pre-
existing tone, stimulation of chemoreceptors in the ca-
rotid or eral chemoreceptors and baroreceptors. Depending on
the experimental conditions, the stimuli, and the pre-
existing tone, stimulation of chemoreceptors in the ca-
rotid or aortic bodies increases PVR (Aviado et al., 1957;
 the experimental conditions, the stimuli, and the pre-
existing tone, stimulation of chemoreceptors in the ca-
rotid or aortic bodies increases PVR (Aviado et al., 1957;
Daly and Daly, 1959; Daly and Hebb, 1966), decreases existing tone, stimulation of chemoreceptors in the carotid or aortic bodies increases PVR (Aviado et al., 1957; Daly and Daly, 1959; Daly and Hebb, 1966), decreases PVR (Daly and Daly, 1957; Fitzgerald et al., 1992), caus rotid or aortic bodies increases PVR (Aviado et al., 1957;
Daly and Daly, 1959; Daly and Hebb, 1966), decreases
PVR (Daly and Daly, 1957; Fitzgerald et al., 1992),
causes no change in PVR (Olson et al., 1982), or de-
creas Daly and Daly, 1959; Daly and Hebb, 1966), decreases PVR (Daly and Daly, 1957; Fitzgerald et al., 1992), causes no change in PVR (Olson et al., 1982), or decreases pulmonary vascular compliance (Szidon and Flint, 1977). Th PVR (Daly and Daly, 1957; Fitzgerald et al., 1992), causes no change in PVR (Olson et al., 1982), or decreases pulmonary vascular compliance (Szidon and Flint, 1977). The increase in PVR and decrease in pulmonary vascular causes no change in PVR (Olson et al., 1982), or de-
creases pulmonary vascular compliance (Szidon and
Flint, 1977). The increase in PVR and decrease in pul-
monary vascular compliance are mediated by efferent
sympathetic creases pulmonary vascular compliance (Szidon and
Flint, 1977). The increase in PVR and decrease in pul-
monary vascular compliance are mediated by efferent
sympathetic nerves (Daly and Hebb, 1966; Szidon and
Flint, 1977), Flint, 1977). The increase in PVR and decrease in pul-
monary vascular compliance are mediated by efferent
sympathetic nerves (Daly and Hebb, 1966; Szidon and
Flint, 1977), whereas the decrease in PVR is likely to be
media monary vascular compliance are mediated by efferent
sympathetic nerves (Daly and Hebb, 1966; Szidon and
Flint, 1977), whereas the decrease in PVR is likely to be
mediated via parasympathetic nerves (Daly and Daly,
1957; Ol sympathetic nerves (Daly and Hebb, 1966; Szidon and Flint, 1977), whereas the decrease in PVR is likely to be mediated via parasympathetic nerves (Daly and Daly, 1957; Olson et al., 1982; Wilson and Levitzky, 1989). Stimul Flint, 1977), whereas the decrease in PVR is likely to be mediated via parasympathetic nerves (Daly and Daly, 1957; Olson et al., 1982; Wilson and Levitzky, 1989).
Stimulation of baroreceptors in the carotid sinus or aorti 1957; Olson et al., 1982; Wilson and Levitzky, 1989).
Stimulation of baroreceptors in the carotid sinus or aor-
tic arch by an elevation in blood pressure by reflex
induces pulmonary vasodilation via a decrease in sym-1957; Olson et al., 1982; Wilson and Levitzky, 1989).
Stimulation of baroreceptors in the carotid sinus or aor-
tic arch by an elevation in blood pressure by reflex
induces pulmonary vasodilation via a decrease in sym-
pat Stimulation of baroreceptors in the carotid sinus or aortic arch by an elevation in blood pressure by reflex
induces pulmonary vasodilation via a decrease in sym-
pathetic outflow or activation of sympathetic vasodilator
n tic arch by an elevation in blood pressure by reflex
induces pulmonary vasodilation via a decrease in sym-
pathetic outflow or activation of sympathetic vasodilator
nerves (Daly and Hebb, 1966). It has been reported that
b induces pulmonary vasodilation via a decrease in sympathetic outflow or activation of sympathetic vasodilator
nerves (Daly and Hebb, 1966). It has been reported that
bilateral carotid occlusion has little modulatory effect

PHARMACOLOGICAL REVIEWS

REGULATION OF PULMONARY VASCULAR TONE
though this does not exclude reflex modulation of pul- (Kawasaki et al., 19
monary vasomotor activity (Pace, 1978). roeffector transmism REGUL
though this does not exclude reflex modu
monary vasomotor activity (Pace, 1978).
Additionally, stimulation of receptors wi

REGULATION OF PULMON.

Nonary vasomotor activity (Pace, 1978).

Additionally, stimulation of receptors within the lungs (

Additionally, stimulation of receptors within the lungs (

n elicit a pulmonary reflex. Distension though this does not exclude reflex modulation of pul-
monary vasomotor activity (Pace, 1978). To
Additionally, stimulation of receptors within the lungs (B-
can elicit a pulmonary reflex. Distension of the main no
pulmona though this does not exclude reflex modulation of pul-
monary vasomotor activity (Pace, 1978).
Additionally, stimulation of receptors within the lungs
can elicit a pulmonary reflex. Distension of the main
pulmonary artery monary vasomotor activity (Pace, 1978).

Additionally, stimulation of receptors within the lungs

can elicit a pulmonary reflex. Distension of the main

pulmonary artery produces vasoconstriction (Hyman,

1968; Laks et al. Additionally, stimulation of receptors within the lungs
can elicit a pulmonary reflex. Distension of the main
pulmonary artery produces vasoconstriction (Hyman,
1968; Laks et al., 1975). This mechanism probably me-
diates can elicit a pulmonary reflex. Distension of the main
pulmonary artery produces vasoconstriction (Hyman,
1968; Laks et al., 1975). This mechanism probably me-
diates the pulmonary vasoconstriction observed after
pulmonary pulmonary artery produces vasoconstriction (Hyman, 1968; Laks et al., 1975). This mechanism probably mediates the pulmonary vasoconstriction observed after pulmonary embolism (Stein and Levy, 1974). In contrast, stimulatio 1968; Laks et al., 1975). This mechanism probably mediates the pulmonary vasoconstriction observed after pulmonary embolism (Stein and Levy, 1974). In contrast, stimulation of receptors in small pulmonary vessels by small diates the pulmonary vaso
pulmonary embolism (Stein
trast, stimulation of recept
sels by small emboli induo
(Kealey and Brody, 1977).
Airway dynamics also aff dmonary embolism (Stein and Levy, 1974). In
ast, stimulation of receptors in small pulmonary
ls by small emboli induces pulmonary vasodil:
saley and Brody, 1977).
Airway dynamics also affect pulmonary hemody:
s, via either

trast, stimulation of receptors in small pulmonary vessels by small emboli induces pulmonary vasodilation therm (Kealey and Brody, 1977). polynomics also affect pulmonary hemodynamics, via either central and/or local refle sels by small emboli induces pulmonary vasodilation
(Kealey and Brody, 1977).
Airway dynamics also affect pulmonary hemodynam
ics, via either central and/or local reflex pathways. One
example is the decrease in the pulmona (Kealey and Brody, 1977).

Airway dynamics also affect pulmonary he

ics, via either central and/or local reflex path

example is the decrease in the pulmonary ar

pliance after lung inflation (Ingram, 1972).

F. Resible ics, via either central and/or local reflex pathways. One example is the decrease in the pulmonary arterial compliance after lung inflation (Ingram, 1972).
E. Possible Role in Pulmonary Vascular Disease

pliance after lung inflation (Ingram, 1972). effectively effectively studied. The role of pulmonary vascular Disease
The role of pulmonary innervation in the HPV has with
been intensively studied. There are two components E. Possible Role in Pulmonary Vascular Disease tors

The role of pulmonary innervation in the HPV has

been intensively studied. There are two components to NP^N

the pulmonary vasoconstrictor response to hypoxia in acti
 E. Possible Role in Pulmonary vascular Disease
The role of pulmonary innervation in the HPV has
been intensively studied. There are two components to
the pulmonary vasoconstrictor response to hypoxia in
intact animals, a l The role of pulmonary innervation in the HPV has
been intensively studied. There are two components to
the pulmonary vasoconstrictor response to hypoxia in
intact animals, a local pulmonary vasoconstrictor re-
sponse, and the pulmonary vasoconstrictor response to hypoxia in intact animals, a local pulmonary vasoconstrictor response, and a reflex response. Although pulmonary in-
nervation does not seem to play a role in the powerful local pu the pulmonary vasoconstrictor response to hypoxia in intact animals, a local pulmonary vasoconstrictor response, and a reflex response. Although pulmonary innervation does not seem to play a role in the powerful local pulm intact animals, a local pulmonary vasoconstrictor response, and a reflex response. Although pulmonary in-
nervation does not seem to play a role in the powerful
local pulmonary vasoconstrictor response to acute hy-
poxia (sponse, and a reflex response. Although pulmonary in-
nervation does not seem to play a role in the powerful
local pulmonary vasoconstrictor response to acute hy-
poxia (Fishman, 1976; McLean, 1986), adrenergic nerves
are nervation does not seem to play a role in the powerlocal pulmonary vasoconstrictor response to acute h poxia (Fishman, 1976; McLean, 1986), adrenergic nervare likely to mediate the reflex increase in pulmonary vascular res local pulmonary vasoconstrictor response to acute hypoxia (Fishman, 1976; McLean, 1986), adrenergic nerve are likely to mediate the reflex increase in pulmonar vascular resistance or the decrease in pulmonary vascular comp poxia (Fishman, 1976; McLean, 1986), adrenergic nerves move the eight of carotid and aortic chemoreceptors (Daly and Hebb, 1966; Szidon and Flint, 1977; McLean, 1986). considered to the decrease in pulmonary vascular compl are likely to mediate the reflex increase in pulmonary
vascular resistance or the decrease in pulmonary vascular compliance resulting from systemic hypoxemic stim-
ulation of carotid and aortic chemoreceptors (Daly and
Heb vascular resistance or the decrease in pulmonary vascular compliance resulting from systemic hypoxemic stimulation of carotid and aortic chemoreceptors (Daly and Hebb, 1966; Szidon and Flint, 1977; McLean, 1986).
Stimulati lar compliance resulting from systemic hypoxemic stim-
ulation of carotid and aortic chemoreceptors (Daly and ha
Hebb, 1966; Szidon and Flint, 1977; McLean, 1986). con
Stimulation of carotid chemoreceptors during a local ulation of carotid and aortic chemoreceptors (Daly and Hebb, 1966; Szidon and Flint, 1977; McLean, 1986).
Stimulation of carotid chemoreceptors during a local
hypoxic pulmonary vasoconstrictor response blunts the
HPV respo Hebb, 1966; Szidon and Flint, 1977; McLean, 1986).
Stimulation of carotid chemoreceptors during a local
hypoxic pulmonary vasoconstrictor response blunts the
HPV response. This attenuation of HPV has been sug-
gested to b Stimulation of carotid chemoreceptors during a lockupoxic pulmonary vasoconstrictor response blunts the HPV response. This attenuation of HPV has been supersted to be mediated via cholinergic nerves (Olson al., 1982; Wilso hypoxic pulmonary vasoconstrictor response blunts the HPV response. This attenuation of HPV has been suggested to be mediated via cholinergic nerves (Olson et al., 1982; Wilson and Levitzky, 1989), although inconsistent re HPV response. This attenuation of HPV has been suggested to be mediated via cholinergic nerves (Olson et al., 1982; Wilson and Levitzky, 1989), although inconsistent results have been reported (Lejeune et al., 1989). It ha

al., 1982; Wilson and Levitzky, 1989), although incon-
sistent results have been reported (Lejeune et al., 1989). nar
It has been suggested that adrenergic nerves may pro-
Altitect against the development of pulmonary hype sistent results have been reported (Lejeune et al., 1989).
It has been suggested that adrenergic nerves may pro-
tect against the development of pulmonary hypertension ((McLean, 1986). However, there is no good evidence t tect against the development of pulmonary hyperten
(McLean, 1986). However, there is no good evidence
support it. Adrenergic nerves are likely to mediate the
monary vasoconstriction seen in cold exposure (McL
1986), reperf (McLean, 1986). However, there is no good evidence to support it. Adrenergic nerves are likely to mediate the pulmonary vasoconstriction seen in cold exposure (McLean, 1986), reperfusion (hypoperfusion followed by hyperper support it. Adrenergic nerves are likely to mediate the pulmonary vasoconstriction seen in cold exposure (McLean, 1986), reperfusion (hypoperfusion followed by hyperperfusion) (Clougherty et al., 1988), pulmonary embolism monary vasoconstriction seen in cold exposure (McLean, 1986), reperfusion (hypoperfusion followed by hyperperfusion) (Clougherty et al., 1988), pulmonary embolism (Price, 1955; Kabins et al., 1962), and neurogenic pulmonar 1986), reperfusion (hypoperfusion followed by hyperperfusion) (Clougherty et al., 1988), pulmonary embolism (Price 1955; Kabins et al., 1962), and neurogenic pulmonary edema (Colice et al., 1984; Malik, 1985). Adrenergic n 1955; Kabins et al., 1962), and neurogenic pulmonary edema (Colice et al., 1984; Malik, 1985). Adrenergic nerves are also involved in the development of embolic and neurogenic pulmonary edema (Kabins et al., 1962; Colice e 1955; Kabins et al., 1962), and neurogenic pulmonary
edema (Colice et al., 1984; Malik, 1985). Adrenergic nerves
are also involved in the development of embolic and neu-
rogenic pulmonary edema (Kabins et al., 1962; Colice edema (Colice et al., 1984; Malik, 1985). Adrenergic nerve
are also involved in the development of embolic and neu
rogenic pulmonary edema (Kabins et al., 1962; Colice et al
1984). Vagal nerves may also play a role in neur are also involved in the development of embolic and neu-
rogenic pulmonary edema (Kabins et al., 1962; Colice et al.,
1984). Vagal nerves may also play a role in neurogenic
pulmonary edema (Colice et al., 1984; Malik, 1985 rogenic pulmonary edema (Kabins et al., 1962; Colice et al., 1984). Vagal nerves may also play a role in neurogenic pulmonary edema (Colice et al., 1984; Malik, 1985). Stimulation of both sympathetic and vagal nerves can 1984). Vagal nerves may also play a role in neurog
pulmonary edema (Colice et al., 1984; Malik, 1985). S
ulation of both sympathetic and vagal nerves can incr
lung weight gain or pulmonary vascular permeabilit
albumin (Sak ulation of both sympathetic and vagal nerves can increase
hung weight gain or pulmonary vascular permeability to
albumin (Sakakibara et al., 1992; Liu et al., 1994a).
Abnormalities in NANC vasodilator nerves may also

ulation of both sympathetic and vagal nerves can incrownly weight gain or pulmonary vascular permeabilities albumin (Sakakibara et al., 1992; Liu et al., 1994a).
Abnormalities in NANC vasodilator nerves may contribute to t hung weight gain or pulmonary vascular permeability to
albumin (Sakakibara et al., 1992; Liu et al., 1994a).
Abnormalities in NANC vasodilator nerves may also
contribute to the development of pulmonary hyperten-
sion. A de albumin (Sakakibara et al., 1992; Liu et al., 1994a).
Abnormalities in NANC vasodilator nerves may a
contribute to the development of pulmonary hypert
sion. A decrease in CGRP-containing NANC vasodila
nerves has contribute contribute to the development of pulmonary hypertension. A decrease in CGRP-containing NANC vasodilator
nerves has contributed to the development and mainte-
nance of hypertension in spontaneous hypertensive rats

95
(Kawasaki et al., 1990). Hypoxia inhibits NANC neu-
roeffector transmission in some nonvascular tissues FREE START VASCULAR TONE
FREE START (Kawasaki et al., 1990). Hypoxia inhibits NANC neu-
roeffector transmission in some nonvascular tissues
(Bowman and McGrath, 1985). It is possible that the 95
(Kawasaki et al., 1990). Hypoxia inhibits NANC neu-
roeffector transmission in some nonvascular tissues
(Bowman and McGrath, 1985). It is possible that the
normal vasodilator action of NANC nerves is inhibited (Kawasaki et al., 1990). Hypoxia inhibits NANC neu-
roeffector transmission in some nonvascular tissues
(Bowman and McGrath, 1985). It is possible that the
normal vasodilator action of NANC nerves is inhibited
during hypox (Kawasaki et al., 1990). Hypoxia inhibits NANC neuroeffector transmission in some nonvascular tissues
(Bowman and McGrath, 1985). It is possible that the
normal vasodilator action of NANC nerves is inhibited
during hypoxia roeffector transmission in some nonvascular tissues
(Bowman and McGrath, 1985). It is possible that the
normal vasodilator action of NANC nerves is inhibited
during hypoxia and may be impaired with repeated hy-
poxic episo normal vasodilator action of NANC nerves is inhibited
during hypoxia and may be impaired with repeated hypoxic episodes. Because NANC vasodilator nerves repduring hypoxia and may be impaired with repeated hypoxic episodes. Because NANC vasodilator nerves represent the major neural vasodilator mechanism of pulmonary vessels, abnormality in the NANC system could shift the balan during hypoxia and may be impaired with repeated hypoxic episodes. Because NANC vasodilator nerves represent the major neural vasodilator mechanism of pulmonary vessels, abnormality in the NANC system could shift the balan poxic episodes. Because NANC vasodilator nerves represent the major neural vasodilator mechanism of pulmonary vessels, abnormality in the NANC system could shift the balance toward vasoconstriction and potentiate the contr monary vessels, abnormality in the NANC system could
shift the balance toward vasoconstriction and potentiate
the contractile response to vasoconstrictors such as hy-
poxia, thus potentiating HPV.
III. Humoral Mechanisms the contractile response to vasoconstrictors such as hypoxia, thus potentiating HPV.
 III. Humoral Mechanisms

Many circulating mediators and hormones have an e contractile response to vasoconstrictors such as hy-

xia, thus potentiating HPV.
 III. Humoral Mechanisms

Many circulating mediators and hormones have an

fect on pulmonary vascular tone that is mediated via

multiple receptors (table 2). The effects of these media-
tors and hormones on pulmonary vascular tone vary
The role of pulmonary innervation in the HPV has with species, age, and pre-existing tone. In general, A-II,
en in poxia, thus potentiating HPV.
 III. Humoral Mechanisms

Many circulating mediators and hormones have an

effect on pulmonary vascular tone that is mediated via

multiple receptors (table 2). The effects of these media-**III. Humoral Mechanisms**
Many circulating mediators and hormones have
effect on pulmonary vascular tone that is mediated
multiple receptors (table 2). The effects of these med
tors and hormones on pulmonary vascular tone **EXECUTE: INTERT INTERTM INTERTMENT MECHANISMS**
effect on pulmonary vascular tone that is mediated via
multiple receptors (table 2). The effects of these media-
tors and hormones on pulmonary vascular tone vary
with spec Many circulating mediators and hormones have an
effect on pulmonary vascular tone that is mediated via
multiple receptors (table 2). The effects of these media-
tors and hormones on pulmonary vascular tone vary
with specie activation peptide, PGs D_2 , E_2 and $F_{2\alpha}$ are pulmonary multiple receptors (table 2). The effects of these media-
tors and hormones on pulmonary vascular tone vary
with species, age, and pre-existing tone. In general, A-II,
NPY, leucine-enkephalin, thrombin, thrombin receptor
a tors and hormones on pulmonary vascular tone vary
with species, age, and pre-existing tone. In general, A-II,
NPY, leucine-enkephalin, thrombin, thrombin receptor
activation peptide, PGs D_2 , E_2 and $F_{2\alpha}$ are pulm with species, age, and pre-existing tone. In general, A-II,
NPY, leucine-enkephalin, thrombin, thrombin receptor
activation peptide, PGs D_2 , E_2 and $F_{2\alpha}$ are pulmonary
vasoconstrictors, whereas ANP, VIP, CGRP, AM NPY, leucine-enkephalin, thrombin, thrombin receptactivation peptide, PGs D_2 , E_2 and $F_{2\alpha}$ are pulmons vasoconstrictors, whereas ANP, VIP, CGRP, AMP, P E_1 and I_2 are pulmonary vasodilators. There are son ex activation peptide, PGs D_2 , E_2 and $F_{2\alpha}$ are pulmonary vasoconstrictors, whereas ANP, VIP, CGRP, AMP, PGs E_1 and I_2 are pulmonary vasodilators. There are some exceptions; for example, PGD₂ and PGE₂ caus vasoconstrictors, whereas ANP, VIP, CGRP, AMP, PGs E_1 and I_2 are pulmonary vasodilators. There are some exceptions; for example, PGD₂ and PGE₂ cause pulmonary relaxation in fetal lambs, and PGI₂ increases pulm E_1 and I_2 are pulmonary vasodilators. There are some exceptions; for example, PGD_2 and PGE_2 cause pulmonary relaxation in fetal lambs, and PGI_2 increases pulmonary vascular resistance in rabbits (see III.A.13. nary relaxation in fetal lambs, and PGI_2 increases pulmonary vascular resistance in rabbits (see III.A.13. Eicosanoids). BK, AVP, endothelins, PACAP, SP, N-formyl-methionyl-leucyl-phenylalanine, histamine, 5-HT, PAF, ar monary vascular resistance in rabbits (see III.A.13. Eicosanoids). BK, AVP, endothelins, PACAP, SP,
N-formyl-methionyl-leucyl-phenylalanine, histamine,
5-HT, PAF, arachidonic acid, adenosine, ADP and ATP
have dual effects cosanoids). BK, AVP, endothelins, PACAP, SP,
N-formyl-methionyl-leucyl-phenylalanine, histamine,
5-HT, PAF, arachidonic acid, adenosine, ADP and ATP
have dual effects on pulmonary vascular tone, causing
contraction when th 5-HT, PAF, arachidonic acid, adenosine, ADP and ATP
have dual effects on pulmonary vascular tone, causing
contraction when the vascular tone is low but relaxation
when the vascular tone is high.

A. Effects ofHumoral Substances on Pulmonary Vessels

1. Angiotensin II. A-II constricts isolated large pulmonary artery rings (Boe and Simonsson, 1981; Chand and A. Effects of Humoral Substances on Pulmonary
Vessels
1. Angiotensin II. A-II constricts isolated large pulmo-
nary artery rings (Boe and Simonsson, 1981; Chand and
Altura, 1981) and the perfused pulmonary vascular bed A. Effects of Humoral Substances on Pulmonary
Vessels
1. Angiotensin II. A-II constricts isolated large pulmo-
nary artery rings (Boe and Simonsson, 1981; Chand and
Altura, 1981) and the perfused pulmonary vascular bed
(Ka Vessets

1. Angiotensin II. A-II constricts isolated large pulmo-

nary artery rings (Boe and Simonsson, 1981; Chand and

Altura, 1981) and the perfused pulmonary vascular bed

(Kadowitz et al., 1975; McMurtry, 1984; Goll

TABLE 2 *(Kadowitz et al., 1975; McMurtry, 1984; Goll et al., 1986;*
TABLE 2
Humoral receptors in pulmonary vessels

Receptors	Subtypes	Responses	Endothelium- dependency
Adenosine	А,	contraction	no
	А,	relaxation	no
Angiotensin	AT	contraction	no
ANP	ANP.	relaxation	no
	ANP _R	relaxation	no
Bradykinin	B.?	relaxation	yes
	В,	relaxation	yes
Endothelin	ET_{\sim}	contraction	no
	ET_{R}	relaxation	yes
Histamine	н.	relaxation	yes
	Н,	relaxation	no
5-HT	5-HT,	contraction	no
	$5-HT_{1c}$	relaxation	yes
Thromboxane	TP	contraction	no
Vasopressin	v,	relaxation	yes

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BARNES AND LIU
Liu et al., 1991b) via activation of its G-protein coupled attenuated b
receptors. Intravenous infusion of A-II substantially in-BARNES
Liu et al., 1991b) via activation of its G-protein coupled
receptors. Intravenous infusion of A-II substantially in-
creases pulmonary arterial and venous pressure and BARNES AND
Liu et al., 1991b) via activation of its G-protein coupled att
receptors. Intravenous infusion of A-II substantially in-
creases pulmonary arterial and venous pressure and not
decreases pulmonary blood flow volu Liu et al., 1991b) via activation of its G-protein coupled receptors. Intravenous infusion of A-II substantially increases pulmonary arterial and venous pressure and decreases pulmonary blood flow volume, indicating va-soc Liu et al., 1991b) via activation of its G-protein coupled
receptors. Intravenous infusion of A-II substantially in-
creases pulmonary arterial and venous pressure and
decreases pulmonary blood flow volume, indicating va-
 receptors. Intravenous infusion of A-II substantially increases pulmonary arterial and venous pressure and indecreases pulmonary blood flow volume, indicating vasoconstriction (Oakley et al., 1962). Endogenous A-II seems t creases pulmonary arterial and venous pressure and not decreases pulmonary blood flow volume, indicating vasoconstriction (Oakley et al., 1962). Endogenous A-II et seems to be important in the regulation of pulmonary all c decreases pulmonary blood flow volume, indicating vasoconstriction (Oakley et al., 1962). Endogenous A-II seems to be important in the regulation of pulmonary circulation (Goll et al., 1986). A-II has been proposed as a me soconstriction (Oakley et al., 1962). Endogenous A-II
seems to be important in the regulation of pulmonary
circulation (Goll et al., 1986). A-II has been proposed as
a mediator of hypoxic pulmonary vasoconstriction
(Berkov seems to be important in the regulation of pulmonary al., circulation (Goll et al., 1986). A-II has been proposed as vase a mediator of hypoxic pulmonary vasoconstriction where (Berkov, 1974), but this was refuted (McMurt a mediator of hypoxic pulmonary vasoconstriction (Berkov, 1974), but this was refuted (McMurtry, 1984).
Endogenous production of A-II is likely to be reduced in hypoxia, inasmuch as hypoxia inhibits angiotensin-con-
vertin a mediator of hypoxic pulmonary vasoconstriction w

(Berkov, 1974), but this was refuted (McMurtry, 1984). d

Endogenous production of A-II is likely to be reduced in

hypoxia, inasmuch as hypoxia inhibits angiotensin-con hypoxia, inasmuch as hypoxia inhibits angiotensin-converting enzyme (Jin et al., 1987). Exogenous A-II has been reported to prevent hypoxic pulmonary hypertension and associated vascular changes and to inhibit acute HPV in Endogenous production of A-II is likely to be reduced in
hypoxia, inasmuch as hypoxia inhibits angiotensin-con-
verting enzyme (Jin et al., 1987). Exogenous A-II has
been reported to prevent hypoxic pulmonary hyperten-
sio hypoxia, inasmuch as hypoxia inhibits angiotensi
verting enzyme (Jin et al., 1987). Exogenous A-
been reported to prevent hypoxic pulmonary hyp
sion and associated vascular changes and to i
acute HPV in the rat (Rabinovitc *2. Free A. A. Howevert Hypoxic pulmonary hyperten-*
2. King the prevent hypoxic pulmonary hyperten-
2. Kinins. BK and lysyl-BK (kallidin) are peptides
2. Kinins. BK and lysyl-BK (kallidin) are peptides
2. Kinins.

been reported to prevent hypoxic pulmonary hype
sion and associated vascular changes and to in
acute HPV in the rat (Rabinovitch et al., 1988).
2. *Kinins*. BK and lysyl-BK (kallidin) are pep
synthesized de novo from highsion and associated vascular changes and to inhibit
acute HPV in the rat (Rabinovitch et al., 1988). thes
2. Kinins. BK and lysyl-BK (kallidin) are peptides
synthesized de novo from high- and low-molecular-
weight kininog acute HPV in the rat (Rabinovitch et al., 1988).

2. *Kinins*. BK and lysyl-BK (kallidin) are peptides Net

synthesized de novo from high- and low-molecular-

weight kininogen precursors that act via activation of B₂ s 2. Kinins. BK and lysyl-BK (kallidin) are peptides
synthesized de novo from high- and low-molecular-
weight kininogen precursors that act via activation of B_2
(and under some circumstances B_1) receptors. BK is a
pot synthesized de novo from high- and low-molecular-
weight kininogen precursors that act via activation of B_2
(and under some circumstances B_1) receptors. BK is a
potent NO releaser in both systemic and pulmonary
vasc weight kininogen precursors that act via activation of B_2
(and under some circumstances B_1) receptors. BK is a
potent NO releaser in both systemic and pulmonary
vascular endothelial cells (Palmer et al., 1987; Ignar (and under some circumstances B_1) receptors. BK is a potent NO releaser in both systemic and pulmonary vascular endothelial cells (Palmer et al., 1987; Ignarro et al., 1987b). Depending on the species, either only B_2 potent NO releaser in both systemic and pulmonary
vascular endothelial cells (Palmer et al., 1987; Ignarro et
al., 1987b). Depending on the species, either only B₂ or
both B₁ and B₂ kinin receptors are involved this vascular endothelial cells (Palmer et al., 1987; Ignarro
al., 1987b). Depending on the species, either only B_2
both B_1 and B_2 kinin receptors are involved this is
sponse (Sung et al., 1988; Schini et al., 1990). al., 1987b). Depending on the species, either only B_2
both B_1 and B_2 kinin receptors are involved this sponse (Sung et al., 1988; Schini et al., 1990). BK also
stimulates prostacyclin release from pulmonary vasa
 both B_1 and B_2 kinin receptors are involved this response (Sung et al., 1988; Schini et al., 1990). BK also et the stimulates prostacyclin release from pulmonary vascular endothelium (Ignarro et al., 1987a). BK also sponse (Sung et al., 1988; Schini et al., 1990). BK also
stimulates prostacyclin release from pulmonary vascu-
lar endothelium (Ignarro et al., 1987a). BK also stimu-
lates afferent vagal C-fibers and thus may induce the
r stimulates prostacyclin release from pulmonary vascular endothelium (Ignarro et al., 1987a). BK also stimulates afferent vagal C-fibers and thus may induce the release of sensory neuropeptides (Kaufman et al., 1980). Altho lar endothelium (Ignarro et al., 1987a). BK also stimulates afferent vagal C-fibers and thus may induce the release of sensory neuropeptides (Kaufman et al., 1980). Although BK dilates isolated pulmonary vascular rings, i lates afferent vagal C-fibers and thus may induce the
release of sensory neuropeptides (Kaufman et al., 1980).
Although BK dilates isolated pulmonary vascular rings,
tis effects on the intact pulmonary vascular bed depend
 release of sensory neuropeptides (Kaufman et al., 1980).
Although BK dilates isolated pulmonary vascular rings,
its effects on the intact pulmonary vascular bed depend
on species and the preexisting vascular tone. Thus, BK Although BK dilates isolated pulmonary vascular rings,
its effects on the intact pulmonary vascular bed depend
on species and the preexisting vascular tone. Thus, BK
either has no effect or constricts the pulmonary vascula its effects on the intact pulmonary vascular bed depend
on species and the preexisting vascular tone. Thus, BK
either has no effect or constricts the pulmonary vascular
beds of dog, sheep, rabbit, and rat under basal condi on species and the preexisting vascular tone. Thus, BK either has no effect or constricts the pulmonary vascular
beds of dog, sheep, rabbit, and rat under basal conditions (Hauge et al., 1966; Hauge, 1968; Levine et al., either has no effect or constricts the pulmonary vascular
beds of dog, sheep, rabbit, and rat under basal conditions
(Hauge et al., 1966; Hauge, 1968; Levine et al., 1973;
Pang et al., 1982) but induces vasodilation in fet beds of dog, sheep, rabbit, and rat under basal conditions

(Hauge et al., 1966; Hauge, 1968; Levine et al., 1973;

Pang et al., 1982) but induces vasodilation in fetal lamb

(Frantz et al., 1989) or adult cat pulmonary va (Hauge et al., 1966; Hauge, 1968; Levine et al., 1973;
Pang et al., 1982) but induces vasodilation in fetal lamb
(Frantz et al., 1989) or adult cat pulmonary vascular
beds precontracted with a thromboxane analog (Lippton
e Pang et al., 1982) but induces vasodilation in fetal lamb
(Frantz et al., 1989) or adult cat pulmonary vascular
beds precontracted with a thromboxane analog (Lippton
et al., 1984). Infusion of BK has no effects on the norm (Frantz et al., 1989) or adult cat pulmonary vascul
beds precontracted with a thromboxane analog (Lippt
et al., 1984). Infusion of BK has no effects on the norm
human pulmonary vascular bed but induces a modera
fall in PPA beds precontracted with a thromboxane analog (Lippton
et al., 1984). Infusion of BK has no effects on the normal
human pulmonary vascular bed but induces a moderate
fall in PPA in patients with hypoxic pulmonary hyper-
ten human pulmonary vascular bed but induces a moderate
fall in PPA in patients with hypoxic pulmonary hyper-
tension (Bishop et al., 1965). BK reverses hypoxic pul-
monary vasoconstriction in human subjects in vivo and
in iso fall in PPA in patients with hypoxic pulmon
tension (Bishop et al., 1965). BK reverses hy
monary vasoconstriction in human subjects i
in isolated perfused rat lungs, presumably by
NO (Segel et al., 1970; Archer et al., 198 nsion (Bishop et al., 1965). BK reverses hypoxic puonary vasoconstriction in human subjects in vivo are isolated perfused rat lungs, presumably by release O (Segel et al., 1970; Archer et al., 1989).
3. *Vasopressin*. AV monary vasoconstriction in human subjects in vivo and
in isolated perfused rat lungs, presumably by release of
natural SNO (Segel et al., 1970; Archer et al., 1989).
and 3. Vasopressin. AVP is a circulating neurohormone is

in isolated perfused rat lungs, presumably by release of $\frac{10}{100}$ NO (Segel et al., 1970; Archer et al., 1989).
3. Vasopressin. AVP is a circulating neurohormone in and a potent systemic vasoconstrictor. Exogenous AVP NO (Segel et al., 1970; Archer et al., 1989).

3. Vasopressin. AVP is a circulating neurohormone

and a potent systemic vasoconstrictor. Exogenous AVP

is largely ineffective in isolated pulmonary artery rings

(Chand and 3. Vasopressin. AVP is a circulating neurohormone
and a potent systemic vasoconstrictor. Exogenous AVP
is largely ineffective in isolated pulmonary artery rings
(Chand and Altura, 1980; Ignarro et al., 1987a). Under
restin and a potent systemic vasoconstrictor. Exogenous A
is largely ineffective in isolated pulmonary artery rin
(Chand and Altura, 1980; Ignarro et al., 1987a). Und
resting conditions, AVP causes either vasoconstricti
or a mode is largely ineffective in isolated pulmonary artery rings
(Chand and Altura, 1980; Ignarro et al., 1987a). Under
resting conditions, AVP causes either vasoconstriction
or a moderate vasodilator response in pulmonary vascu-(Chand and Altura, 1980; Ignarro et al., 1987a). Under
resting conditions, AVP causes either vasoconstriction 198
or a moderate vasodilator response in pulmonary vascu-
pre
lar beds (Nyhan et al., 1986, 1987; Walker et al resting conditions, AVP causes either vasoconstriction 1
or a moderate vasodilator response in pulmonary vascu-
lar beds (Nyhan et al., 1986, 1987; Walker et al., 1989). e
AVP induces dilation of the pulmonary vascular bed or a moderate vasodilator response in pulmonary vascular beds (Nyhan et al., 1986, 1987; Walker et al., 1989
AVP induces dilation of the pulmonary vascular be
precontracted with either vasoconstrictors or hypoxi
(Walker et lar beds (Nyhan et al., 1986, 1987; Walker et al., 1989). e
AVP induces dilation of the pulmonary vascular bed d
precontracted with either vasoconstrictors or hypoxia w
(Walker et al., 1989; Russ and Walker, 1992). The va AVP induces dilation of the pulmonary vascular bed dil
precontracted with either vasoconstrictors or hypoxia wi
(Walker et al., 1989; Russ and Walker, 1992). The vaso-
dilator response to AVP seems to be mediated via V_1 precontracted with either vasoconstrictors or hypoxia v
(Walker et al., 1989; Russ and Walker, 1992). The vaso-
dilator response to AVP seems to be mediated via V₁-
receptors and NO release, because this response is 1
b

ND LIU
attenuated by an NO synthase inhibitor in an L-arginine
reversible manner (Russ and Walker, 1992). Endoge-ND LIU
attenuated by an NO synthase inhibitor in an L-argin
reversible manner (Russ and Walker, 1992). Endo
nous AVP is unlikely to be important in the regulat ND LIU
attenuated by an NO synthase inhibitor in an L-arginine
reversible manner (Russ and Walker, 1992). Endoge-
nous AVP is unlikely to be important in the regulation
and/or modulation of pulmonary vascular tone (Walker attenuated by an NO synthase inhibitor in an L-arginine
reversible manner (Russ and Walker, 1992). Endoge-
nous AVP is unlikely to be important in the regulation
and/or modulation of pulmonary vascular tone (Walker
et al., attenuated by an NO synthase inhibitor in an L-arginine
reversible manner (Russ and Walker, 1992). Endoge-
nous AVP is unlikely to be important in the regulation
and/or modulation of pulmonary vascular tone (Walker
et al., reversible manner (Russ and Walker, 1992). Endogenous AVP is unlikely to be important in the regulation and/or modulation of pulmonary vascular tone (Walker et al., 1989), although it does delay onset of HPV (Jin et al., 1 nous AVP is unlikely to be important in the regulation
and/or modulation of pulmonary vascular tone (Walker
et al., 1989), although it does delay onset of HPV (Jin et
al., 1989). AVP suppresses DNA synthesis in cultured
va and/or modulation of pulmonary vascular tone (Walker
et al., 1989), although it does delay onset of HPV (Jin et
al., 1989). AVP suppresses DNA synthesis in cultured
vascular smooth muscle (Murase et al., 1992). However,
wh et al., 1989), although it does delay onset of HPV (Jin et al., 1989). AVP suppresses DNA synthesis in cultured vascular smooth muscle (Murase et al., 1992). However, whether chronic treatment with AVP slows down the devel al., 1989). AVP suppre-
vascular smooth muscle
whether chronic treatned
evelopment of hypox-
mains to be determined
4. Atrial natriuretic p scular smooth muscle (Murase et al., 1992). However,
hether chronic treatment with AVP slows down the
welopment of hypoxic pulmonary hypertension re-
ains to be determined.
4. Atrial natriuretic peptides. The natriuretic p

whether chronic treatment with AVP slows down the
development of hypoxic pulmonary hypertension re-
mains to be determined.
4. Atrial natriuretic peptides. The natriuretic peptide
family consists of ANP, BNP, and CNP. Huma development of hypoxic pulmonary hypertension re-
mains to be determined.
4. Atrial natriuretic peptides. The natriuretic peptide
family consists of ANP, BNP, and CNP. Human ANP is
a 28-amino-acid peptide that was original mains to be determined.
4. Atrial natriuretic peptides. The natriuretic peptide
family consists of ANP, BNP, and CNP. Human ANP is
a 28-amino-acid peptide that was originally thought to
be synthesized in the atrium and lat 4. Atrial natriuretic peptides. The natriuretic peptide
family consists of ANP, BNP, and CNP. Human ANP is
a 28-amino-acid peptide that was originally thought to
be synthesized in the atrium and later found to be syn-
thes family consists of ANP, BNP, and CNP. Human ANP is
a 28-amino-acid peptide that was originally thought to
be synthesized in the atrium and later found to be syn-
thesized in several other tissues (Gutkowska and
Nemar, 1989 a 28-amino-acid peptide that was originally thought to
be synthesized in the atrium and later found to be syn-
thesized in several other tissues (Gutkowska and
Nemar, 1989). BNP is a 32-amino-acid peptide first iso-
lated be synthesized in the atrium and later found to be synthesized in several other tissues (Gutkowska and Nemar, 1989). BNP is a 32-amino-acid peptide first isolated from porcine brain (Sudoh et al., 1988); its main source is thesized in several other tissues (Gutkowska and Nemar, 1989). BNP is a 32-amino-acid peptide first lated from porcine brain (Sudoh et al., 1988); its m
source is ventricle (Nakao et al., 1992). CNP is a vas
lar natriureti Nemar, 1989). BNP is a 32-amino-acid peptide fir
lated from porcine brain (Sudoh et al., 1988); its
source is ventricle (Nakao et al., 1992). CNP is a
lar natriuretic peptide produced from vascular en
lial cells. (Koller e ted from porcine brain (Sudoh et al., 1988); its main
urce is ventricle (Nakao et al., 1992). CNP is a vascu-
r natriuretic peptide produced from vascular endothe-
l cells. (Koller et al., 1991; Suga et al., 1992).
Natriur

source is ventricle (Nakao et al., 1992). CNP is a vascular natriuretic peptide produced from vascular endothe-
lial cells. (Koller et al., 1991; Suga et al., 1992).
Natriuretic peptides exert their action via activation
o lar natriuretic peptide produced from vascular endothe-

lial cells. (Koller et al., 1991; Suga et al., 1992).

Natriuretic peptides exert their action via activation

of specific receptors; these have been classified into lial cells. (Koller et al., 1991; Suga et al., 1992).

Natriuretic peptides exert their action via activation

of specific receptors; these have been classified into

three types according to their binding selectivity (Na Natriuretic peptides exert their action via activation
of specific receptors; these have been classified into
three types according to their binding selectivity (Nakao
et al., 1992). The rank order of ligand binding affin of specific receptors; these have been classified into
three types according to their binding selectivity (Nakao
et al., 1992). The rank order of ligand binding affinity for
the ANP-A receptor is $AND \geq BNP \geq CNP$; for the
AN three types according to their binding selectivity (Nakao
et al., 1992). The rank order of ligand binding affinity for
the ANP-A receptor is $ANP \geq BNP \geq CNP$; for the
ANP-B receptor, $CNP > ANP \geq BNP$; and for the
ANP-C receptor et al., 1992). The rank order of ligand binding affinity for
the ANP-A receptor is $ANP \geq BNP \gg CNP$; for the
ANP-B receptor, $CNP > ANP \geq BNP$; and for the
ANP-C receptor, $ANP > CNP > BNP$. Both ANP-A and
ANP-B receptors are guanylyl c the ANP-A receptor is $ANP \geq BNP \geq CNP$; for the ANP-B receptor, $CNP > ANP \geq BNP$; and for the ANP-C receptor, $ANP > CNP > BNP$. Both ANP-A and $ANP-B$ receptors are guanylyl cyclase-coupled receptors, whereas the ANP-C receptor is not ANP-B receptor, $CNP > AND \ge BNP$; and for
ANP-C receptor, $ANP > CNP > BNP$. Both ANP-A a
ANP-B receptors are guanylyl cyclase-coupled recept
whereas the ANP-C receptor is not and is thought to
a clearance receptor, which participates ANP-C receptor, $AND > CNP > BNP$. Both ANP-A and
ANP-B receptors are guanylyl cyclase-coupled receptors,
whereas the ANP-C receptor is not and is thought to be
a clearance receptor, which participates in the degrada-
tion of the ANP-B receptors are guanylyl cyclase-coupled receptors,
whereas the ANP-C receptor is not and is thought to be
a clearance receptor, which participates in the degrada-
tion of these natriuretic peptides (Nussenzveig et al. whereas the ANP-C receptor is not and is thought to be a clearance receptor, which participates in the degradation of these natriuretic peptides (Nussenzveig et al., 1990). All three receptors and their mRNAs have been loc tion of these natriuretic peptides (Nussenzveig et al., 1990). All three receptors and their mRNAs have been localized in the lung by binding and molecular biological techniques (Nakao et al., 1992). A detailed review on t tion of these natriuretic peptides (Nussenzveig et a 1990). All three receptors and their mRNAs have be localized in the lung by binding and molecular biologic techniques (Nakao et al., 1992). A detailed review on t
ANP r 1990). All three receptors and their mRNAs have been
localized in the lung by binding and molecular biological
techniques (Nakao et al., 1992). A detailed review on the
ANP receptors and their signal transduction mecha-
ni techniques (Nakao et al., 1992). A detailed review on th
ANP receptors and their signal transduction mecha
nisms was recently published (Anand-Srivastava an
Trachte, 1993).
Pulmonary vessels exhibit a high density of ANP b the
sized in several other tissues (Gutkowska and Nemar, 1988); BNP is a 32-amino-acid peptide first iso-
lated from porcine brain (Sudoh et al., 1982); CNP is a vascular natriuretic peptide produced from vascular endothe

ANP receptors and their signal transduction mechanisms was recently published (Anand-Srivastava and Trachte, 1993).

Pulmonary vessels exhibit a high density of ANP bind-

ing sites (Anand-Srivastava and Trachte, 1993). Th misms was recently published (Anand-Srivastava and
Trachte, 1993).
Pulmonary vessels exhibit a high density of ANP bind-
ing sites (Anand-Srivastava and Trachte, 1993). The
most intensively studied natriuretic peptide is A Trachte, 1993).

Pulmonary vessels exhibit a high density of ANP bind-

ing sites (Anand-Srivastava and Trachte, 1993). The

most intensively studied natriuretic peptide is ANP,

which has a wide range of biological effect Pulmonary vessels exhibit a high density of ANP bind-
ing sites (Anand-Srivastava and Trachte, 1993). The
most intensively studied natriuretic peptide is ANP,
which has a wide range of biological effects including
natriure ing sites (Anand-Srivastava and Trachte, 1993). The
most intensively studied natriuretic peptide is ANP,
which has a wide range of biological effects including
natriuresis, vasodilation, inhibition of renin secretion,
and most intensively studied natriuretic peptide is ANP,
which has a wide range of biological effects including
natriuresis, vasodilation, inhibition of renin secretion,
and aldosterone secretion (Inagami, 1989). ANP relaxes
i natriuresis, vasodilation, inhibition of renin secreti
and aldosterone secretion (Inagami, 1989). ANP rela
isolated pulmonary vessel rings of several species,
cluding human (Jansen et al., 1987; Lindberg :
Andersson, 1988) and aldosterone secretion (Inagami, 1989). ANP relaxes
isolated pulmonary vessel rings of several species, in-
cluding human (Jansen et al., 1987; Lindberg and
Andersson, 1988). ANP also causes pulmonary vasodila-
tion in tion in the perfused pulmonary vascular bed (Jin et al., 1988; Cigarini, 1989) and reduces pulmonary vascular pressure and resistance in patients with COPD (Adnot cluding human (Jansen et al., 1987; Lindberg and
Andersson, 1988). ANP also causes pulmonary vasodila-
tion in the perfused pulmonary vascular bed (Jin et al.,
1988; Cigarini, 1989) and reduces pulmonary vascular
pressure Andersson, 1988). ANP also causes pulmonary vasodilation in the perfused pulmonary vascular bed (Jin et al., 1989; Cigarini, 1989) and reduces pulmonary vascular pressure and resistance in patients with COPD (Adnot et al., 1988; Cigarini, 1989) and reduces pulmonary veressure and resistance in patients with COPD
et al., 1989). ANP is an endothelium-independer
dilator (Jansen et al., 1987), although it may i
with the endothelium. ANP inhibits pressure and resistance in patients with COPD (Adiet al., 1989). ANP is an endothelium-independent vadilator (Jansen et al., 1987), although it may interwith the endothelium. ANP inhibits endothelium-meated vasorelaxation, dilator (Jansen et al., 1987), although it may interact
with the endothelium. ANP inhibits endothelium-medi-
ated vasorelaxation, presumably via a feedback mecha-
nism caused by an increase of cGMP (Hogan et al.,
1989). Co with the endothelium. ANP inhibits endothelium-mediated vasorelaxation, presumably via a feedback mechanism caused by an increase of cGMP (Hogan et al., 1989). Conversely, NO-releasing agents inhibit endothe-
lin-induced A ated vasorelaxation, presumably via a feedback mecha-

PHARMACOLOGICAL REVIEWS

REGULATION **OF PULMONARY** VASCULAR TONE ⁹⁷

REGULATION OF PULMON
ANP modulates HPV and the development of hypoxic
pulmonary hypertension (Adnot et al., 1988). Acute al-
veolar hypoxia causes the release of ANP (Baertschchi REGULATION OF PUL

ANP modulates HPV and the development of hypoxic

pulmonary hypertension (Adnot et al., 1988). Acute al

veolar hypoxia causes the release of ANP (Baertschch

and Teague, 1989). Circulating ANP level is ANP modulates HPV and the development of hypoxic tors
pulmonary hypertension (Adnot et al., 1988). Acute al-
weolar hypoxia causes the release of ANP (Baertschchi cula
and Teague, 1989). Circulating ANP level is increased ANP modulates HPV and the development of hypoulmonary hypertension (Adnot et al., 1988). Acute
veolar hypoxia causes the release of ANP (Baertscl
and Teague, 1989). Circulating ANP level is increase
animal models of chroni pulmonary hypertension (Adnot et al., 1988). Acute alveolar hypoxia causes the release of ANP (Baertschchi and Teague, 1989). Circulating ANP level is increased in animal models of chronic hypoxic pulmonary hypertension an veolar hypoxia causes the release of ANP (Baertschchi
and Teague, 1989). Circulating ANP level is increased in
animal models of chronic hypoxic pulmonary hyperten-
sion and in patients with pulmonary hypertension
(McKenzie and Teague, 1989). Circulating ANP level is increased in varianal models of chronic hypoxic pulmonary hypertension
sion and in patients with pulmonary hypertension pulmonaries of Ancel McKenzie et al., 1986; Adnot et al., animal models of chronic hypoxic pulmonary hypertension and in patients with pulmonary hypertension
(McKenzie et al., 1986; Adnot et al., 1987; Winter et al.,
1989). Chronic infusion of ANP reduces the thickness of
small p sion and in patients with pulmonary hypertension puln
(McKenzie et al., 1986; Adnot et al., 1987; Winter et al., pare
1989). Chronic infusion of ANP reduces the thickness of et a
small pulmonary vascular wall in rats expos (McKenzie et al., 1986; Adnot et al., 1987; Winter et al., par
1989). Chronic infusion of ANP reduces the thickness of et a
small pulmonary vascular wall in rats exposed to hy-
nist
poxia (Zhao et al., 1991). Elevation of small pulmonary vascular wall in rats exposed to hypoxia (Zhao et al., 1991). Elevation of endogenous ANP levels by inhibition of neutral endopeptidase cause a small pulmonary vascular wall in rats exposed to hy-
poxia (Zhao et al., 1991). Elevation of endogenous ANP Depending on vasomotor tone, ET isopeptides can
levels by inhibition of neutral endopeptidase cause a cause either poxia (Zhao et al., 1991). Elevation of endogenous ANP
levels by inhibition of neutral endopeptidase cause a
significant reduction in the hypoxia-induced pulmonary
vascular remodelling and right ventricular hypertrophy
s (levels by inhibition of neutral endopeptidase cause a
significant reduction in the hypoxia-induced pulmonary
vascular remodelling and right ventricular hypertrophy
(Stewart et al., 1992). Furthermore, treatment of rats
wit vascular remodelling and right ventricular hypertrophy (Stewart et al., 1992). Furthermore, treatment of rats with a monoclonal antibody to ANP before hypoxia exposure aggravates pulmonary hypertension and right vascular remodelling and right ventricular hypertrop
(Stewart et al., 1992). Furthermore, treatment of rivith a monoclonal antibody to ANP before hypoxia
(posure aggravates pulmonary hypertension and rig
ventricular hypert (Stewart et al., 1992). Furthermore, treatment of rats 19
with a monoclonal antibody to ANP before hypoxia ex-
posure aggravates pulmonary hypertension and right In
ventricular hypertrophy (Raffestin et al., 1992). Trans-
 with a monoclonal antibody to ANP before hypoxia ex-
posure aggravates pulmonary hypertension and right
ventricular hypertrophy (Raffestin et al., 1992). Trans-
genic mice that carry a fusion gene composed of the
transthyr posure aggravates pulmonary hypertension and right I
ventricular hypertrophy (Raffestin et al., 1992). Trans-
genic mice that carry a fusion gene composed of the n
transthyretin promoter and the mouse ANP structural a
gene ventricular hypertrophy (Raffestin et al., 1992). Trans-
genic mice that carry a fusion gene composed of the
transthyretin promoter and the mouse ANP structural
gene (transthyretin-ANP mice) have higher plasma
ANP levels a transthyretin promoter and the mouse ANP structural
gene (transthyretin-ANP mice) have higher plasma
ANP levels and lower pulmonary and right ventricular
systolic pressures. These mice have less right ventricu-
lar hypertr gene (transthyretin-ANP mice) have higher plasma
ANP levels and lower pulmonary and right ventricular
systolic pressures. These mice have less right ventricu-
lar hypertrophy and pulmonary arteriolar musculariza-
tion comp gene (transthyretin-ANP mice) have higher plasma
ANP levels and lower pulmonary and right ventricular
systolic pressures. These mice have less right ventricu-
lar hypertrophy and pulmonary arteriolar musculariza-
tion comp ANP levels and lower pulmonary and right ventricular
systolic pressures. These mice have less right ventricu-
lar hypertrophy and pulmonary arteriolar musculariza-
tion compared with nontransgenic control animals after
exp systolic pressures. These mice have less right ventricular hypertrophy and pulmonary arteriolar muscularization compared with nontransgenic control animals after exposure to hypoxia for 3 weeks (Klinger et al., 1993). ANP lar hypertrophy and pulmonary arteriolar musculariza-
tion compared with nontransgenic control animals after
exposure to hypoxia for 3 weeks (Klinger et al., 1993).
ANP also inhibits the proliferation of cultured vascular
 tion compared with nontransgenic control animals after 199
exposure to hypoxia for 3 weeks (Klinger et al., 1993). 199
ANP also inhibits the proliferation of cultured vascular al.,
smooth muscle cells (Abell et al., 1989; exposure to hypoxia for 3 weeks (Klinger et al., 199
ANP also inhibits the proliferation of cultured vascu
smooth muscle cells (Abell et al., 1989; Itoh et al., 199
These results suggest that ANP can participate ir
negativ ANP also inhibits the proliferation of cu
smooth muscle cells (Abell et al., 1989; It
These results suggest that ANP can p
negative feedback mechanism to slow do
ment of hypoxic pulmonary hypertension
ANP may be involved i hooth muscle cells (Abell et al., 1989; Itoh et al., 1990).
hese results suggest that ANP can participate in a
gative feedback mechanism to slow down the develop-
ent of hypoxic pulmonary hypertension.
ANP may be involved These results suggest that ANP can participate in a fungative feedback mechanism to slow down the development of hypoxic pulmonary hypertension.
ANP may be involved in other pulmonary vascular Huiseases. There is a good co

negative feedback mechanism to slow down the development of hypoxic pulmonary hypertension.
ANP may be involved in other pulmonary vascular diseases. There is a good correlation during exercise between plasma ANP concentra ment of hypoxic pulmonary hypertension. mo

ANP may be involved in other pulmonary vascular ET

diseases. There is a good correlation during exercise me

between plasma ANP concentration and PPA in patients cep

after coro ANP may be involved in other pulmonary vascular
diseases. There is a good correlation during exercise
between plasma ANP concentration and PPA in patients
after coronary angioplasty (Scholz et al., 1990). High
plasma ANP l diseases. There is a good correlation during exercise
between plasma ANP concentration and PPA in patients
after coronary angioplasty (Scholz et al., 1990). High
plasma ANP levels have also been observed in patients
with h between plasma ANP concentration and PPA in patients
after coronary angioplasty (Scholz et al., 1990). High
plasma ANP levels have also been observed in patients
with high-altitude edema (Bartsch et al., 1988). In nor-
mal after coronary angioplasty (Scholz et al., 1990
plasma ANP levels have also been observed in p
with high-altitude edema (Bartsch et al., 1988).
mal mountaineers exposed to hypoxia, ANP impro
monary gas exchange (Westendorp asma ANP levels have also been observed in patie
ith high-altitude edema (Bartsch et al., 1988). In n
al mountaineers exposed to hypoxia, ANP improves p
onary gas exchange (Westendorp et al., 1993).
5. *Endothelins*. End

with high-altitude edema (Bartsch et al., 1988). In nor-
mal mountaineers exposed to hypoxia, ANP improves pul-
monary gas exchange (Westendorp et al., 1993). elu
5. *Endothelins*. Endothelins are a family of 21-amino-
ce mal mountaineers exposed to hypoxia, ANP improves pul-
monary gas exchange (Westendorp et al., 1993).
5. *Endothelins*. Endothelins are a family of 21-amino-
acid isopeptides named ET-1, ET-2, and ET-3, which are
encoded b monary gas exchange (Westendorp et al., 1993).
5. Endothelins. Endothelins are a family of 21-amino-
acid isopeptides named ET-1, ET-2, and ET-3, which are
encoded by three distinct ET genes (Inoue et al., 1989).
The synth 5. *Endothelins*. Endothelins are a family of 21-amino-
acid isopeptides named ET-1, ET-2, and ET-3, which are
encoded by three distinct ET genes (Inoue et al., 1989).
The synthesis and vascular effects of these isopeptide acid isopeptides named ET-1, ET-2, and ET-3, which a
encoded by three distinct ET genes (Inoue et al., 198
The synthesis and vascular effects of these isopeptid
have been reviewed elsewhere (Haynes and Wel
1993). Endotheli encoded by three distinct ET genes (Inoue et al., 1989)
The synthesis and vascular effects of these isopeptide
have been reviewed elsewhere (Haynes and Webl
1993). Endothelins have widespread effects on pulmo
nary function The synthesis and vascular effects of these isopeptides
have been reviewed elsewhere (Haynes and Webb, pu
1993). Endothelins have widespread effects on pulmo-
hary function, including the pulmonary circulation (Bar-
nes, 1 have been reviewed elsewhere (Haynes and Webb, 1993). Endothelins have widespread effects on pulmonary function, including the pulmonary circulation (Barnes, 1994). Immunocytochemistry and molecular biology studies have de 1993). Endothelins have widespread effects on pulmonary function, including the pulmonary circulation (Barnes, 1994). Immunocytochemistry and molecular biology studies have demonstrated that ET-1 is the major isoform expre nary function, including the pulmonary circulation (Barnes, 1994). Immunocytochemistry and molecular biology studies have demonstrated that ET-1 is the major isoform expressed and secreted in endothelial cells, although ET nes, 1994). Immunocytochemistry and molecular biology
studies have demonstrated that ET-1 is the major iso-
form expressed and secreted in endothelial cells, al-
though ET-2 immunoreactivity has been detected in en-
dothel studies have demonstrated that ET-1 is the major iso-
form expressed and secreted in endothelial cells, al-
though ET-2 immunoreactivity has been detected in en-
dothelial cells (Howard et al., 1992; Haynes and Webb,
1993) form expressed and secreted in endothelial cells, although ET-2 immunoreactivity has been detected in endothelial cells (Howard et al., 1992; Haynes and Webb, 1993). ET-3 immunoreactivity or mRNA cannot be detected in endo though ET-4
dothelial ce
1993). ET-3
tected in en
al., 1992).
Endotheli 1993). ET-3 immunoreactivity or mRNA cannot be detected in endothelial cells (Bloch et al., 1989; Howard et al., 1992).
Endothelin effects are mediated through activation of specific receptors designated as ET_A - (ET-1 =

tected in endothelial cells (Bloch et al., 1989; Howard et praid, 1992).

Endothelin effects are mediated through activation of interpretic receptors designated as ET_A - ($ET-1 = ET-2 \ge$ tion ET-3) and ET_B -receptors ($ET-1 = ET$ specific receptors designated as ET_A - (ET-1 = ET-2 \ge ET-3), which have been cloned, and possibly also through ET_C-recep-

REGULATION OF PULMONARY VASCULAR TONE
ANP modulates HPV and the development of hypoxic tors (ET-3 > ET-1 = ET-2). Molecular biology and bind-
pulmonary hypertension (Adnot et al., 1988). Acute al- ing data indicate that ET 97
tors (ET-3 > ET-1 = ET-2). Molecular biology and bind-
ing data indicate that ET-receptors on pulmonary vascular smooth muscle cells are of the ET_A type and on FOR VASCULAR TONE 97
tors (ET-3 > ET-1 = ET-2). Molecular biology and bind-
ing data indicate that ET-receptors on pulmonary vas-
cular smooth muscle cells are of the ET_A type and on
vascular endothelial cells are of th tors (ET-3 > ET-1 = ET-2). Molecular biology and bind-
ing data indicate that ET-receptors on pulmonary vas-
cular smooth muscle cells are of the ET_A type and on
vascular endothelial cells are of the ET_B type (Hosoda tors (ET-3 > ET-1 = ET-2). Molecular biology and bind-
ing data indicate that ET-receptors on pulmonary vas-
cular smooth muscle cells are of the ET_A type and on
vascular endothelial cells are of the ET_B type (Hosoda ing data indicate that ET-receptors on pulmonary vas-
cular smooth muscle cells are of the ET_A type and on
vascular endothelial cells are of the ET_B type (Hosoda et
al., 1991; Ogawa et al., 1991). The exception is rabbi cular smooth muscle cells are of the ET_A type and on vascular endothelial cells are of the ET_B type (Hosoda et al., 1991; Ogawa et al., 1991). The exception is rabbit pulmonary artery, where ET_A - and ET_B -receptors app vascular endothelial cells are of the ET_B type (Hosoda
al., 1991; Ogawa et al., 1991). The exception is rab
pulmonary artery, where ET_{A^-} and ET_B -receptors a
parently coexist on vascular smooth muscle (LaDouce
et al., al., 1991; Ogawa et al., 1991). The exception is rabbi
pulmonary artery, where ET_A - and ET_B -receptors ap
parently coexist on vascular smooth muscle (LaDouceu
et al., 1993). Several ET_A -receptor agonists and antago
nist lmonary artery, where ET_A - and ET_B -receptors ap-
rently coexist on vascular smooth muscle (LaDouceur
al., 1993). Several ET_A -receptor agonists and antago-
sts have been developed (Haynes and Webb, 1993).
Depending on v

parently coexist on vascular smooth muscle (LaDouceu
et al., 1993). Several ET_A -receptor agonists and antagonists have been developed (Haynes and Webb, 1993).
Depending on vasomotor tone, ET isopeptides ca
cause either et al., 1993). Several ET_A -receptor agonists and antagonists have been developed (Haynes and Webb, 1993).
Depending on vasomotor tone, ET isopeptides cancause either pulmonary vasoconstriction or vasodilation.
Under bas nists have been developed (Haynes and Webb, 1993).
Depending on vasomotor tone, ET isopeptides can
cause either pulmonary vasoconstriction or vasodilation.
Under baseline conditions, ETs (ET-1 and ET-2) con-
strict pulmona Depending on vasomotor tone, ET isopeptides can
cause either pulmonary vasoconstriction or vasodilation.
Under baseline conditions, ETs (ET-1 and ET-2) con-
strict pulmonary vascular rings of pig (Sudjarwo et al.,
1993), s cause either pulmonary vasoconstriction or vasodilation.
Under baseline conditions, ETs (ET-1 and ET-2) constrict pulmonary vascular rings of pig (Sudjarwo et al., 1993), sheep (Toga et al., 1992b), guinea pig (Hay et al., strict pulmonary vascular rings of pig (Sudjarwo et al., 1993), sheep (Toga et al., 1992b), guinea pig (Hay et al., 1993).
1993), and human (McKay et al., 1991; Hay et al., 1993).
In perfused pulmonary vascular beds under ditions, ETs (ET-1 and ET-3) increase PPA and/or pul-
monary vascular resistance in several species (Toga et
al., 1991; Mann et al., 1991; Horgan et al., 1991; Crawley 1993), and human (McKay et al., 1991; Hay et al., 1993).
In perfused pulmonary vascular beds under basal conditions, ETs (ET-1 and ET-3) increase PPA and/or pulmonary vascular resistance in several species (Toga et al., 19 In perfused pulmonary vascular beds under basal conditions, ETs (ET-1 and ET-3) increase PPA and/or pulmonary vascular resistance in several species (Toga et al., 1991; Mann et al., 1991; Horgan et al., 1991; Crawley et al ditions, ETs (ET-1 and ET-3) increase PPA and/or pul-
monary vascular resistance in several species (Toga et
al., 1991; Mann et al., 1991; Horgan et al., 1991; Crawley
et al., 1992a). ET-1 is more potent than ET-2 and ET-3 monary vascular resistance in several species (Toga et al., 1991; Mann et al., 1991; Horgan et al., 1991; Crawley et al., 1992a). ET-1 is more potent than ET-2 and ET-3 in the contractile response (McKay et al., 1991; Craw al., 1991; Mann et al., 1991; Horgan et al., 1991; Crawley
et al., 1992a). ET-1 is more potent than ET-2 and ET-3
in the contractile response (McKay et al., 1991; Crawley
et al., 1992a). When vascular tone is elevated eith et al., 1992a). ET-1 is more potent than ET-2 and ET-3
in the contractile response (McKay et al., 1991; Crawley
et al., 1992a). When vascular tone is elevated either
naturally (as in the fetus) (Perreault and de Marte,
199 in the contractile response (McKay et al., 1991; Crawley
et al., 1992a). When vascular tone is elevated either
naturally (as in the fetus) (Perreault and de Marte,
1991; Wong et al., 1993) or artificially (Hasunuma et al., et al., 1992a). When vascular tone is elevated eith
naturally (as in the fetus) (Perreault and de Mar
1991; Wong et al., 1993) or artificially (Hasunuma et a
1990; Toga et al., 1991; Lippton et al., 1991; Crawley
al., 1992 naturally (as in the fetus) (Perreault and de Marte,
1991; Wong et al., 1993) or artificially (Hasunuma et al.,
1990; Toga et al., 1991; Lippton et al., 1991; Crawley et
al., 1992a), these peptides induce a dose-related pu 1991; Wong et al., 1993) or artificially (Hasunuma et al., 1990; Toga et al., 1991; Lippton et al., 1991; Crawley et al., 1992a), these peptides induce a dose-related pulmonary vasodilation. Isolated pulmonary vascular rin 1990; Toga et al., 1991; Lippton et al., 1991; Crawley et al., 1992a), these peptides induce a dose-related pulmonary vascular rings from adult sheep seem to be more sensitive than those from fetal and neonatal sheep, and al., 1992a), these peptides induce a dose-related pulmo-
nary vasodilation. Isolated pulmonary vascular rings
from adult sheep seem to be more sensitive than those
from fetal and neonatal sheep, and vein seems to be
more s mary vasodilation. Isolated pulmonary vascular rings
from adult sheep seem to be more sensitive than those
from fetal and neonatal sheep, and vein seems to be
more sensitive than artery in the contractile response to
ET-1 from adult sheep seem to be more sensitive than the
from fetal and neonatal sheep, and vein seems to
more sensitive than artery in the contractile response
ET-1 (Toga et al., 1992b). The contractile response
mediated by from fetal and neonatal sheep, and vein seems to be
more sensitive than artery in the contractile response to
ET-1 (Toga et al., 1992b). The contractile response is
mediated by ET_A -receptors, and relaxation by ET_B -re-
c more sensitive than artery in the contractile response to ET-1 (Toga et al., 1992b). The contractile response is mediated by ET_A -receptors, and relaxation by ET_B -receptors (Hay et al., 1993; Sudjarwo et al., 1993). An a ET-1 (Toga et al., 1992b). The contractile response is
mediated by ET_A -receptors, and relaxation by ET_B -receptors (Hay et al., 1993; Sudjarwo et al., 1993). An
atypical ET_B -receptor-mediated contraction has been re-
po mediated by ET_A-receptors, and relaxation by ET_B-receptors (Hay et al., 1993; Sudjarwo et al., 1993). An atypical ET_B-receptor-mediated contraction has been reported in swine pulmonary veins (Sudjarwo et al., 1993). ceptors (Hay et al., 1993; Sudjarwo et al., 1993). An
atypical ET_B -receptor-mediated contraction has been re-
ported in swine pulmonary veins (Sudjarwo et al., 1993).
The signal transduction mechanism between receptor
ac atypical ET_B-receptor-mediated contraction has been r
ported in swine pulmonary veins (Sudjarwo et al., 1993)
The signal transduction mechanism between recept
activation and contractile response to ETs remains to l
eluc ported in swine pulmonary veins (Sudjarwo et al., 1993).
The signal transduction mechanism between receptor
activation and contractile response to ETs remains to be
elucidated but may involve mobilization of both extra-
ce The signal transduction mechanism between receptor
activation and contractile response to ETs remains to be
elucidated but may involve mobilization of both extra-
cellular and intracellular Ca, activation of protein ki-
na activation and contractile response to ETs remains to belucidated but may involve mobilization of both extracellular and intracellular Ca, activation of protein knase C (Mann et al., 1991), and inhibition of adenylat cycla elucidated but may involve mobilization of both extra-
cellular and intracellular Ca, activation of protein ki-
nase C (Mann et al., 1991), and inhibition of adenylate
cyclase (Vogelsang et al., 1994). Cyclo-oxygenase prod cellular and intracellular Ca, activation of protein kinemate C (Mann et al., 1991), and inhibition of adenylate cyclase (Vogelsang et al., 1994). Cyclo-oxygenase products may also contribute to ET-1-induced contraction in nase C (Mann et al., 1991), and inhibition of adenylate cyclase (Vogelsang et al., 1994). Cyclo-oxygenase products may also contribute to ET-1-induced contraction in pulmonary veins (Toga et al., 1991; Horgan et al., 1991) cyclase (Vogelsang et al., 1994). Cyclo-oxygenase products may also contribute to ET-1-induced contraction in
pulmonary veins (Toga et al., 1991; Horgan et al., 1991).
Activation of ATP-sensitive K⁺ channels and release ucts may also contribute to ET-1-induced contraction
pulmonary veins (Toga et al., 1991; Horgan et al., 199:
Activation of ATP-sensitive K⁺ channels and release
NO are involved in mediating the relaxant response
ETs (Has pulmonary veins (Toga et al., 1991; Horgan
Activation of ATP-sensitive K⁺ channels and
NO are involved in mediating the relaxar
ETs (Hasunuma et al., 1990; Lippton et al.
ley et al., 1992a; Tod and Cassin, 1992).
Under i Activation of ATP-sensitive K^+ channels and release of
NO are involved in mediating the relaxant response to
ETs (Hasunuma et al., 1990; Lippton et al., 1991; Craw-
ley et al., 1992a; Tod and Cassin, 1992).
Under in vi NO are involved in mediating the relaxant response to ETs (Hasunuma et al., 1990; Lippton et al., 1991; Craw-
ley et al., 1992a; Tod and Cassin, 1992).
Under in vivo conditions, ET may affect pulmonary
vascular tone via ot

dothelial cells (Howard et al., 1992; Haynes and Webb, ported that ET-1 enhances adrenergic contraction 1993). ET-3 immunoreactivity or mRNA cannot be depositionally but inhibits norepinephrine release tected in endotheli ETs (Hasunuma et al., 1990; Lippton et al., 1991; Craw-
ley et al., 1992a; Tod and Cassin, 1992).
Under in vivo conditions, ET may affect pulmonary
vascular tone via other mechanisms. It has been re-
ported that ET-1 enhan ley et al., 1992a; Tod and Cassin, 1992).
Under in vivo conditions, ET may affect pulmonary
vascular tone via other mechanisms. It has been re-
ported that ET-1 enhances adrenergic contraction
postjunctionally but inhibits Under in vivo conditions, ET may affect pulmonary
vascular tone via other mechanisms. It has been re-
ported that ET-1 enhances adrenergic contraction
postjunctionally but inhibits norepinephrine release
prejunctionally (W vascular tone via other mechanisms. It has been re-
ported that ET-1 enhances adrenergic contraction
postjunctionally but inhibits norepinephrine release
prejunctionally (Wiklund et al., 1989b). ET-1 stimulates
the convers postjunctionally but inhibits norepinephrine rele
prejunctionally (Wiklund et al., 1989b). ET-1 stimula
the conversion of A-I to A-II, suggesting that ET-1 in
fluence pulmonary vascular tone through the generation of A-II ejunctionally (Wiklund et al., 1989b). ET-1 stimulat
e conversion of A-I to A-II, suggesting that ET-1 mi
fluence pulmonary vascular tone through the gener
m of A-II (Kawaguchi et al., 1990).
The role of ETs in various pat the conversion of A-I to A-II, suggesting that ET-1 may
influence pulmonary vascular tone through the genera-
tion of A-II (Kawaguchi et al., 1990).
The role of ETs in various pathophysiological condi-
tions have been inte

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end of the state of the state of the Barnes and Liu and the Samuel State of the Barnes and Liu and the Samuel S
Barnes and Liu and Samuel State of the Samuel State of the Samuel State of the Samuel State of the Samuel Stat

reverse HPV (Crawley et al., 1992a; Hasunuma et a!., BARNES AND LIT
1990). Rats exposed to chronic hypoxia for 3 weeks show um-de
1990). Rats exposed to chronic hypoxia for 3 weeks show um-de
an impaired relaxant response to ET-1 (Eddahibi et al., indep BARNES A

reverse HPV (Crawley et al., 1992a; Hasunuma et al.,

1990). Rats exposed to chronic hypoxia for 3 weeks show

an impaired relaxant response to ET-1 (Eddahibi et al.,

1991). However, ET-1 is unlikely to be an im reverse HPV (Crawley et al., 1992a; Hasunuma et al., 1990). Rats exposed to chronic hypoxia for 3 weeks show
an impaired relaxant response to ET-1 (Eddahibi et al., 1991). However, ET-1 is unlikely to be an important
modul reverse HPV (Crawley et al., 1992a; Hasunuma et a
1990). Rats exposed to chronic hypoxia for 3 weeks sho
an impaired relaxant response to ET-1 (Eddahibi et a
1991). However, ET-1 is unlikely to be an importa
modulator of H 1990). Rats exposed to chronic hypoxia for 3 weeks show
an impaired relaxant response to ET-1 (Eddahibi et al., i
1991). However, ET-1 is unlikely to be an important
modulator of HPV but rather a contributor to the develan impaired relaxant response to ET-1 (Eddahibi et al., in
1991). However, ET-1 is unlikely to be an important p
modulator of HPV but rather a contributor to the devel-
opment of pulmonary hypertension. Although hypoxia e
 modulator of HPV but rather a contributor to the development of pulmonary hypertension. Although hypoxia
has been reported to either have no effect or to reduce
ET-1 secretion from cultured porcine or bovine pulmoopment of pulmonary hypertension. Although hypoxia has been reported to either have no effect or to reduce ET-1 secretion from cultured porcine or bovine pulmonary vascular endothelial cells (Wiebke et al., 1992; Hassoun et al., 1992), human vascular endothelial cells cult has been reported to either have no effect or to reduce vas
ET-1 secretion from cultured porcine or bovine pulmo-
nary vascular endothelial cells (Wiebke et al., 1992; Has-
na soun et al., 1992), human vascular endothelial ET-1 secretion from cultured porcine or bovine pulmo-
nary vascular endothelial cells (Wiebke et al., 1992; Has-
soun et al., 1992), human vascular endothelial cells cul-
tured in hypoxic conditions secrete eight-fold mor nary vascular endothelial cells (Wiebke et al., 1992; Has-
soun et al., 1992), human vascular endothelial cells cul-
with no labelling of endothelial cells (Carstairs and Bar-
tured in hypoxic conditions secrete eight-fol compared with ambient oxygen conditions, and there is tured in hypoxic conditions secrete eight-fold more ET-1 network compared with ambient oxygen conditions, and there is non increase in prepro-ET-1 mRNA expression within 1 h p of hypoxia, which is reversible when returned compared with ambient oxygen conditions, and there is
an increase in prepro-ET-1 mRNA expression within 1 h
of hypoxia, which is reversible when returned to $21\% O_2$ I
(Kourembanas et al., 1991). Rats exposed to hypoxia an increase in prepro-ET-1 mRNA expression within 1 h pu
of hypoxia, which is reversible when returned to $21\% O_2$ PA
(Kourembanas et al., 1991). Rats exposed to hypoxia for lov
2 days show a three-fold increase in plasm of hypoxia, which is reversible when returned to $21\% O_2$ PA(

(Kourembanas et al., 1991). Rats exposed to hypoxia for low

2 days show a three-fold increase in plasma ET-1 levels (Min

and a two-fold increase in ET-1 mR (Kourembanas et al., 1991). Rats exposed to hypoxia for 1
2 days show a three-fold increase in plasma ET-1 levels (and a two-fold increase in ET-1 mRNA expression in the et al., 1992). Increased by the systemic circulatio and a two-fold increase in $ET-1$ mRNA expression in the lung and right atrium but not in the organs perfused by the systemic circulation (Elton et al., 1992). Increased $ET-1$ immunoreactivity in lung homogenates or endo-t and a two-fold increase in ET-1 mRNA expression in t
lung and right atrium but not in the organs perfused
the systemic circulation (Elton et al., 1992). Increas
ET-1 immunoreactivity in lung homogenates or ent
thelial cell lung and right atrium but not in the organs perfused by
the systemic circulation (Elton et al., 1992). Increased
ET-1 immunoreactivity in lung homogenates or endo-
thelial cells and increased mRNA expression of prepro-
ETthe systemic circulation (Elton et al., 1992). Increased vase
ET-1 immunoreactivity in lung homogenates or endo-
the ial cells and increased mRNA expression of prepro-
ET-1 has also been observed in rat models of idiopathi ET-1 immunoreactivity in lung homogenates or endo-
thelial cells and increased mRNA expression of prepro-
ET-1 has also been observed in rat models of idiopathic
pulmonary hypertension (Stelzner et al., 1992) and in
patien thelial cells and increased mRNA expression of prepro-
ET-1 has also been observed in rat models of idiopathic
pulmonary hypertension (Stelzner et al., 1992) and in
patients with both hypoxic and other types of pulmonary
h ET-1 has also been observed in rat models of idiopathic
pulmonary hypertension (Stelzner et al., 1992) and in
patients with both hypoxic and other types of pulmonary
hypertension (Stewart et al., 1991; Yoshibayashi et al., pulmonary hypertension (Stelzner et al., 1992) and in
patients with both hypoxic and other types of pulmonary
hypertension (Stewart et al., 1991; Yoshibayashi et al.,
1991; Giaid et al., 1993). ET-1 stimulates (a) DNA synpatients with both hypoxic and other types of pulmonary
hypertension (Stewart et al., 1991; Yoshibayashi et al.
1991; Giaid et al., 1993). ET-1 stimulates (a) DNA syn
thesis and cell proliferation of cultured pulmonary v hypertension (Stewart et al., 1991; Yoshibayashi et al., 1991; Giaid et al., 1993). ET-1 stimulates (*a*) DNA synthesis and cell proliferation of cultured pulmonary vascular smooth muscle cells (Janakidevi et al., 1992; Ha 1991; Giaid et al., 1993). ET-1 stimulates (*a*) DNA synthesis and cell proliferation of cultured pulmonary vascular smooth muscle cells (Janakidevi et al., 1992; Hassoun et al., 1992), and (*b*) the replication of pulmon thesis and cell proliferation of cultured pulmonary vas-
cular smooth muscle cells (Janakidevi et al., 1992; Has-
soun et al., 1992), and (*b*) the replication of pulmonary
artery fibroplasts (Peacock et al., 1992). This cular smooth muscle cells (Janakidevi et al., 1992; Ha
soun et al., 1992), and (*b*) the replication of pulmonar
artery fibroplasts (Peacock et al., 1992). This respons
seems to be mediated via ET_A receptors, because th
 soun et al., 1992), and (b) the replication of pulmonary
artery fibroplasts (Peacock et al., 1992). This response
seems to be mediated via ET_A receptors, because the
 ET_A receptor antagonist, BQ-123, inhibits ET_1 mediartery fibroplasts (Peacock et al., 1992). This response
eems to be mediated via ET_A receptors, because the ET_A receptor antagonist, BQ-123, inhibits ET-1 med
ated proliferation (Zamora, et al., 1993b). In rat mode
of m seems to be mediated via ET_A receptors, because the the ET_A receptor antagonist, BQ-123, inhibits $ET-1$ mediated proliferation (Zamora, et al., 1993b). In rat models 11 of monocrotaline-induced pulmonary hypertension, n ET_A receptor antagonist, BQ-123, inhibits ET-1 mediated proliferation (Zamora, et al., 1993b). In rat models of monocrotaline-induced pulmonary hypertension, chronic infusion of BQ-123 inhibits the progression of pulmona ated proliferation (Zamora, et al., 1993b). In rat models
of monocrotaline-induced pulmonary hypertension,
chronic infusion of BQ-123 inhibits the progression of
pulmonary hypertension, arterial medial thickening,
and righ of monocrotaine-induced pulmonary hypertension,
chronic infusion of BQ-123 inhibits the progression of
pulmonary hypertension, arterial medial thickening,
and right ventricular hypertrophy (Miyauchi et al., 1993).
Plasma E pulmonary hypertension, arterial medial thickening, and right ventricular hypertrophy (Miyauchi et al., 1993).
Plasma ET-1 concentration is elevated during and after pulmonary surgery (Onizuka et al., 1991) and in patients Plasma ET-1 concentration is elevated during and after pulmonary surgery (Onizuka et al., 1991) and in patients with ARDS (Druml et al., 1993; Langleben et al., 1993).
6. Vasoactive intestinal polypeptide. The VIP family c

pulmonary surgery (Onizuka et al., 1991) and in patient with ARDS (Druml et al., 1993; Langleben et al., 1993).
6. Vasoactive intestinal polypeptide. The VIP famil comprises a group of structurally related peptides in clud with ARDS (Druml et al., 1993; Langleben et al., 1993).
6. Vasoactive intestinal polypeptide. The VIP famil
comprises a group of structurally related peptides in
cluding VIP, peptide histidine isoleucine, peptide histidine o. *Vasoactive intestinat potypeptiae*. The VIP lamily comprises a group of structurally related peptides including VIP, peptide histidine isoleucine, peptide histidine methionine, peptide histidine valine, helodermin, PAC comprises a group of structurally related peptides including VIP, peptide histidine isoleucine, peptide histidine valine, helodermin, PACAP, secretin, and growth hormone-releasing factor.
VIP-immunoreactive nerve fibers ar dine methionine, peptide histidine valine, helodermin, pigs (Liu et al., 1992a). In the perfused cat pulmonary PACAP, secretin, and growth hormone-releasing factor. vascular bed at basal condition, CGRP has little effect o PACAP, secretin, and growth hormone-releasing factor.
VIP-immunoreactive nerve fibers are widely distributed
in the lung (Barnes et al., 1991), and seem to innervate
pulmonary vessels (Dey et al., 1981; Dey and Said, 1985; VIP-immunoreactive nerve fibers are widely distributed
in the lung (Barnes et al., 1991), and seem to innervate
pulmonary vessels (Dey et al., 1981; Dey and Said, 1985;
Barnes et al., 1986). VIP relaxes isolated pulmonary
 in the lung (Barnes et al., 1991), and seem to innerva
pulmonary vessels (Dey et al., 1981; Dey and Said, 198
Barnes et al., 1986). VIP relaxes isolated pulmons
vessel rings (Hamasaki et al., 1983; Barnes et al., 198
Green pulmonary vessels (Dey et al., 1981; Dey and Said, 1985; 6
Barnes et al., 1986). VIP relaxes isolated pulmonary
vessel rings (Hamasaki et al., 1983; Barnes et al., 1986;
Greenberg et al., 1987b) and dilates the intact pulm Barnes et al., 1986). VIP relaxes isolated pulmonary the vessel rings (Hamasaki et al., 1983; Barnes et al., 1986; tiss Greenberg et al., 1987b) and dilates the intact pulmo- et anary vascular bed (Nandiwada et al., 1985; vessel rings (Hamasaki et al., 1983; Barnes et al., 1986; times different than isolates the intact pulmo-
nary vascular bed (Nandiwada et al., 1985; Minkes et real., 1992). VIP is 30 times more potent than ACh and ri
1000 Greenberg et al., 1987b) and dilates the intact pulmo-
nary vascular bed (Nandiwada et al., 1985; Minkes et re
al., 1992). VIP is 30 times more potent than ACh and rin
1000 times more potent than isoproterenol in isolated nary vascular bed (Nandiwada et al., 1985; Minkes et rele
al., 1992). VIP is 30 times more potent than ACh and ring
1000 times more potent than isoproterenol in isolated hyp
pulmonary artery rings (Hamasaki et al., 1983) al., 1992). VIP is 30 times more potent than ACh and rings (Wang et al., 1991), and CGRP-induced systemic 1000 times more potent than isoproterenol in isolated hypotension in conscious rat is partially abrogated by pulmon

ND LIU
1985). VIP has been reported to be either an endotl
um-dependent (Ignarro et al., 1987a) or an endotheli ND LIU
1985). VIP has been reported to be either an endo
um-dependent (Ignarro et al., 1987a) or an endothe
independent (Barnes et al., 1986) vasodilator in b ND LIU
1985). VIP has been reported to be either an endotheli-
um-dependent (Ignarro et al., 1987a) or an endothelium-
independent (Barnes et al., 1986) vasodilator in bovine
pulmonary arteries. The reason for this discrep 1985). VIP has been reported to be either an endothelium-
im-dependent (Ignarro et al., 1987a) or an endothelium-
independent (Barnes et al., 1986) vasodilator in bovine
pulmonary arteries. The reason for this discrepancy um-dependent (Ignarro et al., 1987a) or an endothelium-
independent (Barnes et al., 1986) vasodilator in bovine
pulmonary arteries. The reason for this discrepancy is
unclear. The NO synthase inhibitor, L-NAME, has no
effe independent (Barnes et al., 1986) vasodilator in bovine
pulmonary arteries. The reason for this discrepancy is
unclear. The NO synthase inhibitor, L-NAME, has no
effect on the VIP-induced relaxation in cat pulmonary
vascul pulmonary arteries. The reason for this discrepancy
unclear. The NO synthase inhibitor, L-NAME, has
effect on the VIP-induced relaxation in cat pulmons
vascular bed (Minkes et al., 1992). Autoradiograpl
studies show a high unclear. The NO synthase inhibitor, L-NAME, has no
effect on the VIP-induced relaxation in cat pulmonary
vascular bed (Minkes et al., 1992). Autoradiographic
studies show a high density of VIP receptors in pulmo-
nary vasc effect on the VIP-induced relaxation in cat pulmonary
vascular bed (Minkes et al., 1992). Autoradiographic
studies show a high density of VIP receptors in pulmo
nary vascular smooth muscle in guinea pigs and humans
with no vascular bed (Minkes et al., 1992). Autoradiograpl
studies show a high density of VIP receptors in puln
nary vascular smooth muscle in guinea pigs and huma
with no labelling of endothelial cells (Carstairs and B
nes, 1986a studies show a high density of VIP receptors in pulmonary vascular smooth muscle in guinea pigs and humans with no labelling of endothelial cells (Carstairs and Barnes, 1986a). Peptide histidine isoleucine is also a pulmon nary vascular smooth muscle in guinea pigs and humans
with no labelling of endothelial cells (Carstairs and Bar-
nes, 1986a). Peptide histidine isoleucine is also a pulmo-
nary vasculator (Greenberg et al., 1987b). In the with no labelling of endothenal cents (Carstairs and Bar-
nes, 1986a). Peptide histidine isoleucine is also a pulmo-
nary vascular (Greenberg et al., 1987b). In the cat
pulmonary vascular bed perfused at constant flow,
PA nary vasodilator (Greenberg et al., 1987b). In the cat
pulmonary vascular bed perfused at constant flow,
PACAP produces a contraction when vascular tone is
low and a dilation when vascular tone is elevated (Minkes et al., pulmonary vascular bed perfused at constant flow,
PACAP produces a contraction when vascular tone is
low and a dilation when vascular tone is elevated
(Minkes et al., 1992). The contraction is mediated by
endogenous catech PACAP produces a contraction when vascular tone is
low and a dilation when vascular tone is elevated
(Minkes et al., 1992). The contraction is mediated by
endogenous catecholamine release. PACAP is three-fold
more potent t (Minkes et al., 1992). The contraction is mediated by endogenous catecholamine release. PACAP is three-fold more potent than VIP in relaxing the cat pulmonary vasculature. NO is involved in the PACAP-induced relaxation in (Minkes et al., 1992). The contraction is mediated by
endogenous catecholamine release. PACAP is three-fold
more potent than VIP in relaxing the cat pulmonary
vasculature. NO is involved in the PACAP-induced re-
laxation i endogenous catecholamine release. PACAP is three-folograph more potent than VIP in relaxing the cat pulmons vasculature. NO is involved in the PACAP-induced laxation in systemic vessels (Gardiner et al., 199 These mechanis more potent
vasculature. l
laxation in s
These mechar
nary vessels.
7. Calcitoni sculature. NO is involved in the PACAP-induced
xation in systemic vessels (Gardiner et al., 199
nese mechanisms have not yet been reported in puln
ry vessels.
7. *Calcitonin gene-related peptide*. CGRP is a 37-an
-acid

dexation in systemic vessels (Gardiner et al., 1994).

These mechanisms have not yet been reported in pulmonary vessels.

7. Calcitonin gene-related peptide. CGRP is a 37-amino-acid peptide. Two forms, α -CGRP and β -These mechanisms have not yet been reported in pulmo
nary vessels.
7. Calcitonin gene-related peptide. CGRP is a 37-ami
no-acid peptide. Two forms, α -CGRP and β -CGRP, have
been described, and both are expressed in s nary vessels.

7. Calcitonin gene-related peptide. CGRP is a 37-an

no-acid peptide. Two forms, α -CGRP and β -CGRP, ha

been described, and both are expressed in sensory ne

rons (Barnes et al., 1991). CGRP-immunorea 7. Calcitonin gene-related peptide. CGRP is a 37-ami-
no-acid peptide. Two forms, α -CGRP and β -CGRP, have
been described, and both are expressed in sensory neu-
rons (Barnes et al., 1991). CGRP-immunoreactive
nerves no-acid peptide. Two forms, α -CGRP and β -CGRP, have
been described, and both are expressed in sensory neu-
rons (Barnes et al., 1991). CGRP-immunoreactive
nerves are abundant in the lung, frequently innervating
pulm been described, and both are expressed in sensory neurons (Barnes et al., 1991). CGRP-immunoreactive nerves are abundant in the lung, frequently innervating pulmonary vessels (Mulderry et al., 1985; Lauweryns and Ranst, 1 rons (Barnes et al., 1991). CGRP-immunoreactive $\frac{3}{85}$ nerves are abundant in the lung, frequently innervating pulmonary vessels (Mulderry et al., 1985; Lauweryns and Ranst, 1987). CGRP is costored and colocalized wit nerves are abundant in the lung, frequently innervating
pulmonary vessels (Mulderry et al., 1985; Lauweryns
and Ranst, 1987). CGRP is costored and colocalized with
tachykinins, with a distribution pattern consistent with
t pulmonary vessels (Mulderry et al., 1985; Lauweryns
and Ranst, 1987). CGRP is costored and colocalized with
tachykinins, with a distribution pattern consistent with
that of sensory neurons (Lundberg et al., 1985; Martling
 and Ranst, 1987). CGRP is costored and colocalized with tachykinins, with a distribution pattern consistent with that of sensory neurons (Lundberg et al., 1985; Martling, 1987) and is depleted by capsaicin treatment (Martl tachykinins, with a distribution pattern consistent with
that of sensory neurons (Lundberg et al., 1985; Martling,
1987) and is depleted by capsaicin treatment (Martling,
1987). CGRP is released during stimulation of the that of sensory neurons (Lundberg et al., 1985; Martling, 1987) and is depleted by capsaicin treatment (Martling, 1987). CGRP is released during stimulation of the vagus nerve (Martling, 1987) and upon stimulation of the p 1987) and is depleted by capsaicin treatment (Martling, $\frac{28}{5}$ 1987). CGRP is released during stimulation of the vagus nerve (Martling, 1987) and upon stimulation of the perivascular nerves of guinea pig main pulmonar 1987). CGRP is released during stimulation of the vag
nerve (Martling, 1987) and upon stimulation of t
perivascular nerves of guinea pig main pulmonary
teries. CGRP may be a neurotransmitter of i-NAN
vasodilator nerves of nerve (Martling, 1987) and upon stimulation of the perivascular nerves of guinea pig main pulmonary arteries. CGRP may be a neurotransmitter of i-NANC vasodilator nerves of cat and guinea pig large pulmonary arteries (Mag perivascular nerves of guiteries. CGRP may be a r
vasodilator nerves of cat a
nary arteries (Maggi et al.
discussed above in II.C.3.
CGRP is a potent vasodil res. CGRP inay be a neurotransmitter of 1-NANC
sodilator nerves of cat and guinea pig large pulmo-
try arteries (Maggi et al., 1990; Liu et al., 1992a), as
scussed above in II.C.3.
CGRP is a potent vasodilator of guinea pi

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Plasma ET-1 concentration is elevated during and after nary arteries (Maggi et al., 1990; Liu et al., 1992a), as
pulmonary surgery (Onizuka et al., 1991) and in patients discussed above in II.C.3.
with ARDS (Druml et al., vasounator herves of cat and gumea pig large punno-
nary arteries (Maggi et al., 1990; Liu et al., 1992a), as
discussed above in II.C.3.
CGRP is a potent vasodilator of guinea pig and human
pulmonary arteries in vitro (Mc discussed above in II.C.3.

CGRP is a potent vasodilator of guinea pig and human

pulmonary arteries in vitro (McCormack et al., 1989d;

Liu et al., 1992a). CGRP is more potent in relaxing large

than in relaxing smaller p CGRP is a potent vasodilator of guinea pig and human
pulmonary arteries in vitro (McCormack et al., 1989d;
Liu et al., 1992a). CGRP is more potent in relaxing large
than in relaxing smaller pulmonary arteries of guinea
pig pulmonary arteries in vitro (McCormack et al., 1989d;
Liu et al., 1992a). CGRP is more potent in relaxing large
than in relaxing smaller pulmonary arteries of guinea
pigs (Liu et al., 1992a). In the perfused cat pulmonary Liu et al., 1992a). CGRP is more potent in relaxing large than in relaxing smaller pulmonary arteries of guine pigs (Liu et al., 1992a). In the perfused cat pulmonar vascular bed at basal condition, CGRP has little effect than in relaxing smaller pulmonary arteries of guinea
pigs (Liu et al., 1992a). In the perfused cat pulmonary
vascular bed at basal condition, CGRP has little effect on
basal perfusion pressure but dose-dependently de-
cre pigs (Liu et al., 1992a). In the perfused cat pulmonary
vascular bed at basal condition, CGRP has little effect on
basal perfusion pressure but dose-dependently de-
creases perfusion pressure when the vascular tone is
elev vascular bed at basal condition, CGRP has little effect on
basal perfusion pressure but dose-dependently de-
creases perfusion pressure when the vascular tone is
elevated artificially (Lippton et al., 1990). Activation of
 basal perfusion pressure but dose-dependently decreases perfusion pressure when the vascular tone is elevated artificially (Lippton et al., 1990). Activation of the adenylyl cyclase-linked CGRP receptors increases tissue c creases perfusion pressure when the vascular tone is
elevated artificially (Lippton et al., 1990). Activation of
the adenylyl cyclase-linked CGRP receptors increases
tissue cAMP content and results in vasodilation (Barnes
 the adenylyl cyclase-linked CGRP receptors increases
tissue cAMP content and results in vasodilation (Barnes
et al., 1991). CGRP has been demonstrated to induce NO
release and to increase tissue cGMP levels in rat aortic the adenylyl cyclase-linked CGRP receptors increases
tissue cAMP content and results in vasodilation (Barnes
et al., 1991). CGRP has been demonstrated to induce NO
release and to increase tissue cGMP levels in rat aortic
r tissue cAMP content and results in vasodilation (Barnes et al., 1991). CGRP has been demonstrated to induce NO release and to increase tissue cGMP levels in rat aortic rings (Wang et al., 1991), and CGRP-induced systemic h et al., 1991). CGAT has been demonstrated to induce NO
release and to increase tissue cGMP levels in rat aortic
rings (Wang et al., 1991), and CGRP-induced systemic
hypotension in conscious rat is partially abrogated by
Lrings (Wang et al., 1991), and CGRP-induced systemic
hypotension in conscious rat is partially abrogated by
L-NAME (Abdelrahman et al., 1992), suggesting NO
may play a role in the systemic vasodilator response to
CGRP. Whe

REGULATION OF PULMONARY VASCULAR TONE ⁹⁹ REGULATION OF PULMONARY VASCULAR TONE
nary circulation remains to be determined. Mechanical lar pressure in all s
removal of endothelium has no effect on the vasodilator Adnot et al., 1991a; l

REGULATION OF PULM
nary circulation remains to be determined. Mechanical
removal of endothelium has no effect on the vasodilator
responses to CGRP in human pulmonary vessels in REGULATION OF PULMONARY

removal of endothelium has no effect on the vasodilator Adn

responses to CGRP in human pulmonary vessels in cont

vitro, suggesting that CGRP acts directly on vascular oxy nary circulation remains to be determined. Mechanical
removal of endothelium has no effect on the vasodilator
responses to CGRP in human pulmonary vessels in
vitro, suggesting that CGRP acts directly on vascular
smooth mus nary circulation remains to be determined. Mechanical laids removal of endothelium has no effect on the vasodilator Adresponses to CGRP in human pulmonary vessels in covitro, suggesting that CGRP acts directly on vascular removal of endothelium has no effect on the vasodila
responses to CGRP in human pulmonary vessels
vitro, suggesting that CGRP acts directly on vascu
smooth muscle cells (McCormack et al., 1989d). This
consistent with an au responses to CGRP in human pulmonary vessels in corresponses to CGRP acts directly on vascular of smooth muscle cells (McCormack et al., 1989d). This is 1 consistent with an autoradiographic study that demonstrated the CGR vitro, suggesting that CGRP acts directly on vascular oxy
smooth muscle cells (McCormack et al., 1989d). This is 198
consistent with an autoradiographic study that demon-
strated the CGRP receptors on vascular smooth muscl smooth muscle cells (McCormack et al., 1989d). This is 1
consistent with an autoradiographic study that demon-
strated the CGRP receptors on vascular smooth muscle
but not on endothelial cells in pulmonary arteries and S
v consistent with an autoradiographic study that demon-
strated the CGRP receptors on vascular smooth muscle
but not on endothelial cells in pulmonary arteries and
seins of all dimensions (Mak and Barnes, 1988). Al-
intough strated the CGRP receptors on vascular smooth muscle
but not on endothelial cells in pulmonary arteries and
veins of all dimensions (Mak and Barnes, 1988). Al-
though depletion of sensory neuropeptides, including in
CGRP, but not on endothelial cells in pulmonary arteries and
veins of all dimensions (Mak and Barnes, 1988). Al-
though depletion of sensory neuropeptides, including
CGRP, by pretreatment of rats with capsaicin has little
effect veins of all dimensions (Mak and Barnes, 1988). Although depletion of sensory neuropeptides, including CGRP, by pretreatment of rats with capsaicin has little effect on the acute HPV response (McCormack et al., 1993), CGRP CGRP, by pretreatment of rats with capsaicin has little effect on the acute HPV response (McCormack et al., 1993), CGRP may counteract the development of hypoxic pulmonary hypertension. CGRP-like immunoreactivity is increa CGRP, by pretreatment of rats with capsaicin has little in
effect on the acute HPV response (McCormack et al.,
1993), CGRP may counteract the development of hy-
poxic pulmonary hypertension. CGRP-like immunoreac-
tivity is effect on the acute HPV response (McCormack et al. 1993), CGRP may counteract the development of hypoxic pulmonary hypertension. CGRP-like immunoreactivity is increased in lung neuroendocrine cells of rate exposed to chron 1993), CGRP may counteract the development of hypoxic pulmonary hypertension. CGRP-like immunoreactivity is increased in lung neuroendocrine cells of rats exposed to chronic hypoxia (McBride et al., 1990; Roncalli et al., poxic pulmonary hypertension. CGRP-like immunoreactivity is increased in lung neuroendocrine cells of rats exposed to chronic hypoxia (McBride et al., 1990; Roncalli et al., 1993). Chronic infusion of CGRP prevents, and im tivity is increased in lung neuroendocrine cells of ratexposed to chronic hypoxia (McBride et al., 1990; Ron calli et al., 1993). Chronic infusion of CGRP prevents and immunoneutralization with CGRP antibody, or in fusion exposed to chronic hypoxia (McBride et al., 1990; Roncolli et al., 1993). Chronic infusion of CGRP prevents, precent and immunoneutralization with CGRP antibody, or in-
fusion of CGRP receptor antagonist peptides exacerbat and immunoneutralization with CGRP antibody, or infusion of CGRP receptor antagonist peptides exacerbate,
hypoxic pulmonary hypertension in rats exposed to
chronic hypoxia (Tjen-A-Looi et al., 1992).
8. Substance P. SP bel *A* immunoneutralization with CGRP antibody, or insion of CGRP receptor antagonist peptides exacerbate, poxic pulmonary hypertension in rats exposed to ronic hypoxia (Tjen-A-Looi et al., 1992).
8. Substance P. SP belongs

fusion of CGRP receptor antagonist peptides exacerbate,
hypoxic pulmonary hypertension in rats exposed to
chronic hypoxia (Tjen-A-Looi et al., 1992).
8. Substance P. SP belongs to the tachykinin family,
which includes NK hypoxic pulmonary hypertension in rats exposed to
chronic hypoxia (Tjen-A-Looi et al., 1992).
8. Substance P. SP belongs to the tachykinin family,
which includes NK A (NKA), NK B (NKB), NP K (NPK),
and NP- γ (Nakanishi, chronic hypoxia (Tjen-A-Looi et al., 1992).

8. Substance P. SP belongs to the tachykinin family,

which includes NK A (NKA), NK B (NKB), NP K (NPK),

and NP- γ (Nakanishi, 1991). SP is predominantly syn-

thesized in 8. Substance P. SP belongs to the tachykinin family, mon which includes NK A (NKA), NK B (NKB), NP K (NPK), othe and NP- γ (Nakanishi, 1991). SP is predominantly syn-
thesized in the nodose and jugular ganglia of the va which includes NK A (NKA), NK B (NKB), NP K (NH
and NP- γ (Nakanishi, 1991). SP is predominantly is
thesized in the nodose and jugular ganglia of the va
nerve and transported down the vagus to the lungs.
seems to be loc and NP- γ (Nakanishi, 1991). SP is predominantly synthesized in the nodose and jugular ganglia of the vagus
nerve and transported down the vagus to the lungs. SP
seems to be localized predominantly in the capsaicin-
sen thesized in the nodose and jugular ganglia of the vagus
nerve and transported down the vagus to the lungs. SP
seems to be localized predominantly in the capsaicin-
sensitive unmyelinated nerves in the lung. SP-like im-
mun merve and transported down the vagus to the lungs. Sr
seems to be localized predominantly in the capsaicin-
sensitive unmyelinated nerves in the lung. SP-like im-
munoreactive nerve fibers are distributed around pul-
monar sensitive unmyelinated nerves in the lung. SP-like im-
munoreactive nerve fibers are distributed around pul-
monary vessels in several species (Dey et al., 1981;
Furness et al., 1982).
Tachykinin effects are mediated by sp

munoreactive herve mers are ustributed around pul-
monary vessels in several species (Dey et al., 1981; bed.
Furness et al., 1982). the
designed as NK₁, NK₂, and NK₃ receptors. NK₁ recep-
via
tors are activated pr Furness et al., 1982).
Tachykinin effects are mediated by specific receptors
designed as NK_1 , NK_2 , and NK_3 receptors. NK_1 recep-
tors are activated preferentially by SP, NK_2 receptors by
NKA, and NK_3 receptors Tachykinin effects are mediated by specific receptors
designed as NK_1 , NK_2 , and NK_3 receptors. NK_1 receptors are activated preferentially by SP, NK_2 receptors by
NKA, and NK_3 receptors by NKB (Nakanishi, 1991) tors are activated preferentially by SP, NK_2 receptors by NKA, and N K_3 receptors on value (Nakanishi, 1991).
Tachykinin receptors on pulmonary vessels are NK₂ retors are activated preferentially by SP, NK_2 receptor NKA, and NK_3 receptors by NKB (Nakanishi, 19
Tachykinin receptors on pulmonary vessels are NK₂
ceptors on smooth muscle and NK₁ receptors on vasce
endothelium NKA, and NK₃ receptors by NKB (Nakanishi, 1991). str.
Tachykinin receptors on pulmonary vessels are NK₂ re-
ceptors on smooth muscle and NK₁ receptors on vascular als
endothelium (Carstairs and Barnes, 1986b; D'Orle Tachykinin receptors on pulmonary vessels are NK₂ is
ceptors on smooth muscle and NK₁ receptors on vascul
endothelium (Carstairs and Barnes, 1986b; D'Orlear
Juste et al., 1986; McCormack et al., 1989e). NK₂ a
NK₃ ceptors on smooth muscle and NK_1 receptors on vascular also a pulmonary vasoconstrictor (Gillespie et al., 1984).
endothelium (Carstairs and Barnes, 1986b; D'Orleans-
Juste et al., 1986; McCormack et al., 1989e). NK_2 Juste et al., 1986; McCormack et al., 1989e). NK_2 and NK_3 receptors are probably absent on pulmonary vascular endothelium, inasmuch as NKA and NKB have no effects on the precontracted endothelium-intact pulmo-
nary ar nary arteries (Maggi et al., 1990). SP induces constric- NK_3 receptors are probably absent on pulmonary vascular endothelium, inasmuch as NKA and NKB have no effects on the precontracted endothelium-intact pulmonary arteries (Maggi et al., 1990). SP induces constriction of is lar endothelium, inasmuch as NKA and NKB have no
effects on the precontracted endothelium-intact pulmo-
nary arteries (Maggi et al., 1990). SP induces constric-
leu
tion of isolated pulmonary vascular rings at resting ten enects on the precontracted endothendm-mtact pulmo-
nary arteries (Maggi et al., 1990). SP induces constric-
tion of isolated pulmonary vascular rings at resting ten-
sion via stimulation of NK₂ receptors (Tanaka and a
G tion of isolated pulmonary vascular rings at resting tension via stimulation of NK_2 receptors (Tanaka and al., Grunstein, 1985; D'Orleans-Juste et al., 1986) but in transes relaxation of precontracted preparations throu sion via stimulation of NK_2 receptors (Tanaka and a Grunstein, 1985; D'Orleans-Juste et al., 1986) but is causes relaxation of precontracted preparations through activation of endothelial NK_2 receptors (Tanaka and Gru Grunstein, 1985; D'Orleans-Juste et al., 1986) but is causes relaxation of precontracted preparations through activation of endothelial NK_2 receptors (Tanaka and Grunstein, 1985; D'Orleans-Juste et al., 1986; Maggi et a causes relaxation of precontracted preparations through
activation of endothelial NK_2 receptors (Tanaka and
Grunstein, 1985; D'Orleans-Juste et al., 1986; Maggi et
al., 1990; Liu et al., 1992a). In the intact pulmonary
 activation of endothelial NK_2 receptors (Tanaka and Grunstein, 1985; D'Orleans-Juste et al., 1986; Maggi et al., 1990; Liu et al., 1992a). In the intact pulmonary vascular beds perfused at constant flow and under basal al., 1990; Liu et al., 1992a). In the intact pulmonary but preserves hypoxic pulmonary constriction, which devascular beds perfused at constant flow and under basal cays with time (Sakai and Voelkel, 1988). In isolated con al., 1990; Liu et al., 1992a). In the intact pulmonary but vascular beds perfused at constant flow and under basal conditions, SP has no effect in dogs (Archer et al., put 1986a), increases PPA in guinea pigs and rabbits r vascular beds perfused at constant flow and under basal conditions, SP has no effect in dogs (Archer et al., 1986a), increases PPA in guinea pigs and rabbits (Worthen et al., 1985; Selig et al., 1988), and slightly reduces conditions, SP has no effect in dogs (Archer et al., p
1986a), increases PPA in guinea pigs and rabbits re
(Worthen et al., 1985; Selig et al., 1988), and slightly of
reduces PPA in cats (McMahon and Kadowitz, 1993). ir
Wh 1986a), increases PPA in guinea pigs and rabb
(Worthen et al., 1985; Selig et al., 1988), and slight
reduces PPA in cats (McMahon and Kadowitz, 199
When pulmonary vascular tone is elevated by hypoxia
other vasoconstrictors

99
lar pressure in all species studied (Archer et al., 1986a;
Adnot et al., 1991a; McMahon and Kadowitz, 1993). The 99
Adnot et al., 1991a; McMahon and Kadowitz, 1993). The
Contractile response to SP is partially mediated by cyclog
ARY VASCULAR TONE
lar pressure in all species studied (Archer et al., 1986
Adnot et al., 1991a; McMahon and Kadowitz, 1993). Th
contractile response to SP is partially mediated by cyclo
oxygenase products (Worthen et al. lar pressure in all species studied (Archer et al., 1986a;
Adnot et al., 1991a; McMahon and Kadowitz, 1993). The
contractile response to SP is partially mediated by cyclo-
oxygenase products (Worthen et al., 1985; Selig et lar pressure in all species studied (Archer et al., 1986a;
Adnot et al., 1991a; McMahon and Kadowitz, 1993). The
contractile response to SP is partially mediated by cyclo-
oxygenase products (Worthen et al., 1985; Selig et Adnot et al., 1991a; McMahon and Kadowitz, 1993). The
contractile response to SP is partially mediated by cyclo-
oxygenase products (Worthen et al., 1985; Selig et al.,
1988), whereas the endothelium-dependent relaxation i oxygenase products (Worthen et al., 1985; Selig et al., 1988), whereas the endothelium-dependent relaxation is mainly mediated by NO release (Maggi et al., 1990; Liu et al., 1992a; McMahon and Kadowitz, 1993). Recently, S 1988), whereas the endothelium-dependent relaxation is
mainly mediated by NO release (Maggi et al., 1990; Liu
et al., 1992a; McMahon and Kadowitz, 1993). Recently,
SP has been reported to enhance $TNF-\alpha$ secretion in
infla et al., 1992a; McMahon and Kadowitz, 1993). Recently, SP has been reported to enhance $TNF-\alpha$ secretion in inflammatory cells (Luber-Narod et al., 1994), suggesting that SP may induce pulmonary vasodilation via an indirect mechanism under inflammary conditions. et al., 1992a; McMahon and Kadowitz, 1993). Rec
SP has been reported to enhance TNF- α secretic
inflammatory cells (Luber-Narod et al., 1994), su-
ing that SP may induce pulmonary vasodilation
indirect mechanism under i P has been reported to enhance TNF- α secretio
flammatory cells (Luber-Narod et al., 1994), sugg
g that SP may induce pulmonary vasodilation vi
direct mechanism under inflammary conditions.
9. *Neuropeptide Y*. NPY is a

inflammatory cells (Luber-Narod et al., 1994), sugge
ing that SP may induce pulmonary vasodilation via
indirect mechanism under inflammary conditions.
9. Neuropeptide Y. NPY is a 36-amino-acid neurop
tide localized to adre ing that SP may induce pulmonary vasodilation via an
indirect mechanism under inflammary conditions.
9. Neuropeptide Y. NPY is a 36-amino-acid neuropep-
tide localized to adrenergic and other nerves. NPY-im-
munoreactive n indirect mechanism under inflammary conditions.

9. Neuropeptide Y. NPY is a 36-amino-acid neuropeptide localized to adrenergic and other nerves. NPY-im-

munoreactive nerve fibers are present in the adventitia

of pulmona 9. Neuropeptide Y. NPY is a 36-amino-acid neuropeptide localized to adrenergic and other nerves. NPY-im-
munoreactive nerve fibers are present in the adventitia
of pulmonary vessels (Sheppard et al., 1984). NPY has
several tide localized to adrenergic and other nerves. NPY-im-
munoreactive nerve fibers are present in the adventitia
of pulmonary vessels (Sheppard et al., 1984). NPY has
several actions in the lung (Barnes et al., 1991) and act munoreactive nerve fibers are present in the adventitia
of pulmonary vessels (Sheppard et al., 1984). NPY has
several actions in the lung (Barnes et al., 1991) and acts
predominantly as a cotransmitter in adrenergic nerves of pulmonary vessels (Sheppard et al., 1984). NPY has
several actions in the lung (Barnes et al., 1991) and acts
predominantly as a cotransmitter in adrenergic nerves.
NPY is synergistic with adrenergic contraction (Lippto several actions in the lung (Barnes et al., 1991) and acts
predominantly as a cotransmitter in adrenergic nerves.
NPY is synergistic with adrenergic contraction (Lippton
et al., 1990) and is a pulmonary vasconstrictor in v NPY is synergistic with adrenergic contraction (Lippton
et al., 1990) and is a pulmonary vasoconstrictor in vitro
(Obara et al., 1989). However, NPY has little effect on
the pulmonary vascular bed, nor does it alter the pu et al., 1990) and is a pulmonary vasoconstrictor in vitr
(Obara et al., 1989). However, NPY has little effect of
the pulmonary vascular bed, nor does it alter the pulmonary vasoconstrictor response to norepinephrine an
oth (Obara et al., 1989). However, NPY has little effect on the pulmonary vascular bed, nor does it alter the pulmonary vasoconstrictor response to norepinephrine and other vasoconstrictors (Lippton et al., 1990). NPY stimula the pulmonary vascular bed, nor does it
monary vasoconstrictor response to nore
other vasoconstrictors (Lippton et al., 199
ulates prostacyclin production in culture
dothelial cells (Kawamura et al., 1991).
10. Other Pepti onary vasoconstrictor response to norepinephrine and
her vasoconstrictors (Lippton et al., 1990). NPY stim-
ates prostacyclin production in cultured vascular en-
thelial cells (Kawamura et al., 1991).
10. Other Peptides. B

of pulmonary vessels (Sheppard et al., 1984). NPY has
several actions in the lung (Barnes et al., 1990) and acts
predominantly as a cotransmitter in adrenergic nerves.
NPY is synergistic with adrenergic contraction (Lippt other vasoconstrictors (Lippton et al., 1990). NPY stimulates prostacyclin production in cultured vascular endothelial cells (Kawamura et al., 1991).

10. Other Peptides. Bombesin is a weak pulmonary vasoconstrictor in vit ulates prostacyclin production in cultured vascular dothelial cells (Kawamura et al., 1991).

10. Other Peptides. Bombesin is a weak pulm

vasoconstrictor in vitro (Dey and Said, 1985), bu

ther bombesin nor its C-terminal dothelial cells (Kawamura et al., 1991).

10. Other Peptides. Bombesin is a weak pulmonary

vasoconstrictor in vitro (Dey and Said, 1985), but nei-

ther bombesin nor its C-terminal analog, gastrin-releas-

ing peptide, is 10. Other Peptides. Bombesin is a weak pulmonary
vasoconstrictor in vitro (Dey and Said, 1985), but nei-
ther bombesin nor its C-terminal analog, gastrin-releas-
ing peptide, is vasoactive in intact pulmonary vascular
beds ther bombesin nor its C-terminal analog, gastrin-releasing peptide, is vasoactive in intact pulmonary vascular beds (Mulik et al., 1983). Calcitonin is also inactive in the pulmonary vascular bed (Gillespie et al., 1984). ther bombesin nor its C-terminal analog, gastrin-releasing peptide, is vasoactive in intact pulmonary vascular beds (Mulik et al., 1983). Calcitonin is also inactive in the pulmonary vascular bed (Gillespie et al., 1984). ing peptide, is vasoactive in intact pulmonary vascula
beds (Mulik et al., 1983). Calcitonin is also inactive i
the pulmonary vascular bed (Gillespie et al., 1984). Mor
phine increases PPA and pulmonary vascular resistance beds (Mulik et al., 1983). Calcitonin is also inactive
the pulmonary vascular bed (Gillespie et al., 1984). M
phine increases PPA and pulmonary vascular resistar
via activation of opioid receptors and indirectly by sti
ul phine increases PPA and pulmonary vascular resistance
via activation of opioid receptors and indirectly by stim-
ulating the release of histamine, which causes vasocon-
striction through activation of H_1 receptors (Hak phine increases PPA and pulmonary vascular resistance
via activation of opioid receptors and indirectly by stim-
ulating the release of histamine, which causes vasocon-
striction through activation of H_1 receptors (Haki via activation of opioid receptors and indirectly by stimulating the release of histamine, which causes vasoconstriction through activation of H_1 receptors (Hakim et al., 1992). The endogenous opioid, leucine-enkephali ulating the release of histamine, which causes vasocostriction through activation of H_1 receptors (Hakim al., 1992). The endogenous opioid, leucine-enkephalinalso a pulmonary vasoconstrictor (Gillespie et al., 198 Chol striction through activation of H_1 receptors (Hakim et al., 1992). The endogenous opioid, leucine-enkephalin, is also a pulmonary vasoconstrictor (Gillespie et al., 1984). Cholecystokinin relaxes precontracted isolated al., 1992). The endogenous opioid, leucine-enkephalin, is
also a pulmonary vasoconstrictor (Gillespie et al., 1984).
Cholecystokinin relaxes precontracted isolated pulmo-
nary artery rings, whereas neurotensin is inactive
 Cholecystokinin relaxes precontracted isolated pulmo-Cholecystokinin relaxes precontracted isolated
nary artery rings, whereas neurotensin is i
(Obara et al., 1989), although both are constri-
airway smooth muscle (Barnes et al., 1991). The
rial chemoattractant peptide, N-fo nary artery rings, whereas neurotensin is inactively (Obara et al., 1989), although both are constrictors airway smooth muscle (Barnes et al., 1991). The bact rial chemoattractant peptide, N-formyl-methiony leucyl-phenylal airway smooth muscle (Barnes et al., 1991). The bacterial chemoattractant peptide, N-formyl-methionyl-
leucyl-phenylalanine, causes either contraction or relax-
ation of isolated pulmonary vascular rings (Crowell et al., 1 rial chemoattractant peptide, N-formyl-methionyl-
leucyl-phenylalanine, causes either contraction or relax-
ation of isolated pulmonary vascular rings (Crowell et
al., 1989; Laplante et al., 1989) but induces constriction
 leucyl-phenylalanine, causes either contraction or relaxation of isolated pulmonary vascular rings (Crowell et al., 1989; Laplante et al., 1989) but induces constriction in the perfused pulmonary vascular bed (Tanaka et al leucyl-phenylalanine, causes either contraction or relaxation of isolated pulmonary vascular rings (Crowell et al., 1989; Laplante et al., 1989) but induces constriction in the perfused pulmonary vascular bed (Tanaka et al ation of isolated pulmonary vascular rings (Crowell et al., 1989; Laplante et al., 1989) but induces constriction
in the perfused pulmonary vascular bed (Tanaka et al., 1992). Somatostatin has no effect on either isolated al., 1989; Laplante et al., 1989) but induces constriction
in the perfused pulmonary vascular bed (Tanaka et al.,
1992). Somatostatin has no effect on either isolated pul-
monary vascular rings (Obara et al., 1989) or on t in the perfused pulmonary vascular bed (Tanaka et al., 1992). Somatostatin has no effect on either isolated pulmonary vascular rings (Obara et al., 1989) or on the perfused pulmonary vascular bed under basal conditions but 1992). Somatostatin has no effect on either isolated pul-
monary vascular rings (Obara et al., 1989) or on the
perfused pulmonary vascular bed under basal conditions
but preserves hypoxic pulmonary constriction, which de-
 perfused pulmonary vascular bed under basal conditions perfused pulmonary vascular bed under basal conditions
but preserves hypoxic pulmonary constriction, which de-
cays with time (Sakai and Voelkel, 1988). In isolated
pulmonary artery rings, thrombin causes a transient
relax but preserves hypoxic pulmonary constriction, which decays with time (Sakai and Voelkel, 1988). In isolated pulmonary artery rings, thrombin causes a transient relaxation followed by a sustained contraction. Removal of end cays with time (Sakai and Voelkel, 1988). In isolated
pulmonary artery rings, thrombin causes a transient
relaxation followed by a sustained contraction. Removal
of endothelium or an NO synthase inhibitor abolishes or
inhi pulmonary artery rings, thrombin causes a transient
relaxation followed by a sustained contraction. Removal
of endothelium or an NO synthase inhibitor abolishes or
inhibits the relaxant component and augments the con-
trac relaxation followed by a sustained contraction. Removal
of endothelium or an NO synthase inhibitor abolishes or
inhibits the relaxant component and augments the con-
tractile component, suggesting that NO plays a role in
m

100 BARNES
(Glusa et al., 1994). Thrombin and thrombin receptor
activation peptide (a proteolytic thrombin receptor BARNES
(Glusa et al., 1994). Thrombin and thrombin receptor
activation peptide (a proteolytic thrombin receptor
cleaved by thrombin) increases the perfusion pressure in BARNES AND 1
(Glusa et al., 1994). Thrombin and thrombin receptor she
activation peptide (a proteolytic thrombin receptor pull
cleaved by thrombin) increases the perfusion pressure in 198
the guinea pig but decreases the p (Glusa et al., 1994). Thrombin and thrombin receptor she
activation peptide (a proteolytic thrombin receptor pull
cleaved by thrombin) increases the perfusion pressure in 198
the guinea pig but decreases the perfusion pres (Glusa et al., 1994). Thrombin and thrombin receptor sheep (Cocks and Arnold, 1992). 5-HT contracts human activation peptide (a proteolytic thrombin receptor pulmonary arteries and veins in vitro (Raffestin et al., cleave activation peptide (a proteolytic thrombin receptor leaved by thrombin) increases the perfusion pressure in the guinea pig but decreases the perfusion pressure in neonatal piglet pulmonary vascular beds (Lum et al., 1994; cleaved by thrombin) increases the perfusion pressure
the guinea pig but decreases the perfusion pressure
neonatal piglet pulmonary vascular beds (Lum et a
1994; Pinheiro et al., 1993). The increased pulmona
perfusion pres the guinea pig but decreases the perfusion pressure in 19
neonatal piglet pulmonary vascular beds (Lum et al., va
1994; Pinheiro et al., 1993). The increased pulmonary (M
perfusion pressure seems to be caused mainly by pul neonatal piglet pulmonary vascular beds (Lum et al., 1994; Pinheiro et al., 1993). The increased pulmonary (perfusion pressure seems to be caused mainly by pulmonary venoconstriction (Lum et al., 1994), whereas the 1
decre 1994; Pinheiro et al., 1993). The increased pulmonary
perfusion pressure seems to be caused mainly by pulmo-
nary venoconstriction (Lum et al., 1994), whereas the
decreased pulmonary perfusion pressure is primarily
induce perfusion pressure seems to be caused mainly by p
nary venoconstriction (Lum et al., 1994), wherea
decreased pulmonary perfusion pressure is prin
induced through arteriolar dilation (Pinheiro e
1993). Both extracellular C nary venoconstriction (Lum et al., 1994), whereas decreased pulmonary perfusion pressure is primal induced through arteriolar dilation (Pinheiro et 1993). Both extracellular Ca^{2+} entry and phosphoinoide hydrolysis are decreased pulmonary perfusion pressure is primarily
induced through arteriolar dilation (Pinheiro et al.
1993). Both extracellular Ca²⁺ entry and phosphoinosit-
ide hydrolysis are involved in the pulmonary vasocon-
stri induced through arteriolar dilation (Pinheiro et al.
1993). Both extracellular Ca^{2+} entry and phosphoinosis
ide hydrolysis are involved in the pulmonary vasocor
strictor response to thrombin or thrombin receptor act
va 93). Both extracellular Ca^{2+} entry and phosphoinosite hydrolysis are involved in the pulmonary vasocon-
rictor response to thrombin or thrombin receptor acti-
tion peptide (Glusa et al., 1994; Lum et al., 1994).
11. *H*

ide hydrolysis are involved in the pulmonary vasocon-
strictor response to thrombin or thrombin receptor acti-
vation peptide (Glusa et al., 1994; Lum et al., 1994).
11. Histamine. Histamine is released from mast cells
i strictor response to thrombin or thrombin receptor activation peptide (Glusa et al., 1994; Lum et al., 1994).
11. Histamine. Histamine is released from mast cells
in the lung. These cells are localized to the adventitia of vation peptide (Glusa et al., 1994; Lum et al., 1994). ter

11. Histamine. Histamine is released from mast cells

in the lung. These cells are localized to the adventitia of et a

pulmonary vessels. Histamine causes eithe 11. Histamine. Histamine is released from mast cells n
in the lung. These cells are localized to the adventitia of
pulmonary vessels. Histamine causes either constriction
or dilation of the isolated pulmonary vascular rin pulmonary vessels. Histamine causes either constriction
or dilation of the isolated pulmonary vascular rings and
perfused pulmonary vascular bed depending on existing
tone, inducing constriction when the vessels are at res pulmonary vessels. Histamine causes either constriction c-not or dilation of the isolated pulmonary vascular rings and stilust perfused pulmonary vascular bed depending on existing accume, inducing constriction when the ve or dilation of the isolated pulmonary vascular rings and
perfused pulmonary vascular bed depending on existing
tone, inducing constriction when the vessels are at rest-
ing tension (Okpaka, 1972) but eliciting dilation whe perfused pulmonary vascular bed depending on exist
tone, inducing constriction when the vessels are at re
ing tension (Okpaka, 1972) but eliciting dilation wh
the tone is elevated by norepinephrine (Abcioglu et
1987) or hy tone, inducing constriction when the vessels are at rest-
ing tension (Okpaka, 1972) but eliciting dilation when
the tone is elevated by norepinephrine (Abcioglu et al.,
1987) or hypoxia (Silove and Simcha, 1973). The con ing tension (Okpaka, 1972) but eliciting dilation whe
the tone is elevated by norepinephrine (Abcioglu et a
1987) or hypoxia (Silove and Simcha, 1973). The contra
tile response is mediated by H_1 -receptors on vascula
sm the tone is elevated by norepinephrine (Abcioglu et al., p
1987) or hypoxia (Silove and Simcha, 1973). The contrac-
tile response is mediated by H_1 -receptors on vascular
smooth muscle cells, and the relaxant response i 1987) or hypoxia (Silove and Simcha, 1973). The contrac-
tile response is mediated by H_1 -receptors on vascular endothelial cells, and the relaxant response is mediated by both H_2 -receptors on smooth muscle and H_1 tile response is mediated by H_1 -receptors on vascular smooth muscle cells, and the relaxant response is mediated by both H_2 -receptors on smooth muscle and H_1 -receptors located on vascular endothelial cells (Abcio ated by both H_2 -receptors on smooth muscle and H_1 -receptors located on vascular endothelial cells (Abcioglu et al., 1987; Matsuki and Ohhashi, 1990; Szarek et al., 1992). NO seems to be responsible for the endotheli ated by both H_2 -receptors on smooth muscle and H_1
receptors located on vascular endothelial cells (Abciogli
et al., 1987; Matsuki and Ohhashi, 1990; Szarek et al
1992). NO seems to be responsible for the endothelium receptors located on vascular endothelial cells (Abcioglu pool
et al., 1987; Matsuki and Ohhashi, 1990; Szarek et al., by
1992). NO seems to be responsible for the endothelium- Ca^2
dependent relaxation in pulmonary arte et al., 1987; Matsuki and Ohhashi, 1990; Szarek et al., 1992). NO seems to be responsible for the endothelium-
dependent relaxation in pulmonary arteries of rats (Szarek et al., 1992), but both PGL_2 and NO are involv 1992). NO seems to be responsible for the endothelium-
dependent relaxation in pulmonary arteries of rats (Sza-
rek et al., 1992), but both PGI_2 and NO are involved in curre
the relaxation of human pulmonary arteries (O dependent relaxation in pulmonary arteries of rats (Sza-
rek et al., 1992), but both PGI_2 and NO are involved in curs
the relaxation of human pulmonary arteries (Ortiz et al., met
1992). Histamine also constricts pulmon rek et al., 1992), but both PGI_2 and NO are involved in cur
the relaxation of human pulmonary arteries (Ortiz et al., me
1992). Histamine also constricts pulmonary veins by pat
activation of H_1 -receptors (Barman and the relaxation of human pulmonary arteries (Ortiz et al., 1992). Histamine also constricts pulmonary veins by pactivation of H_1 -receptors (Barman and Taylor, 1989). In the intact lung, histamine has both precapillary a 1992). Histamine also constricts pulmonary veins by path
activation of H_1 -receptors (Barman and Taylor, 1989). In oxy,
the intact lung, histamine has both precapillary and Tx Λ
postcapillary actions, with the latter activation of H_1 -receptors (Barman and Taylor, 1989). In ox
the intact lung, histamine has both precapillary and Tx
postcapillary actions, with the latter dominant (Shirai et
al., 1987). There seem to be developmental the intact lung, histamine h
postcapillary actions, with the
al., 1987). There seem to be
the pulmonary vascular resp
sheep (Gordon et al., 1991).
Histamine evokes oscillate al., 1987). There seem to be developmental change
the pulmonary vascular response to histamine in
sheep (Gordon et al., 1991).
Histamine evokes oscillatory membrane potass
and chloride currents through the release of intr

the pulmonary vascular response to histamine in the et sheep (Gordon et al., 1991).

Histamine evokes oscillatory membrane potassium ber

and chloride currents through the release of intracellu-

lar Ca²⁺ from caffeinesheep (Gordon et al., 1991). be

Histamine evokes oscillatory membrane potassium be

and chloride currents through the release of intracellu-

lar Ca²⁺ from caffeine-sensitive Ca²⁺ stores (Wang and T₁

Large, 1993), vasoconstrictor action. *n* d chloride currents through the release of intracellu-
 $r Ca^{2+}$ from caffeine-sensitive Ca^{2+} stores (Wang and
 $r r g e$, 1993), and this may be the mechanism of its

soconstrictor action.
 12. 5-Hydroxytryptamine. lar Ca²⁺ from caffeine-sensitive Ca²⁺ stores (Wang and Tx₄
Large, 1993), and this may be the mechanism of its et a
vasoconstrictor action.
12. 5-Hydroxytryptamine. 5-HT or serotonin is pro- et a
duced by activated p

Large, 1993), and this may be the mechanism of its et vasoconstrictor action.

12. 5-Hydroxytryptamine. 5-HT or serotonin is pro-

duced by activated platelets and has been suggested as a

mediator of pulmonary hypertensio 12. 5-Hydroxytryptamine. 5-HT or serotonin is produced by activated platelets and has been suggested as a mediator of pulmonary hypertension in the presence of pulmonary thromboemboli (Comroe et al., 1953). Indeed, 5-HT i 12. $5-Hydroxytryptamine$. $5-HT$ or serotonin is produced by activated platelets and has been suggested as a mediator of pulmonary hypertension in the presence of pulmonary thromboemboli (Comroe et al., 1953). Indeed, $5-HT$ is a pote duced by activated platelets and has been suggested as a
mediator of pulmonary hypertension in the presence of
epulmonary thromboemboli (Comroe et al., 1953). Indeed,
the 5-HT is a potent pulmonary vasoconstrictor in sever mediator of pulmonary hypertension in the presence of et
pulmonary thromboemboli (Comroe et al., 1953). Indeed, th
5-HT is a potent pulmonary vasoconstrictor in several P
species (Hyman et al., 1982; McMurtry, 1986), causi pulmonary thromboemboli (Comroe et al., 1953). Indeed,
5-HT is a potent pulmonary vasoconstrictor in several
species (Hyman et al., 1982; McMurtry, 1986), causing
vasoconstriction even under conditions of elevated tone
(Hy 5-HT is a potent pulmonary vasoconstrictor in several
species (Hyman et al., 1982; McMurtry, 1986), causing
vasoconstriction even under conditions of elevated tone
(Hyman et al., 1982). However, 5-HT relaxes pulmonary
vess species (Hyman et al., 1982; McMurtry, 1986), causing
vasoconstriction even under conditions of elevated tone
(Hyman et al., 1982). However, 5-HT relaxes pulmonary
vessels in other species when vascular tone is high.
Thus, vasoconstriction even under conditions of elevated (Hyman et al., 1982). However, 5-HT relaxes pulmor
vessels in other species when vascular tone is h
Thus, 5-HT relaxes precontracted pulmonary vasc
beds of cats (Neely et (Hyman et al., 1982). However, 5-HT relaxes pulmonary
vessels in other species when vascular tone is high.
Thus, 5-HT relaxes precontracted pulmonary vascular
beds of cats (Neely et al., 1993), and induces endotheli-
um-de

ND LIU
sheep (Cocks and Arnold, 1992). 5-HT contracts human
pulmonary arteries and veins in vitro (Raffestin et al., ND LIU
sheep (Cocks and Arnold, 1992). 5-HT contracts human
pulmonary arteries and veins in vitro (Raffestin et al.,
1985) yet has no effect on PPA in vivo (Harris et al., ND LIU
sheep (Cocks and Arnold, 1992). 5-HT contracts human
pulmonary arteries and veins in vitro (Raffestin et al.,
1985) yet has no effect on PPA in vivo (Harris et al.,
1960). This may be caused by the balancing between sheep (Cocks and Arnold, 1992). 5-HT contracts human
pulmonary arteries and veins in vitro (Raffestin et al.,
1985) yet has no effect on PPA in vivo (Harris et al.,
1960). This may be caused by the balancing between its
v sheep (Cocks and Arnold, 1992). 5-HT contracts human
pulmonary arteries and veins in vitro (Raffestin et al.,
1985) yet has no effect on PPA in vivo (Harris et al.,
1960). This may be caused by the balancing between its
v punionary arteries and vents in viro (Kanestin et al., 1985) yet has no effect on PPA in vivo (Harris et al., 1960). This may be caused by the balancing between its vasoconstrictor and vasodilator effects. Both 5-HT₁ (Ma 1960). This may be caused by the balancing between its vasoconstrictor and vasodilator effects. Both 5-HT₁ (MacIntyre et al., 1993) and 5-HT₂-receptors (Raffestin et al., 1985; Le Roux and Syce, 1989; McMahon et al., vasoconstrictor and vasodilator effects. Both $5\text{-}HT_1$
(MacIntyre et al., 1993) and $5\text{-}HT_2$ -receptors (Raffestin
et al., 1985; Le Roux and Syce, 1989; McMahon et al.,
1993b) are involved in the contractile response t (MacIntyre et al., 1993) and 5-HT₂-receptors (Raffestin et al., 1985; Le Roux and Syce, 1989; McMahon et al., 1993b) are involved in the contractile response to 5-HT, whereas the relaxant response to 5-HT is mediated vi et al., 1985; Le Roux and Syce, 1989; McMahon et al., 1993b) are involved in the contractile response to 5-HT, whereas the relaxant response to 5-HT is mediated via 5-HT₁ receptors (Neely et al., 1993; Glusa and Richter, 1993b) are involved in the contractile response to 5-HT,
whereas the relaxant response to 5-HT is mediated via
5-HT₁ receptors (Neely et al., 1993; Glusa and Richter,
1993). 5-HT stimulates the endothelial 5-HT_{1C} rece whereas the relaxant response to 5-HT is mediated vi
5-HT₁ receptors (Neely et al., 1993; Glusa and Richte
1993). 5-HT stimulates the endothelial 5-HT_{1C} receptor
and triggers the release of NO, leading to pulmonar
vas 5-HT₁ receptors (Neely et al., 1993; Glusa and Richt 1993). 5-HT stimulates the endothelial 5-HT_{1C} recept
and triggers the release of NO, leading to pulmonary vasodilation (Cocks and Arnold, 1992; Glusa and Riter, 199 1993). 5-HT stimulates the endothelial 5-HT_{1C} receptors
and triggers the release of NO, leading to pulmonary
vasodilation (Cocks and Arnold, 1992; Glusa and Rich-
ter, 1993). 5-HT stimulates and inhibits bovine pulmo-
n and triggers the release of NO, leading to pulmonary
vasodilation (Cocks and Arnold, 1992; Glusa and Rich-
ter, 1993). 5-HT stimulates and inhibits bovine pulmo-
nary vascular smooth muscle proliferation in vitro (Lee
et a vasodilation (Cocks and Arnold, 1992; Glusa and Richter, 1993). 5-HT stimulates and inhibits bovine pulmonary vascular smooth muscle proliferation in vitro (Lee et al., 1991a). Tyrosine phosphorylation and elevation of *c*ter, 1993). 5-HT stimulates and inhibits bovine pulmonary vascular smooth muscle proliferation in vitro (Lee et al., 1991a). Tyrosine phosphorylation and elevation of c -*myc* and actin mRNA seem to be prerequisites for nary vascular smooth muscle proliferation in vitro (Lee
et al., 1991a). Tyrosine phosphorylation and elevation of
c-myc and actin mRNA seem to be prerequisites for the
stimulation of DNA synthesis (Lee et al., 1994), wh et al., 1991a). Tyrosine phosphorylation and elevation of $c\text{-}myc$ and actin mRNA seem to be prerequisites for the stimulation of DNA synthesis (Lee et al., 1994), whereas activation of $5\text{-}HT_{1\text{A}}$ receptors and elev c-myc and actin mRNA seem to be prerequisites for the
stimulation of DNA synthesis (Lee et al., 1994), whereas
activation of 5-HT_{1A} receptors and elevation of cAMP
mediate the inhibitory effect of 5-HT on smooth muscle
 stimulation of DNA synthesis (Lee et al., 1994), whereas
activation of 5- HT_{1A} receptors and elevation of cAMP
mediate the inhibitory effect of 5-HT on smooth muscle
proliferation (Lee et al., 1991a). 5-HT released from activation of 5- HT_{1A} receptors and elevation of cAMP mediate the inhibitory effect of 5-HT on smooth muscle proliferation (Lee et al., 1991a). 5-HT released from platelets contributes to the initiation and progression mediate the ir
proliferation (platelets contr
monocrotaline
et al., 1993).
13. Eicosano

platelets contributes to the initiation and progression of monocrotaline-induced pulmonary hypertension (Kanai et al., 1993).
 13. Eicosanoids. Arachidonic acid is an essential fatty acid and an integral component of dif acid and an integral component of different phospholipid by a variety of stimuli via either Ca^{2+} -dependent or et al., 1993).

13. Eicosanoids. Arachidonic acid is an essential fatty

acid and an integral component of different phospholipid

pools in the cell membranes. Activation of phospholipase

by a variety of stimuli via eith 13. Eicosanoids. Arachidonic acid is an essential fatty
acid and an integral component of different phospholipid
pools in the cell membranes. Activation of phospholipase
by a variety of stimuli via either Ca^{2+} -dependen acid and an integral component of different phospholipase
pools in the cell membranes. Activation of phospholipase
by a variety of stimuli via either Ca^{2+} -dependent or
 Ca^{2+} -independent pathways induces the release o by a variety of stimuli via either Ca^{2+} -dependent or Ca^{2+} -independent pathways induces the release of arachidonic acid and lyso-PAF, the latter being the precursor of PAF. Upon release, arachidonic acid may be metab arachidonic acid and lyso-PAF, the latter being the pre-
cursor of PAF. Upon release, arachidonic acid may be
metabolized via two main pathways: the 5'-lipoxygenase
pathway leading to the production of LTs and the cyclo-
 cursor of PAF. Upon release, arachidonic acid may be metabolized via two main pathways: the 5'-lipoxygenase etabolized via two main pathways: the 5'-lipoxygenic
thway leading to the production of LTs and the cyc
ygenase pathway leading to the formation of PGs a
 κA_2 (TxA₂).
Arachidonic acid itself constricts the perfused

postcapillary actions, with the latter dominant (Shirai et Arachidonic acid itself constricts the perfused pulmo-
al., 1987). There seem to be developmental changes in mary vascular bed when the vascular tone is low (Wicks vessels in other species when vascular tone is high. and $PGF_{2\alpha}$ usually act as pulmonary vasoconstrictors
Thus, 5-HT relaxes precontracted pulmonary vascular (Kadowitz, 1975), with $PGF_{2\alpha}$ being the most potent
beds pathway leading to the production of LTs and the cyclo-
oxygenase pathway leading to the formation of PGs and
Tx A_2 (Tx A_2).
Arachidonic acid itself constricts the perfused pulmo-
nary vascular bed when the vascular oxygenase pathway leading to the formation of PGs and $Tx A_2$ ($Tx A_2$).
Arachidonic acid itself constricts the perfused pulmonary vascular bed when the vascular tone is low (Wicks et al., 1976; Selig et al., 1986) but rela Tx A_2 (Tx A_2).
Arachidonic acid itself constricts the perfused pulm
nary vascular bed when the vascular tone is low (Wick
et al., 1976; Selig et al., 1986) but relaxes the vascula
bed when the vascular tone is elevat Arachidonic acid itself constricts the perfused puln
nary vascular bed when the vascular tone is low (Wie
et al., 1976; Selig et al., 1986) but relaxes the vascu
bed when the vascular tone is elevated by hypoxia (G
ber et nary vascular bed when the vascular tone is low (Wicks
et al., 1976; Selig et al., 1986) but relaxes the vascular
bed when the vascular tone is elevated by hypoxia (Ger-
ber et al., 1980). The contractile responses to arac 1976; Selig et al., 1986) but relaxes the vascular
then the vascular tone is elevated by hypoxia (Ger-
t al., 1980). The contractile responses to arachi-
acid are caused in large part by the formations of
and other prosta bed when the vascular tone is elevated by hypoxia (Gerber et al., 1980). The contractile responses to arachidonic acid are caused in large part by the formations of TxA_2 and other prostanoids (Selig et al., 1986; McMahon ber et al., 1980). The contractile responses to arachidonic acid are caused in large part by the formations of TxA_2 and other prostanoids (Selig et al., 1986; McMahon et al., 1991b). The endoperoxide intermediate, PGH_2 donic acid are caused in large part by the formations of TxA_2 and other prostanoids (Selig et al., 1986; McMahon et al., 1991b). The endoperoxide intermediate, PGH_2 , is also a pulmonary vasoconstrictor in the adult (K TxA_2 and other prostanoids (Selig et al., 1986; McMahon
et al., 1991b). The endoperoxide intermediate, PGH_2 , is
also a pulmonary vasoconstrictor in the adult (Kadowitz
et al., 1977; Gruetter et al., 1978), but in feta et al., 1991b). The endoperoxide intermediate, PGH_2 , is
also a pulmonary vasoconstrictor in the adult (Kadowitz
et al., 1977; Gruetter et al., 1978), but in fetal lambs, a
pulmonary vasodilator response has been reporte also a pulmonary vasoconstrictor in the adult (Kadowitz
et al., 1977; Gruetter et al., 1978), but in fetal lambs, a
pulmonary vasodilator response has been reported (Tod
et al., 1986). The primary prostaglandins formed fr pulmonary vasodilator response has been reported (Tod
et al., 1986). The primary prostaglandins formed from
this intermediate include PGD_2 , PGE_2 , $PGF_{2\alpha}$, and
 PGI_2 . Although pulmonary vasodilator responses to
 $PGD_$ et al., 1986). The primary prostaglandins formed from
this intermediate include PGD_2 , PGE_2 , $PGF_{2\alpha}$, and
 PGI_2 . Although pulmonary vasodilator responses to
 PGD_2 (Ford et al., 1990); Perreault et al., 1990) or PGE this intermediate include PGD_2 , PGE_2 , $PGF_{2\alpha}$, and PGI_2 . Although pulmonary vasodilator responses to PGD_2 (Ford et al., 1990; Perreault et al., 1990) or PGE_2 (Lock et al., 1980; Cassin et al., 1981a) have been PGI₂. Although pulmonary vasodilator responses to PGD₂ (Ford et al., 1990); Perreault et al., 1990) or PGE₂ (Lock et al., 1980; Cassin et al., 1981a) have been reported in fetal and early neonatal lambs, PGD₂, PGE PGD_2 (Ford et al., 1990; Perreault et al., 1990) or PGE_2
(Lock et al., 1980; Cassin et al., 1981a) have been re-
ported in fetal and early neonatal lambs, PGD_2 , PGE_2
and $PGF_{2\alpha}$ usually act as pulmonary vasocons (Lock et al., 1960; Cassin et al., 1961a) have been re-
ported in fetal and early neonatal lambs, PGD_2 , PGE_2
and $PGF_{2\alpha}$ usually act as pulmonary vasoconstrictors
(Kadowitz, 1975; Hyman et al., 1982). In contrast, ported in fetal and early neonatal lambs, PGD_2 , PGE_2 and $PGF_{2\alpha}$ usually act as pulmonary vasoconstrictors (Kadowitz, 1975), with $PGF_{2\alpha}$ being the most potent (Kadowitz, 1975; Hyman et al., 1982). In contrast, PG

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REGULATION OF PULMONARY VASCULAR TONE
resistance in the blood-perfused rabbit pulmonary vas- ondary to congenita
cular bed, via stimulation of TxA₂ synthesis (Kaapa et higher plasma TxA REGULATION OF PULMON

resistance in the blood-perfused rabbit pulmonary vas-

cular bed, via stimulation of TxA₂ synthesis (Kaapa et lal., 1991). PGE₁ relaxes pulmonary vessels at elevated REGULATION OF PULMONA
resistance in the blood-perfused rabbit pulmonary vas-
cular bed, via stimulation of TxA_2 synthesis (Kaapa et h
al., 1991). PGE₁ relaxes pulmonary vessels at elevated w
tone (Hyman and Kadowitz, resistance in the blood-perfused rabbit pulmonary vas-
cular bed, via stimulation of TxA_2 synthesis (Kaapa et h
al., 1991). PGE₁ relaxes pulmonary vessels at elevated w
tone (Hyman and Kadowitz, 1979). Tx A_2 and its resistance in the blood-periused rabolt pullmolary vas-
cular bed, via stimulation of TxA_2 synthesis (Kaapa et
al., 1991). PGE₁ relaxes pulmonary vessels at elevated
tone (Hyman and Kadowitz, 1979). TxA_2 and its sta al., 1991). PGE₁ relaxes pulmonary vessels at elevated value (Hyman and Kadowitz, 1979). TxA₂ and its stable chreakdown product TxB₂ are pulmonary vasoconstrictors (Friedman et al., 1979; Kadowitz and Hyman, a 1980) tone (Hyman and Kadowitz, 1979). TxA₂ and its stable
breakdown product TxB₂ are pulmonary vasoconstrictors (Friedman et al., 1979; Kadowitz and Hyman, aft
1980). Some of the vasoconstrictor effect of TxA₂ seems oxy
 breakdown product TxB_2 are pulmonary vasoconstri
tors (Friedman et al., 1979; Kadowitz and Hyma
1980). Some of the vasoconstrictor effect of TxA_2 seen
to be mediated by the induction of LTC_4 and LTT
formation (Soif tors (Friedman et al., 1979; Kadowitz and Hyman, afte 1980). Some of the vasoconstrictor effect of TxA_2 seems oxyg to be mediated by the induction of LTC_4 and LTD_4 puln formation (Soifer et al., 1989). TxA_2 is rep 1980). Some of the vasoconstrictor effect of TxA_2 seems
to be mediated by the induction of LTC_4 and LTD_4
formation (Soifer et al., 1989). TxA_2 is reported to medi-
ate the endothelium-dependent contractile respons to be mediated by the induction of l
formation (Soifer et al., 1989). TxA₂ is n
ate the endothelium-dependent contra
arachidonic acid and methacholine in r
artery in vitro (Buzzard et al., 1993).
The lipoxygenase metabo rmation (Soifer et al., 1989). Tx A_2 is reported to medi-
e the endothelium-dependent contractile response to
achidonic acid and methacholine in rabbit pulmonary
tery in vitro (Buzzard et al., 1993).
The lipoxygenase me

ate the endothelium-dependent contractile response to
arachidonic acid and methacholine in rabbit pulmonary
artery in vitro (Buzzard et al., 1993).
The lipoxygenase metabolites of arachidonic acid,
LTA₄, LTB₄, LTC₄, arachidonic acid and methacholine in rabbit pulmonary
artery in vitro (Buzzard et al., 1993).
The lipoxygenase metabolites of arachidonic acid,
LTA₄, LTB₄, LTC₄, and LTD₄, have diverse biological
activities, inclu artery in vitro (Buzzard et al., 1993).
The lipoxygenase metabolites of arachidonic acid,
LTA₄, LTB₄, LTC₄, and LTD₄, have diverse biological
activities, including effects on pulmonary vessels. LTB₄,
C₄, and D The lipoxygenase metabolites of arachidonic acid,
LTA₄, LTB₄, LTC₄, and LTD₄, have diverse biological
activities, including effects on pulmonary vessels. LTB₄,
C₄, and D₄ cause contraction of isolated pulmon activities, including effects on pulmonary vessels. LTB₄, C_4 , and D_4 cause contraction of isolated pulmonary ves-
sel rings of guinea pig (Hand et al., 1981), pig (Ohtaka et al., 1987; Paterson et al., 1988), and C_4 , and D_4 cause contraction of isolated pulmonary vessel rings of guinea pig (Hand et al., 1981), pig (Ohtaka et al., 1987; Paterson et al., 1988), and human (Hanna et al., 1981), and the intact pulmonary vascular al., 1981), and the intact pulmonary vascular bed in viv
(Ahmed et al., 1985; Noonan and Malik, 1986) or in sit
(Voelkel et al., 1984; Albert et al., 1989). The effects of
LTs are mediated by specific LT-receptors (Voelkel (Ahmed et al., 1985; Noonan and Malik, 1986) or in
(Voelkel et al., 1984; Albert et al., 1989). The effection
LTs are mediated by specific LT-receptors (Voelkel
1984) and also via the release of cyclo-oxygenase
ucts (Ahme (Voelkel et al., 1984; Albert et al., 1989). The effects of

LTs are mediated by specific LT-receptors (Voelkel et al.,

1984) and also via the release of cyclo-oxygenase prod-

ucts (Ahmed et al., 1985). Both endothelium LTs are mediated by specific LT-receptors (Voelkel et al.,
1984) and also via the release of cyclo-oxygenase products (Ahmed et al., 1985). Both endothelium-dependent
contractile and relaxant responses to LTC_4 and LTD_4 1984) and also via the release of cyclo-oxygenase products (Ahmed et al., 1985). Both endothelium-dependent
contractile and relaxant responses to LTC_4 and LTD_4
have been reported in systemic vessels (McLeod and
Piper, ucts (Ahmed et al., 1985). Both endothelium-dependent

contractile and relaxant responses to LTC_4 and LTD_4

have been reported in systemic vessels (McLeod and

Piper, 1992; Pawloski and Chapnick, 1993). Whether the

s contractile and relaxant responses to LTC_4 and LTD_4
have been reported in systemic vessels (McLeod and
Piper, 1992; Pawloski and Chapnick, 1993). Whether the
same mechanism exists in pulmonary vessels remains to
be de mave been reported in systemic vessels (included and

Piper, 1992; Pawloski and Chapnick, 1993). Whether the

same mechanism exists in pulmonary vessels remains to

be determined.

Recently, a noncyclo-oxygenase, free radi

be determined.

be determined.

Recently, a noncyclo-oxygenase, free radical-cata-

lyzing effect of arachidonic acid through this pathway leads

to the production of $PGF_{2\alpha}$ -like compounds in humans in

vivo (Kang et a Recently, a noncyclo-oxygenase, free radical-cata-
lyzing effect of arachidonic acid has been described. Metabolism of arachidonic acid through this pathway leads
to the production of $\text{PGF}_{2\alpha}$ -like compounds in humans lyzing effect of arachidonic acid has been described. Metabolism of arachidonic acid through this pathway leads
to the production of $PGF_{2\alpha}$ -like compounds in humans in
vivo (Kang et al., 1993). One of the compounds for Example and through this pathway leads
to the production of $PGF_{2\alpha}$ -like compounds in humans in
vivo (Kang et al., 1993). One of the compounds formed by
this pathway is 8-epiprostaglandin $F_{2\alpha}$, which causes
pulmonar to the production of $PGF_{2\alpha}$ -like compounds in humans in
vivo (Kang et al., 1993). One of the compounds formed by
this pathway is 8-epiprostaglandin $F_{2\alpha}$, which causes
pulmonary vasoconstriction via the generation o wivo (Kang et al., 1993). One of the compounds formed by
this pathway is 8-epiprostaglandin $F_{2\alpha}$, which causes
pulmonary vasoconstriction via the generation of TxA₂
(Kang, et al., 1993). This compound constricts bot ulmonary vasoconstriction via the generation of TxA_2 may a

fang, et al., 1993). This compound constricts both pul-

pulmonary arteries and veins with a potency twice as great
 $PGF_{2\alpha}$.

The role of these arachidonic

(Kang, et al., 1993). This compound constricts both pulmonary arteries and veins with a potency twice as great as $\mathrm{PGF}_{2\alpha}$.
The role of these arachidonic acid metabolites in HPV and various pulmonary vascular patholog monary arteries and veins with a potency twice as greas $PGF_{2\alpha}$.
The role of these arachidonic acid metabolites in HI
and various pulmonary vascular pathological condition
especially in hypoxic or other types of pulmona as $\text{PGF}_{2\alpha}$.
The role of these arachidonic acid metabolites in HP and various pulmonary vascular pathological condition especially in hypoxic or other types of pulmonary hype tension, has been the subject of intensive The role of these arachidonic acid metabolites in HPV
and various pulmonary vascular pathological conditions,
especially in hypoxic or other types of pulmonary hyper-
tension, has been the subject of intensive investigatio and various pulmonary vascular pathological conditions,
especially in hypoxic or other types of pulmonary hyper-
tension, has been the subject of intensive investigation.
However, their definitive roles under these conditi especially in hypoxic or other types of pulmonary hyper-
tension, has been the subject of intensive investigation.
However, their definitive roles under these conditions
are still unclear. Some of the metabolites may cont behavior, has been the subject of intensive investigation.
However, their definitive roles under these conditions
are still unclear. Some of the metabolites may contribute
to development of pulmonary vascular disease, such are still unclear. Some of the metabolites may contribute to development of pulmonary vascular disease, such as pulmonary hypertension, in some animal models but P have no clear role in other animals. The complex inter-
a to development of pulmonary vascular disease, such as
pulmonary hypertension, in some animal models but
have no clear role in other animals. The complex inter-
action between these mediators, either synergistic or
antagon pulmonary hypertension, in some animal models but
have no clear role in other animals. The complex inter-
action between these mediators, either synergistic or
antagonistic, makes it very difficult to evaluate their
role. have no clear role in other animals. The complex inter-
action between these mediators, either synergistic or
antagonistic, makes it very difficult to evaluate their
role. Cyclo-oxygenase products (especially TxB_2) and action between these mediators, either synergistic or antagonistic, makes it very difficult to evaluate their role. Cyclo-oxygenase products (especially TxB_2) and li-poxygenase (LTB₄) seem to contribute to the early p antagonistic, makes it very difficult to evaluate their
role. Cyclo-oxygenase products (especially TxB_2) and li-
poxygenase (LTB₄) seem to contribute to the early pul-
monary hypertension seen in sepsis or TNF_{α} -in role. Cyclo-oxygenase products (especially TxB_2) and poxygenase (LTB_4) seem to contribute to the early monary hypertension seen in sepsis or TNF_{α} -indulung injury (Wheeler et al., 1992; Kuratomi et al., 19 TxB_2 may poxygenase (LTB₄) seem to contribute to the early pulmonary hypertension seen in sepsis or TNF_a-induced lung injury (Wheeler et al., 1992; Kuratomi et al., 1993). ITxB₂ may also contribute to the pulmonary hypertens monary hypertension seen in sepsis or TNF_{α} -induced
lung injury (Wheeler et al., 1992; Kuratomi et al., 1993).
 TxB_2 may also contribute to the pulmonary hypertension seen in ischemia-reperfusion lung injury (Za

MARY VASCULAR TONE

ondary to congenital heart disease have significantly

higher plasma TxA_2 and lower PGI_2 levels compared MARY VASCULAR TONE

ondary to congenital heart disease have significantly

higher plasma TxA_2 and lower PGI_2 levels compared

with normal subjects, suggesting an imbalance between where variables is a star of the normal subjects, suggesting an imbalance between constrictor and dilator cyclo-oxygenase products. Inter ondary to congenital heart disease have significant
higher plasma TxA_2 and lower PGI_2 levels compare
with normal subjects, suggesting an imbalance betwee
constrictor and dilator cyclo-oxygenase products. Inte
estingly ondary to congenital heart disease have significantly
higher plasma TxA_2 and lower PGI_2 levels compared
with normal subjects, suggesting an imbalance between
constrictor and dilator cyclo-oxygenase products. Inter-
es with normal subjects, suggesting an imbalance between
constrictor and dilator cyclo-oxygenase products. Inter-
estingly, plasma TxA_2 levels return to normal 1 year
after corrective surgery (Adatia et al., 1993a). Cycloonstrictor and dilator cyclo-oxygenase products. Inter-
estingly, plasma TxA_2 levels return to normal 1 year
after corrective surgery (Adatia et al., 1993a). Cyclo-
oxygenase products may participate in the regulation o estingly, plasma TxA₂ levels return to normal 1 yeafter corrective surgery (Adatia et al., 1993a). Cycloxygenase products may participate in the regulation pulmonary vascular tone during cardiopulmonary pre ervation (Mas ter corrective surgery (Adatia et al., 1993a). Cyclo-
14. Platelet-activating factorial in the regulation of
14. Platelet-activating factor. PAF is a lipid mediator
14. Platelet-activating factor. PAF is a lipid medi

LTA₄, LTB₄, LTC₄, and LTD₄, have diverse biological tors. PAF has potent cardiovascular effects that vary activities, including effects on pulmonary vessels. LTB₄, according to species, age, physiological condit al., 1987; Paterson et al., 1988), and human (Hanna et temic hypotension, pulmonary hypertension, and pul-
al., 1981), and the intact pulmonary vascular bed in vivo
(Ahmed et al., 1985; Noonan and Malik, 1986) or in situ
(al., 1981), and the intact pulmonary vascular bed in vivo

(Ahmed et al., 1985; Noonan and Malik, 1986) or in situ

(Voelkel et al., 1982; Burhop et al., 1986;

(Voelkel et al., 1984; Albert et al., 1989). The effects of
 oxygenase products may participate in the regulation opulmonary vascular tone during cardiopulmonary pre
ervation (Mashburn et al., 1989).
14. Platelet-activating factor. PAF is a lipid mediate
derived from lyso-PAF, which pulmonary vascular tone during cardiopulmonary pres-
ervation (Mashburn et al., 1989).
14. Platelet-activating factor. PAF is a lipid mediator
derived from lyso-PAF, which is released from mem-
brane phospholipids by the s ervation (Mashburn et al., 1989).
14. Platelet-activating factor. PAF is a lipid medi
derived from lyso-PAF, which is released from m
brane phospholipids by the same conditions that rela
arachidonic acid and acts on specif 14. Platelet-activating factor. PAF is a lipid mediator
derived from lyso-PAF, which is released from mem-
brane phospholipids by the same conditions that release
arachidonic acid and acts on specific surface PAF-recep-
to derived from lyso-PAF, which is released from mem-
brane phospholipids by the same conditions that release
arachidonic acid and acts on specific surface PAF-recep-
tors. PAF has potent cardiovascular effects that vary
acco brane phospholipids by the same conditions that release
arachidonic acid and acts on specific surface PAF-recep-
tors. PAF has potent cardiovascular effects that vary
according to species, age, physiological conditions, an arachidonic acid and acts on specific surface PAF-receptors. PAF has potent cardiovascular effects that vary according to species, age, physiological conditions, and concentration (McMurtry, 1986; vandongen, 1991). In adul tors. PAF has potent cardiovascular effects that vary
according to species, age, physiological conditions, and
concentration (McMurtry, 1986; vandongen, 1991). In
adult animals under resting conditions, PAF causes sys-
tem according to species, age, physiological conditions, and
concentration (McMurtry, 1986; vandongen, 1991). In
adult animals under resting conditions, PAF causes sys-
temic hypotension, pulmonary hypertension, and pul-
monar concentration (McMurtry, 1986; vandongen, 1991). In
adult animals under resting conditions, PAF causes systemic hypotension, pulmonary hypertension, and pul-
monary edema (Voelkel et al., 1982; Burhop et al., 1986;
Bellan, adult animals under resting conditions, PAF causes systemic hypotension, pulmonary hypertension, and pulmonary edema (Voelkel et al., 1982; Burhop et al., 1986; Bellan, et al., 1992; Shibamoto et al., 1993). By contrast, P temic hypotension, pulmonary hypertension, and pul-
monary edema (Voelkel et al., 1982; Burhop et al., 1986;
Bellan, et al., 1992; Shibamoto et al., 1993). By contrast,
PAF constricts both systemic and pulmonary vessels,
w monary edema (Voelkel et al., 1982; Burhop et al., 1986
Bellan, et al., 1992; Shibamoto et al., 1993). By contrass
PAF constricts both systemic and pulmonary vessels
with significant venoconstriction occurring in the feta
 Bellan, et al., 1992; Shibamoto et al., 1993). By contrast,
PAF constricts both systemic and pulmonary vessels,
with significant venoconstriction occurring in the fetal
lamb (Toga et al., 1992a). PAF induces pulmonary vaso PAF constricts both systemic and pulmonary vessels,
with significant venoconstriction occurring in the fetal
lamb (Toga et al., 1992a). PAF induces pulmonary vaso-
constriction when the vascular tone is low (Voelkel et al. with significant venoconstriction occurring in the fetal
lamb (Toga et al., 1992a). PAF induces pulmonary vaso-
constriction when the vascular tone is low (Voelkel et al.,
1982; Burhop et al., 1986; Pritze et al., 1991) bu lamb (Toga et al., 1992a). PAF induces pulmonary vaso-
constriction when the vascular tone is low (Voelkel et al.,
1982; Burhop et al., 1986; Pritze et al., 1991) but causes
vasodilation when the vascular tone is high (McM constriction when the vascular tone is low (Voelkel et 1982; Burhop et al., 1986; Pritze et al., 1991) but cau vasodilation when the vascular tone is high (McMur and Morris, 1986; Chen et al., 1992). Leukotrienes a ${\rm TxA}_$ 1982; Burhop et al., 1986; Pritze et al., 1991) but causes
vasodilation when the vascular tone is high (McMurtry
and Morris, 1986; Chen et al., 1992). Leukotrienes and
 TxA_2 play an important role in mediating the vasoco vasodilation when the vascular tone is high (McMurtry and Morris, 1986; Chen et al., 1992). Leukotrienes and TxA_2 play an important role in mediating the vasoconstrictor response to PAF in dog (Yamanaka et al., 1992), r TxA₂ play an important role in mediating the vasoconstrictor response to PAF in dog (Yamanaka et al., 1992), rat (Davidson and Drafta, 1992), and lamb (Toga et al., 1992a), but have no role in the PAF-induced vasoconstr rat (Davidson and Drafta, 1992), and lamb (Toga et al., rictor response to PAF in dog (Yamanaka et al., 1992),
t (Davidson and Drafta, 1992), and lamb (Toga et al.,
92a), but have no role in the PAF-induced vasocon-
riction in the cat (Bellan et al., 1992).
Prostaglandins may c

rat (Davidson and Drafta, 1992), and lamb (Toga et al., 1992a), but have no role in the PAF-induced vasoconstriction in the cat (Bellan et al., 1992).

Prostaglandins may contribute to the pulmonary vasodilator response t 1992a), but have no role in the PAF-induced vasoconstriction in the cat (Bellan et al., 1992).

Prostaglandins may contribute to the pulmonary vasodilator response to PAF (Yamanaka et al., 1992). NO

may also be involved i striction in the cat (Bellan et al., 1992).
Prostaglandins may contribute to the pulmonary vasodilator response to PAF (Yamanaka et al., 1992). NO
may also be involved in this response, inasmuch as the
pulmonary vasorelaxa Prostaglandins may contribute to the pulmonary vasodilator response to PAF (Yamanaka et al., 1992). NO
may also be involved in this response, inasmuch as the
pulmonary vasorelaxant response to PAF in vitro is en-
dothelium sodilator response to PAF (Yamanaka et al., 1992). NO
may also be involved in this response, inasmuch as the
pulmonary vasorelaxant response to PAF in vitro is en-
dothelium-dependent (McMurtry and Morris, 1986).
PAF is ab may also be involved in this response, inasmuch as the pulmonary vasorelaxant response to PAF in vitro is endothelium-dependent (McMurtry and Morris, 1986).
PAF is able to trigger NO release in systemic vessels or vascular pulmonary vasorelaxant response to PAF in vitro is endothelium-dependent (McMurtry and Morris, 1986).
PAF is able to trigger NO release in systemic vessels or vascular beds (Moritoki et al., 1992; Bellan et al., 1992).
Alt dothelium-dependent (McMurtry and Morris, 1986).
PAF is able to trigger NO release in systemic vessels or
vascular beds (Moritoki et al., 1992; Bellan et al., 1992).
Although PAF reverses HPV (McMurtry and Morris,
1986; Ch PAF is able to trigger NO release in systemic vessels or vascular beds (Moritoki et al., 1992; Bellan et al., 1992).
Although PAF reverses HPV (McMurtry and Morris, 1986; Chen et al., 1992), it is unlikely to be involved, vascular beds (Moritoki et al., 1992; Bellan et al., 1992).
Although PAF reverses HPV (McMurtry and Morris,
1986; Chen et al., 1992), it is unlikely to be involved,
because PAF antagonists do not modify the response
(Hayne Although PAF reverses HPV (McMurtry and Morris, 1986; Chen et al., 1992), it is unlikely to be involved, because PAF antagonists do not modify the response (Haynes et al., 1988; McCormack et al., 1989a). PAF may contribute 1986; Chen et al., 1992), it is unlikely to be involved,
because PAF antagonists do not modify the response
(Haynes et al., 1988; McCormack et al., 1989a). PAF
may contribute to the development of chronic hypoxic
pulmonary because PAF antagonists do not modify the response
(Haynes et al., 1988; McCormack et al., 1989a). PAF
may contribute to the development of chronic hypoxic
pulmonary hypertension, however. Chronic infusion of
PAF into rabb (Haynes et al., 1988; McCormack et al., 1989a). PAF
may contribute to the development of chronic hypoxic
pulmonary hypertension, however. Chronic infusion of
PAF into rabbits over a 4-week period results in both
hemodynami pulmonary hypertension, however. Chronic infusion of PAF into rabbits over a 4-week period results in both hemodynamic and morphological changes similar to those seen in pulmonary hypertension (Ohar et al., 1990; Ohar et a pulmonary hypertension, however. Chronic infusion of
PAF into rabbits over a 4-week period results in both
hemodynamic and morphological changes similar to
those seen in pulmonary hypertension (Ohar et al., 1990;
Ohar et a PAF into rabbits over a 4-week period results in both
hemodynamic and morphological changes similar to
those seen in pulmonary hypertension (Ohar et al., 1990;
Ohar et al., 1991). PAF is released into lavage fluids in
rats hemodynamic and morphological changes similar to
those seen in pulmonary hypertension (Ohar et al., 1990;
Ohar et al., 1991). PAF is released into lavage fluids in
rats exposed to hypoxia (Prevost et al., 1984). Newborn
hu those seen in pulmonary hypertension (Ohar et al., 1990;
Ohar et al., 1991). PAF is released into lavage fluids in
rats exposed to hypoxia (Prevost et al., 1984). Newborn
humans with persistent pulmonary hypertension have
 Ohar et al., 1991). PAF is released into lavage fluids in
rats exposed to hypoxia (Prevost et al., 1984). Newborn
humans with persistent pulmonary hypertension have
high plasma PAF levels (Caplan et al., 1990). Chronic
PAF rats exposed to hypoxia (Prevost et al., 1984). Newborn
humans with persistent pulmonary hypertension have
high plasma PAF levels (Caplan et al., 1990). Chronic
PAF treatment enhances pulmonary arterial reactivity
to some humans with persistent pulmonary hypertension have
high plasma PAF levels (Caplan et al., 1990). Chronic
PAF treatment enhances pulmonary arterial reactivity
to some vasoconstrictors in isolated pulmonary vascular
beds (Oh PAF treatment enhances pulmonary arterial reactivity
to some vasoconstrictors in isolated pulmonary vascular
beds (Ohar et al., 1993). Moreover, treatment of rats
with a specific PAF receptor antagonist slows down the

development of hypoxic pulmonary hypertension (Ono et al., 1992). 102
developmen
al., 1992).
15. Purin

¹⁹²

15. Purines. Purine nucleosides and nucleotides in-

15. *Purines*. Purine nucleosides and nucleotides in-

16. *Purines*. Purine nucleosides and nucleotides in-

16. *Purine*, AMP, ADP, and ATP. These purine development of hypoxic pulmonary hypertension (Ono et ad., 1992).
 A. 1992.
 A. To. Purines. Purine nucleosides and nucleotides include adenosine, AMP, ADP, and ATP. These purine rempounds have long been known to be va development of hypoxic pulmonary hypertension (Ono et act al., 1992).

Ad., 1992).

15. Purines. Purine nucleosides and nucleotides in-

clude adenosine, AMP, ADP, and ATP. These purine ral

compounds have long been known al., 1992).

15. Purines. Purine nucleosides and nucleotides :

clude adenosine, AMP, ADP, and ATP. These puri

compounds have long been known to be vasoactive a

have been implicated in many physiological and path

physio 15. Purines. Purine nucleosides and nucleotides include adenosine, AMP, ADP, and ATP. These purine compounds have long been known to be vasoactive and have been implicated in many physiological and pathophysiological proce clude adenosine, AMP, ADP, and ATP. These purine ral
compounds have long been known to be vasoactive and 199
have been implicated in many physiological and patho-
physiological processes (Olsson and Pearson, 1990; Da-
val compounds have long been known to be vasoactive and have been implicated in many physiological and path physiological processes (Olsson and Pearson, 1990; Dival et al., 1991). Purine receptors can be subdivided in P_1 have been implicated in many physiological and patho-
physiological processes (Olsson and Pearson, 1990; Da-
val et al., 1991). Purine receptors can be subdivided into
 P_1 - and P_2 -purinoceptors, which are selective f physiological processes (Olsson and Pearson, 1990; Daval et al., 1991). Purine receptors can be subdivided into P_1 - and P_2 -purinoceptors, which are selective for adenosine and ATP, respectively (Burnstock and Kenned val et al., 1991). Purine receptors can be subdivided into P_1 - and P_2 -purinoceptors, which are selective for adenosine and ATP, respectively (Burnstock and Kennedy, 1985). P_1 -receptors (adenosine receptors) can b P_1 - and P_2 -purinoceptors, which are selective for adenosine and ATP, respectively (Burnstock and Kennedy, 1985). P_1 -receptors (adenosine receptors) can be further subclassified into A_1 , A_2 (A_{2A} and A_{2 osine and ATP, respectively (Burnstock and Kennec
1985). P_1 -receptors (adenosine receptors) can be furth
subclassified into A_1 , A_2 (A_{2A} and A_{2B}) and A_3 recepto
(Collis and Hourani, 1993). These subtype 1985). P_1 -receptors (adenosine receptors) can be further subclassified into A_1 , A_2 (A_{2A} and A_{2B}) and A_3 receptors can (Collis and Hourani, 1993). These subtypes of adenosine sia receptor belong to the succlassified into A_1 , A_2 (A_{2A} and A_{2B}) and A_3 receptors

(Collis and Hourani, 1993). These subtypes of adenosine

receptor belong to the G-protein coupled receptor super-

family and are encoded by diffe receptor belong to the G-protein coupled receptor super-
family and are encoded by different genes (Collis and
Hourani, 1993). Likewise, P_2 -receptors can also be fur-
ther divided into P_{2x} and P_{2y} subtypes (Bur family and are encoded by different genes (Collis and
Hourani, 1993). Likewise, P_2 -receptors can also be fur-
ther divided into P_{2x} and P_{2y} subtypes (Burnstock and
Kennedy, 1985; Olsson and Pearson 1990). Other ther divided into P_{2x} and P_{2y} subtypes (Burnstock and Kennedy, 1985; Olsson and Pearson 1990). Other subtypes have been proposed but need to be confirmed (Olsson and Pearson, 1990). P_1 -receptors on pulmonary vessels have been characterized as A_1 and A_2 subtypes (McCormack et al., 1989c) and P_2 -receptors as P_{2x} and Kennedy, 1985; Olsson and Pearson 1990). Other sub-
types have been proposed but need to be confirmed (Ol-
sson and Pearson, 1990). P_1 -receptors on pulmonary
vessels have been characterized as A_1 and A_2 subtypes
 types have been proposed but need to be confirmed (Olson)

sson and Pearson, 1990). P₁-receptors on pulmonary

vessels have been characterized as A_1 and A_2 subtypes

(McCormack et al., 1989c) and P₂-receptors as sson and Pearson, 1990). P_1 -receptors on pulmonary
vessels have been characterized as A_1 and A_2 subtypes
(McCormack et al., 1989c) and P_2 -receptors as P_{2x} and
 P_{2y} subtypes (Liu et al., 1989a, b). P_{2x vessels have been characterized as A_1 and A_2 subtypes

(McCormack et al., 1989c) and P_2 -receptors as P_{2x} and
 P_{2y} subtypes (Liu et al., 1989a, b). P_{2x} receptors are

located on smooth muscle, whereas (McCormack et al., 1989c) and P_2 -receptors as P_{2x} and P_{2y} subtypes (Liu et al., 1989a, b). P_{2x} receptors are located on smooth muscle, whereas P_{2y} receptors are located on endothelium of rat pulmonary v P_{2y} subtypes (Liu et al., 1989a, b). P_{2x} receptors are
located on smooth muscle, whereas P_{2y} receptors are
located on endothelium of rat pulmonary vessels, but on
the vascular smooth muscle of human small pulm is located on smooth muscle, whereas P_{2y} receptors are
located on endothelium of rat pulmonary vessels, but on
the vascular smooth muscle of human small pulmonary
arteries (Liu et al., 1989a, b). It is not clear wheth cated on endothelium of rat pulmonary vessels, but on
e vascular smooth muscle of human small pulmonary
teries (Liu et al., 1989a, b). It is not clear whether this
a regional or a species-dependent variation.
Both adenosi

the vascular smooth muscle of human small pulm
arteries (Liu et al., 1989a, b). It is not clear whethe
is a regional or a species-dependent variation.
Both adenosine and ATP have dual effects on is
pulmonary vessels, causi arteries (Liu et al., 1989a, b). It is not clear whether this
is a regional or a species-dependent variation.
Both adenosine and ATP have dual effects on isolated
pulmonary vessels, causing concentration-dependent
contract is a regional or a species-dependent variation.

Both adenosine and ATP have dual effects on isolated

pulmonary vessels, causing concentration-dependent

contraction in vessels at resting tension and inducing

relaxation Both adenosine and ATP have dual effects on isolated
pulmonary vessels, causing concentration-dependent
contraction in vessels at resting tension and inducing
relaxation of precontracted vessel rings (McCormack et
al., 19 pulmonary vessels, causing concentration-dependent
contraction in vessels at resting tension and inducing
relaxation of precontracted vessel rings (McCormack et
al., 1989c; Wiklund et al., 1989a; Liu et al., 1989a, b).
Th contraction in vessels at resting tension and inducing
relaxation of precontracted vessel rings (McCormack et
al., 1989c; Wiklund et al., 1989a; Liu et al., 1989a, b).
The contraction is mediated via A_1 or P_{2x} rece relaxation of precontracted vessel rings (McCormack et al., 1989c; Wiklund et al., 1989a; Liu et al., 1989a, b).
The contraction is mediated via A_1 or P_{2x} receptors located on smooth muscle, whereas relaxation is m al., 1989c; Wiklund et al., 1989a; Liu et al., 1989a, b).
The contraction is mediated via A_1 or P_{2x} receptors located on smooth muscle, whereas relaxation is mediated by A_2 or P_{2y} receptors (McCormack et al. The contraction is mediated via A_1 or P_{2x} receptors located on smooth muscle, whereas relaxation is mediated by A_2 or P_{2y} receptors (McCormack et al., 1989c; Liu et al., 1989a, b). Adenosine increases PPA an cated on smooth muscle, whereas relaxation is mediated
by A_2 or P_{2y} receptors (McCormack et al., 1989c; Liu et $16.$ Cytokines. Cytokines are a group of small protein
al., 1989a, b). Adenosine increases PPA and pul by A_2 or P_{2y} receptors (McCormack et al., 1989c; Liu et al., 1989a, b). Adenosine increases PPA and pulmonary vascular resistance in adult sheep and cat pulmonary vascular beds (Biaggioni et al., 1989; Lippton et a al., 1989a, b). Adenosine increases PPA and pulmonary vascular resistance in adult sheep and cat pulmonary vascular beds (Biaggioni et al., 1989; Lippton et al., 1992) but decreases PPA and vascular resistance in fetal and vascular resistance in adult sheep and cat pulmonary
vascular beds (Biaggioni et al., 1989; Lippton et al., 1992) but decreases PPA and vascular resistance in fetal
and newborn lambs (Konduri et al., 1992a, b). Adenosine
i 1992) but decreases PPA and vascular resistance in feta
and newborn lambs (Konduri et al., 1992a, b). Adenosin
is a pulmonary vasodilator, both in normal volunteer
(Reid et al., 1990) and in patients with various types o
p and newborn lambs (Konduri et al., 1992a, b). Adenosine
is a pulmonary vasodilator, both in normal volunteers
(Reid et al., 1990) and in patients with various types of
pulmonary hypertension (Morgan et al., 1991b; Hay-
woo is a pulmonary vasodilator, both in normal volunteers $\frac{1}{2}$
(Reid et al., 1990) and in patients with various types of $\frac{1}{2}$
pulmonary hypertension (Morgan et al., 1991b; Hay-
wood et al., 1992). Similarly, ATP con (Reid et al., 1990) and in patients with various types pulmonary hypertension (Morgan et al., 1991b; Ha, wood et al., 1992). Similarly, ATP constricts adult copulmonary vascular beds (Lippton et al., 1992) but relaxes the pulmonary hypertension (Morgan et al., 1991b; Haywood et al., 1992). Similarly, ATP constricts adult cat pulmonary vascular beds (Lippton et al., 1992) but relaxes the pulmonary vascular beds of fetal sheep (Konduri et al. wood et al., 1992). Similarly, ATP constricts adult cat
pulmonary vascular beds (Lippton et al., 1992) but re-
laxes the pulmonary vascular beds of fetal sheep (Kon-
duri et al., 1992a). ATP reduces pulmonary vascular
resi monary hypertension (Gaba et al., 1986). These results suggest that there are both vascular tone- and specieslaxes the pulmonary vascular beds of fetal sheep (K
duri et al., 1992a). ATP reduces pulmonary vascu
resistance in patients with COPD with and without p
monary hypertension (Gaba et al., 1986). These resu
suggest that ther duri et al., 1992a). ATP reduces pulmona
resistance in patients with COPD with and v
monary hypertension (Gaba et al., 1986). Th
suggest that there are both vascular tone-
dependent variation in response to purines.
Purine sistance in patients with COPD with and without pul-
onary hypertension (Gaba et al., 1986). These results cyt
ggest that there are both vascular tone- and species-
fer-
pendent variation in response to purines. pro
Purine monary hypertension (Gaba et al., 1986). These results
suggest that there are both vascular tone- and species-
dependent variation in response to purines.
Purines may regulate pulmonary vascular tone via
neuronal pathways.

suggest that there are both vascular tone- and species-
dependent variation in response to purines. The pre-
primes may regulate pulmonary vascular tone via cel-
neuronal pathways. ATP is coreleased from sympathetic end
ne dependent variation in response to purines. In Furines may regulate pulmonary vascular tone via consumed all the neuronal pathways. ATP is coreleased from sympathetic enerve endings with norepinephrine (von Kugelgen and ge Purines may regulate pulmonary vascular tone via celebrational pathways. ATP is coreleased from sympathetic enerve endings with norepinephrine (von Kugelgen and gestarke, 1991) but inhibits norepinephrine release purejunct

ND LIU
activation of P_{2y} purinoceptors (Allgaier et al., 1994).
Adenosine, ADP, and AMP are also coreleased with nor-Au Liu
activation of P_{2y} purinoceptors (Allgaier et al., 1994).
Adenosine, ADP, and AMP are also coreleased with nor-
epinephrine upon electrical field stimulation of intramu-ND LIU
activation of P_{2y} purinoceptors (Allgaier et al., 19
Adenosine, ADP, and AMP are also coreleased with epinephrine upon electrical field stimulation of intra
ral nerves in rabbit pulmonary arteries (Mohri et activation of P_{2y} purinoceptors (Allgaier et al., 1994).
Adenosine, ADP, and AMP are also coreleased with nor-
epinephrine upon electrical field stimulation of intramu-
ral nerves in rabbit pulmonary arteries (Mohri e activation of P_{2y} purinoceptors (Allgaier et al., 1994).
Adenosine, ADP, and AMP are also coreleased with nor-
epinephrine upon electrical field stimulation of intramu-
ral nerves in rabbit pulmonary arteries (Mohri e Adenosine, ADP, and AMP are also coreleased with nor-
epinephrine upon electrical field stimulation of intramu-
ral nerves in rabbit pulmonary arteries (Mohri et al.,
1993). ATP may act as neurotransmitter or mediator of
p epinephrine upon electrical field stimulation of intramu-
ral nerves in rabbit pulmonary arteries (Mohri et al.,
1993). ATP may act as neurotransmitter or mediator of
pulmonary NANC vasodilator nerves (Liu et al., 1992a).
 The Habove pullished and the case of the case,
1993). ATP may act as neurotransmitter or mediator of
pulmonary NANC vasodilator nerves (Liu et al., 1992a).
Adenosine also modulates adrenergic neuroeffector
transmission (Wi 1993). ATP may act as neurotransmitter or mediator of
pulmonary NANC vasodilator nerves (Liu et al., 1992a).
Adenosine also modulates adrenergic neuroeffector
transmission (Wiklund et al., 1989a) and has been re-
ported t pulmonary NANC vasodilator nerves (Liu et al., 1992a).
Adenosine also modulates adrenergic neuroeffector
transmission (Wiklund et al., 1989a) and has been re-
ported to inhibit vagal motor neurone excitability via
activati ransmission (Wiklund et al., 1989a) and has been re-
ported to inhibit vagal motor neurone excitability via
activation of A₁ receptors (Markes et al., 1993). Shear
stress caused by flow evokes ATP release, which in turn
 ported to inhibit vagal motor neurone excitability via
activation of A_1 receptors (Markes et al., 1993). Shear
stress caused by flow evokes ATP release, which in turn
causes NO release and pulmonary vasodilation (Hasse activation of A_1 receptors (Markes et al., 1993). Shear
stress caused by flow evokes ATP release, which in turn
causes NO release and pulmonary vasodilation (Hasses-
sian et al., 1993). Under in vivo conditions, this c stress caused by flow evoke
causes NO release and puln
sian et al., 1993). Under in
another mechanism for the
pulmonary vascular tone.
Cyclo-oxygenase product discusses IVO Telease and punifolially vasoundation (Hasses-
an et al., 1993). Under in vivo conditions, this could be
nother mechanism for the ATP-mediated regulation of
ilmonary vascular tone.
Cyclo-oxygenase products (p

sian et al., 1993). Under in vivo conditions, this could
another mechanism for the ATP-mediated regulation
pulmonary vascular tone.
Cyclo-oxygenase products (probably ${\rm TxA}_2$) are
volved in the adenosine-induced pulmonar another mechanism for the ATP-mediated regulation of
pulmonary vascular tone.
Cyclo-oxygenase products (probably TxA_2) are in-
volved in the adenosine-induced pulmonary vasocon-
striction (Biaggioni et al., 1989; Lippto pulmonary vascular tone.
Cyclo-oxygenase products (probably TxA_2) are in-
volved in the adenosine-induced pulmonary vasocon-
striction (Biaggioni et al., 1989; Lippton et al., 1992).
Inhibition of adenylyl cyclase and l Cyclo-oxygenase products (probably TxA_2) are
volved in the adenosine-induced pulmonary vasoo
striction (Biaggioni et al., 1989; Lippton et al., 19
Inhibition of adenylyl cyclase and lowering of cellu
cAMP levels are ano volved in the adenosine-induced pulmonary vasoconstriction (Biaggioni et al., 1989; Lippton et al., 1992).
Inhibition of adenylyl cyclase and lowering of cellular cAMP levels are another mechanism for the A_1 receptor-
 striction (Biaggioni et al., 1989; Lippton et al., 198
Inhibition of adenylyl cyclase and lowering of cellu
cAMP levels are another mechanism for the A₁ recept
mediated contraction (Olsson and Pearson, 1990; Da
et al., Inhibition of adenylyl cyclase and lowering of cellular cAMP levels are another mechanism for the A_1 receptor-
mediated contraction (Olsson and Pearson, 1990; Daval
et al., 1991). Mechanisms contributing to the A_2 -m mediated contraction (Olsson and Pearson, 1990; Daval
et al., 1991). Mechanisms contributing to the A₂-medi-
ated relaxation include activation of adenylyl cyclase
(Olsson and Pearson, 1990; Daval et al., 1991), inhibiet al., 1991). Mechanisms contributing to the A_2 -mediated relaxation include activation of adenylyl cyclase (Olsson and Pearson, 1990; Daval et al., 1991), inhibition of Ca^{2+} influx, and modulation of inositol phosp et al., 1991). Mechanisms contributing to the A_2 -me
ated relaxation include activation of adenylyl cycli
(Olsson and Pearson, 1990; Daval et al., 1991), inhi
tion of Ca^{2+} influx, and modulation of inositol phospi
li ated relaxation include activation of adenylyl cyclase (Olsson and Pearson, 1990; Daval et al., 1991), inhibition of Ca²⁺ influx, and modulation of inositol phospholipid turnover (Zhou et al., 1992). An important mechan (Olsson and Pearson, 1990; Daval et al., 1991), inhibition of Ca²⁺ influx, and modulation of inositol phospholipid turnover (Zhou et al., 1992). An important mechanism for ATP-induced vasorelaxation is stimulation of NO tion of Ca²⁺ influx, and modulation of inositol phospho-
lipid turnover (Zhou et al., 1992). An important mecha-
nism for ATP-induced vasorelaxation is stimulation of
NO release (Liu et al., 1989a, 1992a). Adenosine and lipid turnover (Zhou et al., 1992). An important mechanism for ATP-induced vasorelaxation is stimulation of NO release (Liu et al., 1989a, 1992a). Adenosine and ATP may also participate the O_2 -induced pulmonary vasodil nism for ATP-induced vasorelaxation is stimulation of
NO release (Liu et al., 1989a, 1992a). Adenosine and
ATP may also participate the O_2 -induced pulmonary
vasodilation that occurs at birth (Konduri et al., 1993).
Bot ATP may also participate the O_2 -induced pulmonary
vasodilation that occurs at birth (Konduri et al., 1993).
Both adenosine and ATP have been reported to have
mitogenic effects on cultured human endothelial and
vascular vasodilation tless
mitogenic effects
mitogenic effects
vascular smood
et al., 1993).
16. Cytokine th adenosine and ATP have been reported to have
itogenic effects on cultured human endothelial and
scular smooth muscle cells (Ethier et al., 1993; Erling
al., 1993).
16. Cytokines. Cytokines are a group of small protein
e

mitogenic effects on cultured human endothelial and
vascular smooth muscle cells (Ethier et al., 1993; Erling
et al., 1993).
16. Cytokines. Cytokines are a group of small protein
mediators with diverse biological actions, vascular smooth muscle cells (Ethier et al., 1993; Erling
et al., 1993).
16. Cytokines. Cytokines are a group of small protein
mediators with diverse biological actions, including me-
diation or modulation of inflammatio et al., 1993).

16. Cytokines. Cytokines are a group of small protein

mediators with diverse biological actions, including me-

diation or modulation of inflammation, cell growth and

differentiation, immunity and tissue 16. Cytokines. Cytokines are a group of small protein mediators with diverse biological actions, including mediation or modulation of inflammation, cell growth and differentiation, immunity and tissue repair. Cytokines th mediators with diverse biological actions, including mediation or modulation of inflammation, cell growth and differentiation, immunity and tissue repair. Cytokines themselves are not vasoactive, but they can influence vas differentiation, immunity and tissue repair. Cytokines
themselves are not vasoactive, but they can influence
vascular tone via stimulation or inhibition of vasoactive
mediators. One example of this is the cytokine or endotoxin induction of an iNOS, leading to the formation of large amounts of NO, which is believed to be an imporvascular tone via stimulation or inhibition of vasoactive
mediators. One example of this is the cytokine or endo-
toxin induction of an iNOS, leading to the formation of
large amounts of NO, which is believed to be an impo vascular tone via stimulation or inhibition of vasoactive
mediators. One example of this is the cytokine or endo
toxin induction of an iNOS, leading to the formation o
large amounts of NO, which is believed to be an impor
 mediators. One example of this is the cytokine or endo-
toxin induction of an iNOS, leading to the formation of
large amounts of NO, which is believed to be an impor-
tant contributor to hypotension in septic shock (Kil-
b toxin induction of an iNOS, leading to the formation of large amounts of NO, which is believed to be an important contributor to hypotension in septic shock (Kilbourn et al., 1990; Stoclet et al., 1993). The iNOS gene is n large amounts of NO, which is believed to be an important contributor to hypotension in septic shock (Kilbourn et al., 1990; Stoclet et al., 1993). The iNOS gene is not transcribed under normal conditions but is switched o cant contributor to hypotension in septic shock (Kin-
bourn et al., 1990; Stoclet et al., 1993). The iNOS gene is
not transcribed under normal conditions but is switched
on during inflammation and after stimulation with i not transcribed under normal conditions but is switched
on during inflammation and after stimulation with in-
flammatory mediators or bacterial endotoxin. Several
cytokines, including interleukin-1 β , TNF- α , and inte on during inflammation and after stimulation with in-
flammatory mediators or bacterial endotoxin. Several
cytokines, including interleukin-1 β , TNF- α , and inter-
feron- γ , have been shown to induce the iNOS gene e flammatory mediators or bacterial endotoxin. Several cytokines, including interleukin-1 β , TNF- α , and interferon- γ , have been shown to induce the iNOS gene expression in cultured pulmonary vascular smooth muscle c cytokines, including interleukin-1 β , TNF- α , and inter-
feron- γ , have been shown to induce the iNOS gene ex-
pression in cultured pulmonary vascular smooth muscle
cells (Nakayama et al., 1992). Treatment with bact feron- γ , have been shown to induce the iNOS gene expression in cultured pulmonary vascular smooth muscle cells (Nakayama et al., 1992). Treatment with bacterial endotoxin in vivo also induces the expression of iNOS gen pression in cultured pulmonary vascular smooth muscle
cells (Nakayama et al., 1992). Treatment with bacterial
endotoxin in vivo also induces the expression of iNOS
gene in the lung (Liu et al., 1993), heart, aorta, and
pul cells (Nakayama et al., 1992). Treatment with bacterial
endotoxin in vivo also induces the expression of iNOS
gene in the lung (Liu et al., 1993), heart, aorta, and
pulmonary arteries (Liu et al., 1994b). Induction of
iNOS

REGULATION OF PUI
nary vascular hyporeactivity seen in endotoxemia (Grif
fiths et al., 1993). nary vascular hypor
fiths et al., 1993).
Cytokines also af

REGULATION OF PULMONART

The et al., 1993).

Cytokines also affect the constitutive eNOS. After a tive

rigle dose of TNF- α in vivo, rats show an impaired cus mary vascular hyporeactivity seen in endotoxemia (Grif-
fiths et al., 1993).
Cytokines also affect the constitutive eNOS. After a
single dose of TNF- α in vivo, rats show an impaired
dilator response to ACh and an enhan mary vascular hyporeactivity seen in endotoxemia (Griffiths et al., 1993).

Cytokines also affect the constitutive eNOS. After a

single dose of TNF- α in vivo, rats show an impaired

dilator response to ACh and an enha (Liu et al., 1993).

Cytokines also affect the constitutive eNOS. After a

single dose of TNF- α in vivo, rats show an impaired

dilator response to ACh and an enhanced HPV response

(Liu et al., 1992c), whereas the rel Cytokines also affect the constitutive eNOS. After a
single dose of TNF- α in vivo, rats show an impaired
dilator response to ACh and an enhanced HPV response
(Liu et al., 1992c), whereas the relaxant response to
nitrop single dose of TNF- α in vivo, rats show an impaired
dilator response to ACh and an enhanced HPV response
(Liu et al., 1992c), whereas the relaxant response to
nitroprusside is similar to that in saline-treated control
 dilator response to ACh and an enhanced HPV response in (Liu et al., 1992c), whereas the relaxant response to distribution introprusside is similar to that in saline-treated control dungs (Liu et al., 1992c). Similar resu (Liu et al., 1992c), whereas the relaxant response to
nitroprusside is similar to that in saline-treated control
lungs (Liu et al., 1992c). Similar results have been re-
ported in pulmonary vascular beds of rats and guine ported in pulmonary vascular beds of rats and guinea
pigs treated with TNF- α in vivo (Stevens et al., 1992;
Johnson and Ferro, 1992). Treatment of isolated bovine
pulmonary artery rings with TNF- α in vitro causes a
 ported in pulmonary vascular beds of rats and guinea
pigs treated with TNF- α in vivo (Stevens et al., 1992;
Johnson and Ferro, 1992). Treatment of isolated bovine
pulmonary artery rings with TNF- α in vitro causes a
 pigs treated with TNF- α in vivo (Stevens et al., 1992; of the independent of isolated bovine in 1986).

pulmonary artery rings with TNF- α in vitro causes a the poid

concentration-dependent inhibition of the relaxan Johnson and Ferro, 1992). Treatment of isolated b
pulmonary artery rings with TNF- α in vitro cau
concentration-dependent inhibition of the relaxas
sponse to ACh and BK associated with a reduction
release as detected by pulmonary artery rings with TNF- α in vitro causes
concentration-dependent inhibition of the relaxant r
sponse to ACh and BK associated with a reduction of N
release as detected by both bioassay and chemilumine
cence NO concentration-dependent inhibition of the relaxant response to ACh and BK associated with a reduction of NO
release as detected by both bioassay and chemilumines-
cence NO (Xie et al., 1993). Moreover, TNF- α down-
regu sponse to ACh and BK associated with a reduction of NO
release as detected by both bioassay and chemilumines-
cence NO (Xie et al., 1993). Moreover, TNF- α down-
regulates eNOS mRNA in cultured human umbilical
vein endo cence NO (Xie et al., 1993). Moreover, TNF- α down-regulates eNOS mRNA in cultured human umbilical vein endothelial cells (Yoshizumi et al., 1993). Thus, cytokines inhibit eNOS and induce iNOS gene expression. gulates eNOS mRNA in cultured human umbilica
in endothelial cells (Yoshizumi et al., 1993). Thus
tokines inhibit eNOS and induce iNOS gene expres
in.
The effects of cytokines on pulmonary vascular reac-
ity or vascular ton

vein endothelial cells (Yoshizumi et al., 1993). Thus, put
cytokines inhibit eNOS and induce iNOS gene expres-
sion.
The effects of cytokines on pulmonary vascular reac-
tivity or vascular tone may depend on the balance of cytokines inhibit eNOS and induce iNOS gene expres-
sion.
The effects of cytokines on pulmonary vascular reac-
tivity or vascular tone may depend on the balance of the
opposing effects of cytokines on eNOS and iNOS. It is sion.

The effects of cytokines on pulmonary vascular reactivity or vascular tone may depend on the balance of the

opposing effects of cytokines on eNOS and iNOS. It is of

interest that treatment of rats with identical The effects of cytokines on pulmonary vascular reac-
tivity or vascular tone may depend on the balance of the
opposing effects of cytokines on eNOS and iNOS. It is of
interest that treatment of rats with identical doses o tivity or vascular tone may depend on the balance of the
opposing effects of cytokines on eNOS and iNOS. It is of
interest that treatment of rats with identical doses of
 $TNF-\alpha$ for 20 min, but not for 3 min or 24 h, enhan opposing effects of cytokines on eNOS and iNOS. It is of
interest that treatment of rats with identical doses of
 $\text{TNF-}\alpha$ for 20 min, but not for 3 min or 24 h, enhances
the pulmonary pressor response to hypoxia and A-I interest that treatment of rats with identical doses of latter TNF- α for 20 min, but not for 3 min or 24 h, enhances tions the pulmonary pressor response to hypoxia and A-II tens (Stevens et al., 1992). Likewise, chron TNF- α for 20 min, but not for 3 min or 24 h, enhances
the pulmonary pressor response to hypoxia and A-II t
(Stevens et al., 1992). Likewise, chronic treatment of
rats with TNF- α for 1 week increases—whereas for 2 (
 (Stevens et al., 1992). Likewise, chronic treatment c
rats with TNF- α for 1 week increases—whereas for
weeks decreases—pulmonary vascular reactivit
(Stevens et al., 1992, 1993), suggesting that the effects of
TNF- α rats with TNF- α for 1 week increases—whereas for 2
weeks decreases—pulmonary vascular reactivity
(Stevens et al., 1992, 1993), suggesting that the effects of
TNF- α on iNOS and eNOS may be dose- and/or time-
dependen weeks decreases—pulmonary vascular reactivity (Stevens et al., 1992, 1993), suggesting that the effects of $\frac{1}{2}$ TNF- α on iNOS and eNOS may be dose- and/or time-
dependent. More studies are needed to determine (whe (Stevens et al., 1992, 1993), suggesting that the

TNF- α on iNOS and eNOS may be dose- an

dependent. More studies are needed to

whether these changes are similar to the p

hemodynamic changes seen in septic shock.

T $NF-\alpha$ on iNOS and eNOS may be dose- and/or time-
pendent. More studies are needed to determine de-
nether these changes are similar to the pulmonary examodynamic changes seen in septic shock. AN
There may be a species-de

whether these changes are similar to the pulmonary
hemodynamic changes seen in septic shock.
There may be a species-dependent variation in the
response to TNF- α . In isolated perfused canine lobes,
TNF- α treatment fo whether these changes are similar to the pulmonary
hemodynamic changes seen in septic shock. ANP,
There may be a species-dependent variation in the PGD_2 ,
response to TNF- α . In isolated perfused canine lobes, pulmo
TN hemodynamic changes seen in septic shock. A
There may be a species-dependent variation in the
response to TNF- α . In isolated perfused canine lobes,
TNF- α treatment for 30 minutes abolishes the HPV in
response (Johns There may be a species-dependent variation in the
response to TNF- α . In isolated perfused canine lobes
TNF- α treatment for 30 minutes abolishes the HPV
response (Johnson et al., 1993). However, the loss of
HPV may n response to TNF- α . In isolated perfused canine lobes, puln
TNF- α treatment for 30 minutes abolishes the HPV ing
response (Johnson et al., 1993). However, the loss of oxyg
HPV may not be related to the induction of i TNF- α treatment for 30 minutes abolishes the HPV ir response (Johnson et al., 1993). However, the loss of α : HPV may not be related to the induction of iNOS, inas-
much as the NO synthase inhibitor L-NMMA has no eff HPV may not be related to the induction of iNOS, inas-
much as the NO synthase inhibitor L-NMMA has no
effect on the loss of HPV response induced by TNF- α ti
(Johnson et al., 1993). This is consistent with the lack of effect on the loss of HPV response induced by TNF- α
(Johnson et al., 1993). This is consistent with the lack of
basal NO activity in dog pulmonary vessels (Nishiwaki
et al., 1992; Barnard et al., 1993).
Like NOS, cyclo Freed on the loss of HPV response induced by TNF- α
ohnson et al., 1993). This is consistent with the lack of
sal NO activity in dog pulmonary vessels (Nishiwaki
al., 1992; Barnard et al., 1993).
Like NOS, cyclo-oxygena

(Johnson et al., 1993). This is consistent with the lack of basal NO activity in dog pulmonary vessels (Nishiwaki et al., 1992; Barnard et al., 1993).
Like NOS, cyclo-oxygenase also has its constitutive (COX-1) and inducib basal NO activity in dog pulmonary vessels (Nishiwaki
et al., 1992; Barnard et al., 1993).
Like NOS, cyclo-oxygenase also has its constitutive
(COX-1) and inducible (COX-2) isoforms. Cytokines,
LPS and other inflammatory m et al., 1992; Barnard et al., 1993).
Like NOS, cyclo-oxygenase also has its constitute (COX-1) and inducible (COX-2) isoforms. Cytok:
LPS and other inflammatory mediators induce the
pression of COX-2 mRNA and protein in a Like NOS, cyclo-oxygenase also has its constitutive
(COX-1) and inducible (COX-2) isoforms. Cytokines
LPS and other inflammatory mediators induce the ex
pression of COX-2 mRNA and protein in a dexametha
sone-inhibitable ma (COX-1) and inducible (COX-2) isoforms. Cytokines,
LPS and other inflammatory mediators induce the ex-
pression of COX-2 mRNA and protein in a dexametha-
sone-inhibitable manner (Fu et al., 1990; Hla and Neil-
son, 1992). LPS and other inflammatory mediators induce the ex-
pression of COX-2 mRNA and protein in a dexametha-
sone-inhibitable manner (Fu et al., 1990; Hla and Neil-
son, 1992). This provides molecular and biochemical
evidence of pression of COX-2 mRNA and protein in a dexametha-
sone-inhibitable manner (Fu et al., 1990; Hla and Neil-
son, 1992). This provides molecular and biochemical
evidence of the involvement of cyclo-oxygenase products
in the sone-inhibitable manner (Fu et al., 1990; Hla and Ne
son, 1992). This provides molecular and biochemic
evidence of the involvement of cyclo-oxygenase produce
in the pulmonary vasomotor changes during endoxen
(Hales et al., son, 1992). This provides molecular and biochemical (Fevidence of the involvement of cyclo-oxygenase products coin the pulmonary vasomotor changes during endoxemia exceptions (Hales et al., 1981). Thus, cytokines can affec in the pulmonary vasomotor changes during endoxemia
(Hales et al., 1981). Thus, cytokines can affect pulmo-
nary vascular tone through the alterations of NOS or
COX activities, or both.

REGULATION OF PULMONARY VASCULAR TONE
n endotoxemia (Grif-*B. Humoral Control of Pulmonary Vascular Tone*

ntroprusside is similar to that in saline-treated control or blockade of their receptors, have no effect on basal
lungs (Liu et al., 1992c). Similar results have been re-
ported in pulmonary vascular beds of rats and guin RET VASCULAR TONE

Humoral Control of Pulmonary Vascular Tone

Although the pulmonary vasculature responds ac-

Hely to many humoral and autacoid factors, as disthat vascolate form
B. Humoral Control of Pulmonary Vascular Tone
Although the pulmonary vasculature responds ac-
tively to many humoral and autacoid factors, as dis-
cussed in III.A., their precise physiological roles and B. Humoral Control of Pulmonary Vascular Tone
Although the pulmonary vasculature responds ac-
tively to many humoral and autacoid factors, as dis-
cussed in III.A., their precise physiological roles and
involvement in dise Elemental control of 1 atmostary vasculature responds at
ively to many humoral and autacoid factors, as dis
cussed in III.A., their precise physiological roles an
involvement in disease states have not yet been eluc
dated. Although the pulmonary vasculature responds actively to many humoral and autacoid factors, as dis cussed in III.A., their precise physiological roles and involvement in disease states have not yet been elucidated. Inhibiti tively to many humoral and autacoid factors, as dis-
cussed in III.A., their precise physiological roles and
involvement in disease states have not yet been eluci-
dated. Inhibition of the production of these substances,
o cussed in III.A., their precise physiological roles and
involvement in disease states have not yet been eluci-
dated. Inhibition of the production of these substances,
or blockade of their receptors, have no effect on basa involvement in disease states have not yet been elucidated. Inhibition of the production of these substances, or blockade of their receptors, have no effect on basal pulmonary vascular tone, suggesting that none of these s dated. Inhibition of the production of these substances
or blockade of their receptors, have no effect on basa
pulmonary vascular tone, suggesting that none of these
substance is primarily responsible for the maintenance
o by blockade of their receptors, have no effect on basal
pulmonary vascular tone, suggesting that none of these
substance is primarily responsible for the maintenance
of the normal low pulmonary vascular tone (McMurtry,
198 pulmonary vascular tone, suggesting that holie of these
substance is primarily responsible for the maintenance
of the normal low pulmonary vascular tone (McMurtry,
1986). However, these results do not necessarily exclude
t of the normal low pulmonary vascular tone (McMurtry, 1986). However, these results do not necessarily exclude the possibility that these substances contribute to the low pulmonary vascular tone to some extent. Inasmuch as as the pulmonary vascular box (includedly), 1986). However, these results do not necessarily exclude the possibility that these substances contribute to the low pulmonary vascular tone to some extent. Inasmuch as the pulmo stance in the state substances contribute to the
low pulmonary vascular tone to some extent. Inasmuch
as the pulmonary vascular bed is under the influence of
a large number of vasoconstrictor and vasodilator sub-
stances, low pulmonary vascular tone to some extent. Inasmuch
as the pulmonary vascular bed is under the influence of
a large number of vasoconstrictor and vasodilator sub-
stances, it is possible that eliminating the effects of o as the pulmonary vascular bed is under the influence of
a large number of vasoconstrictor and vasodilator sub-
stances, it is possible that eliminating the effects of one
or two mediators may not result in a clear-cut chan a large number of vasoconstrictor and vasodilator substances, it is possible that eliminating the effects of one
or two mediators may not result in a clear-cut change in
pulmonary vascular tone, because such a change could diators. two mediators may not result in a clear-cut change in
imonary vascular tone, because such a change could
ell be compensated by increased activity of other me-
ators.
The maintenance of low pulmonary vascular tone
ems to be

the pulmonary pressor response to hypoxia and A-II tensibility of the pulmonary vasculature, the meager-

(Stevens et al., 1992). Likewise, chronic treatment of ness of smooth muscle, low basal α -adrenergic activities
 well be compensated by increased activity of other mediators.
The maintenance of low pulmonary vascular ton
seems to be the result of a balance between these vase-
constrictors and vasodilators (Robin, 1982), with th diators.

The maintenance of low pulmonary vascular tone

seems to be the result of a balance between these vaso-

constrictors and vasodilators (Robin, 1982), with the

latter holding sway under normal physiological condi The manuculative of low punifolary vasculations.
Seems to be the result of a balance between these vaso-
constrictors and vasodilators (Robin, 1982), with the
latter holding sway under normal physiological condi-
tions. Ot tensibility of the result of a statute setween ancse veconstrictors and vasodilators (Robin, 1982), with latter holding sway under normal physiological contions. Other factors such as recruitment of vessels, the meagers of latter holding sway under normal physiological conditions. Other factors such as recruitment of vessels, distensibility of the pulmonary vasculature, the meagerness of smooth muscle, low basal α -adrenergic activities (latter holding sway under normal physiological conditions. Other factors such as recruitment of vessels, distensibility of the pulmonary vasculature, the meagerness of smooth muscle, low basal α -adrenergic activities (tions. Other factors such as recruitment of vessels, densibility of the pulmonary vasculature, the meageness of smooth muscle, low basal α -adrenergic activit (Vogal and Blount, 1965), and the ability of pulmona endothe tensibility of the pulmonary vasculature, the meagerness of smooth muscle, low basal α -adrenergic activities (Vogal and Blount, 1965), and the ability of pulmonary endothelial cells to take up and/or remove many system (Vogal and Blount, 1965), and the ability of pulmonary
endothelial cells to take up and/or remove many system-
ically or locally released vasoconstrictor substances may
also contribute to the low pulmonary vascular tone. A endothelial cells to take up and/or remove many systemically or locally released vasoconstrictor substances may
also contribute to the low pulmonary vascular tone. As
detailed above, autacoid and inflammatory mediators
exe ically or locally released vasoconstrictor substances may
also contribute to the low pulmonary vascular tone. As
detailed above, autacoid and inflammatory mediators
exert many effects on the pulmonary circulation. A-II,
AN also contribute to the low pulmonary vascular tone. As
detailed above, autacoid and inflammatory mediators
exert many effects on the pulmonary circulation. A-II,
ANP, AVP, ATP, ACh, BK, dopamine, ET-1, ET-3, PAF,
PGD₂, P detailed above, autacoid and inflammatory mediat
exert many effects on the pulmonary circulation. A
ANP, AVP, ATP, ACh, BK, dopamine, ET-1, ET-3, P.
PGD₂, PGI₂, and SP have been reported to inhibit ac
pulmonary vasocon Exert many checks on the punnomity enculation. IT ANP, AVP, ATP, ACh, BK, dopamine, ET-1, ET-3, PA
PGD₂, PGI₂, and SP have been reported to inhibit acu
pulmonary vasoconstriction elicited by hypoxia, sugges
ing that th PGD_2 , PGI_2 , and SP have been reported to inhibit acute
pulmonary vasoconstriction elicited by hypoxia, suggesting that these substances may modulate HPV. Cyclo-
oxygenase and 5'-lipoxygenase may be involved in HPV
(se pulmonary vasoconstriction elicited by hypoxia, suggesting that these substances may modulate HPV. Cyclo-
oxygenase and 5'-lipoxygenase may be involved in HPV
(see Physiological adaptation, next section).
1. Physiological Imonary vasoconstriction elicited by hypoxia, sugge
 1. Physiological adaptation, next section.
 1. Physiological adaptation, next section.
 1. Physiological adaptation. The pulmonary circu
 n undergoes significant

ing that these substances may modulate HPV. Cyclo-
oxygenase and 5'-lipoxygenase may be involved in HPV
(see Physiological adaptation, next section).
1. *Physiological adaptation*. The pulmonary circula-
tion undergoes sig oxygenase and 5'-lipoxygenase may be involved in HPV
(see Physiological adaptation, next section).
1. Physiological adaptation. The pulmonary circula-
tion undergoes significant changes during physiological
adaptations to (see Physiological adaptation, next section).

1. Physiological adaptation. The pulmonary circula-

tion undergoes significant changes during physiological

adaptations to exercise, pregnancy, cold exposure and

perinatal 1. Physiological adaptation. The pulmonary circulation undergoes significant changes during physiologics
adaptations to exercise, pregnancy, cold exposure an
perinatal pulmonary vascular adaptation. Humora
mechanisms may p ion undergoes significant changes during physiological
adaptations to exercise, pregnancy, cold exposure a
perinatal pulmonary vascular adaptation. Humo
mechanisms may play an important role in these ph
iological adaptatio auaptations to exercise, pregnancy, cold exposure and
perinatal pulmonary vascular adaptation. Humoral
mechanisms may play an important role in these phys-
iological adaptation responses. The pulmonary circula-
tory respon iological adaptation responses. The pulmonary circulatory response to exercise is an increase in blood flow caused by increased cardiac output, an increase in PPA, and a slight decrease in PVR. Both passive factors and act caused by increased cardiac output, an increase in PPA, and a slight decrease in PVR. Both passive factors and active vasodilation contribute to the decrease in PVR (Reeves et al., 1989). Vasodilator prostaglandins may be (Reeves et al., 1989). Vasodilator prostaglandins may be contributory but are unlikely to be important in the exercise-induced pulmonary vasodilation (Reeves et al., 1989). and a slight decrease in PVR. Both passive factors and
active vasodilation contribute to the decrease in PVR
(Reeves et al., 1989). Vasodilator prostaglandins may be
contributory but are unlikely to be important in the
exe active vasodilation contribute to the decrease in PV.

Reeves et al., 1989). Vasodilator prostaglandins may

contributory but are unlikely to be important in t

exercise-induced pulmonary vasodilation (Reeves et a

1989). (Reeves et al., 1989). Vasoundoor prostagrammis may be
contributory but are unlikely to be important in the
exercise-induced pulmonary vasodilation (Reeves et al.,
1989). An increase in blood flow during exercise stimu-
la exercise-induced pulmonary vasodilation (Reeves et al., 1989). An increase in blood flow during exercise stimulates NO release, which may be responsible for the pulmonary vasodilation during exercise (Kane et al., 1994).

PHARMACOLOGICAL REVIEWS

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105 BARNES AND LIU

105 BARNES AND LIU BARNES
The pulmonary circulation during pregnancy is in a
dilated state with low PPA and PVR, despite blood vol-
ume expansion and an increase in cardiac output. Al-BARNES
The pulmonary circulation during pregnancy is in a
dilated state with low PPA and PVR, despite blood vol-
ume expansion and an increase in cardiac output. Al-
though no mediator has been identified to account for The pulmonary circulation during pregnancy is in a
dilated state with low PPA and PVR, despite blood vol-
ume expansion and an increase in cardiac output. Al-
though no mediator has been identified to account for
this, the The pulmonary circulation during pregnancy is in a ingediated state with low PPA and PVR, despite blood volume expansion and an increase in cardiac output. Al-
though no mediator has been identified to account for devertin dilated state with low PPA and PVR, despite blood vo
ume expansion and an increase in cardiac output. A
though no mediator has been identified to account fo
this, the decreased PVR is likely to be induced by
general reduct ume expansion and an increase in cardiac output.
though no mediator has been identified to account
this, the decreased PVR is likely to be induced b
general reduction in pulmonary vasoreactivity to va
constrictors, thus sh this, the decreased PVR is likely to be induced by a general reduction in pulmonary vasoreactivity to vaso-constrictors, thus shifting the balance toward vasodilation (Moore, 1989). Vasodilators may also increase during pr this, the decreased PVR is likely to be induced by a constrictors, thus shifting the balance toward vaso-
constrictors, thus shifting the balance toward vasodila-
tion (Moore, 1989). Vasodilators may also increase dur-
ing constrictors, thus shifting the balance toward vasodilation (Moore, 1989). Vasodilators may also increase during pregnancy. One of many humoral changes during pregnancy is an increase in circulating estrone/estradiol, whic constrictors, thus shifting the balance toward vasodil
tion (Moore, 1989). Vasodilators may also increase du
ing pregnancy. One of many humoral changes durin
pregnancy is an increase in circulating estrone/estradio
which a tion (Moore, 1989). Vasodilators may also increase dur-
ing pregnancy. One of many humoral changes during a
pregnancy is an increase in circulating estrone/estradiol,
which are pulmonary vasodilators (Moore, 1989). Estro-
 ing pregnancy. One of many humoral changes during al., pregnancy is an increase in circulating estrone/estradiol, tabet which are pulmonary vasodilators (Moore, 1989). Estrocont gen receptors are located on vascular endoth pregnancy is an increase in circulating estronevestration,
which are pulmonary vasodilators (Moore, 1989). Estro-
gen receptors are located on vascular endothelial cells
(Moore, 1989). Estradiol or estrogen has been shown which are pulmonary vasodilators (Moore, 1989). Estrogen receptors are located on vascular endothelial cells of (Moore, 1989). Estradiol or estrogen has been shown to it enhance the constitutive nitric oxide synthase gene (Moore, 1989). Estradiol or estrogen has been shown to itin
enhance the constitutive nitric oxide synthase gene ex-
pression and constitutive nitric oxide synthase activity por
(Schray-Utz et al., 1993; Lizasoain et al., 1 enhance the constitutive nitric oxide synthase gene ex-
pression and constitutive nitric oxide synthase activity ported
(Schray-Utz et al., 1993; Lizasoain et al., 1993). An al., 19
increased NO synthesis has been reported pression and constitutive nitric oxide synthase activity ported
(Schray-Utz et al., 1993; Lizasoain et al., 1993). An al., 198
increased NO synthesis has been reported in pregnant reduce
rats (Conrad et al., 1993). Thus, a (Schray-Utz et increased NO s
rats (Conrad e release during $_1$ and low PVR.
The pulmona creased NO synthesis has been reported in pregnant reduts (Conrad et al., 1993). Thus, an increase in NO 1987
lease during pregnancy can contribute to the low PPA the complete to the low PVR.
d low PVR. cific
The pulmonary

rats (Conrad et al., 1993). Thus, an increase in NO 1987).

release during pregnancy can contribute to the low PPA the devand low PVR.

The pulmonary circulatory responses to short-term 2. Pr

cold exposure are increases i release during pregnancy can contribute to the low PPA
and low PVR.
The pulmonary circulatory responses to short-term
cold exposure are increases in cardiac output and PPA
and pulmonary vasoconstriction, resulting in an in and low PVR.
The pulmonary circulatory responses to short-term
cold exposure are increases in cardiac output and PPA
and pulmonary vasoconstriction, resulting in an in-
crease in PVR (McMurtry, 1986). HPV and increased t
 The pulmonary circulatory responses to short-term
cold exposure are increases in cardiac output and PPA
and pulmonary vasoconstriction, resulting in an in-
grease in PVR (McMurtry, 1986). HPV and increased to
 α -adrenoc cold exposure are increases in cardiac output and PPA also and pulmonary vasoconstriction, resulting in an in-
crease in PVR (McMurtry, 1986). HPV and increased the p
 α -adrenoceptor stimulation by neurally and humorall and pulmonary varease in PVR (Mc)
 α -adrenoceptor stim

released norepineph

(McMurtry, 1986).

2. Changes at birt PER (McMurtry, 1986). HPV and increased adrenoceptor stimulation by neurally and humoral leased norepinephrine account for the increase in PV (CMurtry, 1986).
2. *Changes at birth*. There seem to be multiple mechanges at

released norepinephrine account for the increase in P
(McMurtry, 1986).
2. *Changes at birth*. There seem to be multiple me
anisms mediating the transition of the fetal pulmons
circulation to that of the adult, with a comp (McMurtry, 1986).

2. *Changes at birth*. There seem to be multiple mechanisms mediating the transition of the fetal pulmonary

circulation to that of the adult, with a complex interac-

tion between anatomical, mechanica 2. Changes at birth. There seem to be multiple mech-
anisms mediating the transition of the fetal pulmonary
circulation to that of the adult, with a complex interac-
tion between anatomical, mechanical, physical, and hu-
 anisms mediating the transition of the fetal pulmonary
circulation to that of the adult, with a complex interac-
tion between anatomical, mechanical, physical, and hu-
moral factors. Changing from fluid-filled to gas-fille circulation to that of the adult, with a complex interaction between anatomical, mechanical, physical, and humoral factors. Changing from fluid-filled to gas-filled lungs by ventilation results in the formation of an airli moral factors. Changing from fluid-filled to gas-filled
lungs by ventilation results in the formation of an air-
liquid interface, which tends to reduce perivascular
pressure (Cassin et al., 1964). Hypoxia is an important
 moral factors. Changing from fluid-filled to gas-filled
lungs by ventilation results in the formation of an air-
liquid interface, which tends to reduce perivascular
pressure (Cassin et al., 1964). Hypoxia is an important
 lungs by ventilation results in the formation of an air-

liquid interface, which tends to reduce perivascular

pressure (Cassin et al., 1964). Hypoxia is an important

encedencianism underlying the high pressure and high liquid interface, which tends to reduce perivascular na
pressure (Cassin et al., 1964). Hypoxia is an important en
mechanism underlying the high pressure and high re-
sistance of fetal pulmonary circulation (Rudolph and l pressure (Cassin et al., 1964). Hypoxia is an important
mechanism underlying the high pressure and high re-
sistance of fetal pulmonary circulation (Rudolph and
Yuan, 1966). A high PCO₂ content also contributes to the
h mechanism underlying the high pressure and high re-

sistance of fetal pulmonary circulation (Rudolph and los

Yuan, 1966). A high PCO₂ content also contributes to the

high pulmonary blood pressure (Rudolph and Yuan, c sistance of fetal pulmonary circulation (Rudolph and Yuan, 1966). A high PCO_2 content also contributes to the high pulmonary blood pressure (Rudolph and Yuan, 1966). Increases in inspiratory O_2 and decreases in blood Yuan, 1966). A high PCO₂ content also contributes to the
high pulmonary blood pressure (Rudolph and Yuan,
1966). Increases in inspiratory O₂ and decreases in blood
PCO₂ could exert vasodilator effects (Morin et al., high pulmonary blood pressure (Rudolph and 1966). Increases in inspiratory O_2 and decreases in PCO_2 could exert vasodilator effects (Morin et al., 1968) and (Davidson, 1987) may also play a role. Endothe derived $PGI_$ 1966). Increases in inspiratory O_2 and decreases in blood
PCO₂ could exert vasodilator effects (Morin et al., 1988).
Mediators such as BK (Melmon et al., 1968) and A-II
(Davidson, 1987) may also play a role. Endothel *Mediators such as BK (Melmon et al., 1968) and A-II* (Davidson, 1987) may also play a role. Endothelium-
derived PGI₂ and NO play an important role (see V.H.).
C. Possible Role in Pulmonary Vascular Disease
Although m

(Davidson, 1987) may also play a role. Endothelium-
derived PGI_2 and NO play an important role (see V.H.). letter
C. Possible Role in Pulmonary Vascular Disease
have impressive actions on pulmonary vascular tone and to C. Possible Role in Pulmonary Vascular Disease and the pulmonary value of the humoral substances discussed (Ma have impressive actions on pulmonary vascular tone and to rother cellular functions, their pathophysiological r Although most of the humoral substances discussed (large impressive actions on pulmonary vascular tone and to other cellular functions, their pathophysiological roles in pulmonary vascular diseases largely remain unclear. have impressive actions on pulmonary vascular to
other cellular functions, their pathophysiological
pulmonary vascular diseases largely remain u
This is mainly caused by a lack of specific inhib-
receptor antagonists that

pulmonary vascular diseases largely remain unclear.

This is mainly caused by a lack of specific inhibitors or

receptor antagonists that are effective in vivo.
 I. Role in hypoxic pulmonary hypertension. The roles

of h This is mainly caused by a lack of specific inhibitors of receptor antagonists that are effective in vivo.

1. Role in hypoxic pulmonary hypertension. The role of humoral substances in the development of chronic

HPH have receptor antagonists that are effective in vivo. (Tu

1. Role in hypoxic pulmonary hypertension. The roles

of humoral substances in the development of chronic

HPH have been intensively studied. There are two com-

ponent 1. Role in hypoxic pulmonary hypertension. The rc of humoral substances in the development of chro
HPH have been intensively studied. There are two concents to the HPH: pulmonary vasoconstriction at vascular remodelling,

ND LIU
ing of small pulmonary arteries and right ventricular
hypertrophy. Although there exists no conclusive evi-ND LIU
ing of small pulmonary arteries and right ventricular
hypertrophy. Although there exists no conclusive evi-
dence of a role of any single humoral mediator in the ND LIU
ing of small pulmonary arteries and right ventricular
hypertrophy. Although there exists no conclusive evi-
dence of a role of any single humoral mediator in the
development of HPH, several humoral mediators may ing of small pulmonary arteries and right ventricular
hypertrophy. Although there exists no conclusive evi-
dence of a role of any single humoral mediator in the
development of HPH, several humoral mediators may
contribute hypertrophy. Although there exists no conclusive evi-
dence of a role of any single humoral mediator in the
development of HPH, several humoral mediators may
contribute the process of HPH through the mediation of
pulmonary my pertrophy. Anthough there exists no conclusive evidence of a role of any single humoral mediators may contribute the process of HPH through the mediation of pulmonary vasoconstriction or stimulation of pulmonary vascula development of HPH, several humoral mediators may
contribute the process of HPH through the mediation of
pulmonary vasoconstriction or stimulation of pulmonary
vascular smooth muscle proliferation, or both. Sub-
stances co contribute the process of HPH through the mediation of pulmonary vasoconstriction or stimulation of pulmonary vascular smooth muscle proliferation, or both. Substances contributing to HPH include ET-1 (Miyauchi et al., 199 pulmonary vasoconstriction or stimulation of pulmonary
vascular smooth muscle proliferation, or both. Sub-
stances contributing to HPH include ET-1 (Miyauchi et
al., 1993), PAF (Ono et al., 1992), arachidonic acid me-
tabo vascular smooth muscle proliferation, or both. Sub
stances contributing to HPH include ET-1 (Miyauchi e
al., 1993), PAF (Ono et al., 1992), arachidonic acid me
tabolites, 5-HT, and histamine (McMurtry, 1986). In
contrast, stances contributing to HPH include ET-1 (Miyauchi
al., 1993), PAF (Ono et al., 1992), arachidonic acid m
tabolites, 5-HT, and histamine (McMurtry, 1986).
contrast, ANP, AVP, and CGRP inhibit the developme
of HPH, either v al., 1993), PAF (Ono et al., 1992), arachidonic acid metabolites, 5-HT, and histamine (McMurtry, 1986). In contrast, ANP, AVP, and CGRP inhibit the development of HPH, either via pulmonary vasodilation, or by inhibiting va tabolites, 5-HT, and histamine (McMurtry, 1986). In contrast, ANP, AVP, and CGRP inhibit the development of HPH, either via pulmonary vasodilation, or by inhibiting vascular smooth muscle proliferation, or both. Angiotensi contrast, ANP, AVP, and CGRP inhibit the development
of HPH, either via pulmonary vasodilation, or by inhib-
iting vascular smooth muscle proliferation, or both. An-
giotensin-converting enzyme inhibitors have been re-
por of HPH, either via pulmonary vasodilation, or by inhibiting vascular smooth muscle proliferation, or both. Angiotensin-converting enzyme inhibitors have been reported to inhibit the development of HPH (Kentera et al., 1981 iting vascular smooth muscle proliferation, or both. Angiotensin-converting enzyme inhibitors have been reported to inhibit the development of HPH (Kentera et al., 1981). However, the enzyme activity is likely to be reduce giotensin-converting enzyme inhibitors have been re-
ported to inhibit the development of HPH (Kentera et
al., 1981). However, the enzyme activity is likely to be
reduced under conditions of chronic hypoxia (Jin et al.,
19 ported to inhibit the development of HPH (Kentera
al., 1981). However, the enzyme activity is likely to
reduced under conditions of chronic hypoxia (Jin et
1987). Several conventionally used vasodilators inhi
the developme al., 1981). However, the enzyme activity is likely to be reduced under conditions of chronic hypoxia (Jin et al. 1987). Several conventionally used vasodilators inhibited development of HPH, presumably through a nonspecifi duced under conditions of chronic hypoxia (Jin et al., 187). Several conventionally used vasodilators inhibit
e development of HPH, presumably through a nonspe-
fic pulmonary vasodilator action (McMurtry, 1986).
2. Pulmona

released norepinephrine account for the increase in PVR TxA₂, ET-1, and 5-HT are reported to contribute to the (McMurtry, 1986).

(McMurtry, 1986).

2. *Changes at birth*. There seem to be multiple mech-

pertension (Mi 1987). Several conventionally used vasodilators inhibit
the development of HPH, presumably through a nonspe-
cific pulmonary vasodilator action (McMurtry, 1986).
2. Pulmonary hypertension. Humoral mediators may
also play a the development of HPH, presumably through a nonspecific pulmonary vasodilator action (McMurtry, 1986).

2. Pulmonary hypertension. Humoral mediators may

also play a role in the development of other types of

pulmonary hy cific pulmonary vasodilator action (McMurtry, 1986).

2. Pulmonary hypertension. Humoral mediators may

also play a role in the development of other types of

pulmonary hypertension. 5-HT has been implicated in

the patho 2. *Fullmonary hypertension*. Fiamoral mediators may
also play a role in the development of other types of
pulmonary hypertension. 5-HT has been implicated in
the pathogenesis of pulmonary hypertension due to fa-
milial pl also play a role in the development of other types of
pulmonary hypertension. 5-HT has been implicated in
the pathogenesis of pulmonary hypertension due to fa-
milial platelet storage pool disease (Herve et al., 1990).
TxA pulmonary hypertension. 5-HT has been implicated in
the pathogenesis of pulmonary hypertension due to fa-
milial platelet storage pool disease (Herve et al., 1990).
TxA₂, ET-1, and 5-HT are reported to contribute to the
 the pathogenesis of pulmonary hypertension due to fa-
milial platelet storage pool disease (Herve et al., 1990).
TxA₂, ET-1, and 5-HT are reported to contribute to the
development of monocrotaline-induced pulmonary hy-
p milial platelet storage pool disease (Herve et al., 1990).
TxA₂, ET-1, and 5-HT are reported to contribute to the
development of monocrotaline-induced pulmonary hy-
pertension (Miyauchi et al., 1993; Kanai et al., 1993). development of monocrotaline-induced pulmonary hypertension (Miyauchi et al., 1993; Kanai et al., 1993).
ET-1 may also play a role in rat model of idiopathic
pulmonary hypertension (Stelzner et al., 1992). Because
PGI₂ plays an important role in the perinatal pulmonary pertension (Miyauchi et al., 1993; Kanai et al., 1993).
ET-1 may also play a role in rat model of idiopathic
pulmonary hypertension (Stelzner et al., 1992). Because
PGI₂ plays an important role in the perinatal pulmonary ET-1 may also play a role in rat model of idiopatl
pulmonary hypertension (Stelzner et al., 1992). Becau
 PGI_2 plays an important role in the perinatal pulmons
vasodilation, loss of this mechanism due to endothel
dama pulmonary hypertension (Stelzner et al., 1992). Because PGI₂ plays an important role in the perinatal pulmonary vasodilation, loss of this mechanism due to endothelial damage may contribute to newborn persistent pulmonar PGI_2 plays an important role in the perinatal pulmonary
vasodilation, loss of this mechanism due to endothelial
damage may contribute to newborn persistent pulmo-
nary hypertension (Stenmark et al., 1989). Likewise,
end vasodilation, loss of this mechanism due to endothelial
damage may contribute to newborn persistent pulmo-
nary hypertension (Stenmark et al., 1989). Likewise,
endothelium-derived NO may also play a part in the
perinatal p nary hypertension (Stenmark et al., 1989). Likewise, endothelium-derived NO may also play a part in the perinatal pulmonary vasodilation (Abman et al., 1990); loss of NO might contribute to this condition.

other cellular functions, their pathophysiological roles in pulmonary hypertension during embolism (Utsunomiya
pulmonary vascular diseases largely remain unclear. et al., 1981). Similarly, glass bead or clot embolism in
T *3. Pulmonary embolism.* Two major pathophysiologiendothelium-derived NO may also play a part in the
perinatal pulmonary vasodilation (Abman et al., 1990);
loss of NO might contribute to this condition.
3. Pulmonary embolism. Two major pathophysiologi-
cal changes seen in perinatal pulmonary vasodilation (Abman et al., 1990);
loss of NO might contribute to this condition.
3. *Pulmonary embolism*. Two major pathophysiologi-
cal changes seen in pulmonary embolism are pulmonary
hypertension an nechanical obstruction of the pulmonary publism. Two major pathophysiological changes seen in pulmonary embolism are pulmonary hypertension and pulmonary vascular injury. Although mechanical obstruction of the pulmonary va cal changes seen in pulmonary embolism are pulmonar
hypertension and pulmonary vascular injury. Althoug
mechanical obstruction of the pulmonary vascular bed
an important factor resulting in pulmonary hyperte-
sion, humoral hypertension and pulmonary vascular injury. Althounechanical obstruction of the pulmonary vascular be an important factor resulting in pulmonary hypert
sion, humoral factors released from leukocytes, plates, mast cells, ma mechanical obstruction of the pulmonary vascular bed is
an important factor resulting in pulmonary hyperten-
sion, humoral factors released from leukocytes, plate-
lets, mast cells, macrophages, and pulmonary endothe-
lial an important factor resulting in pulmonary hypertension, humoral factors released from leukocytes, plate-
lets, mast cells, macrophages, and pulmonary endothe-
lial cells contribute to the development of both
pulmonary hyp sion, humoral factors released from leukocytes, plate-
lets, mast cells, macrophages, and pulmonary endothe-
lial cells contribute to the development of both
pulmonary hypertension (Malik, 1983) and lung injury
(Malik and lets, mast cells, macrophages, and pulmonary endothe-
lial cells contribute to the development of both
pulmonary hypertension (Malik, 1983) and lung injury
(Malik and Johnson, 1989). Clot embolism in dogs leads
to release nal cells contribute to the development of both
pulmonary hypertension (Malik, 1983) and lung injury
(Malik and Johnson, 1989). Clot embolism in dogs leads
to release of 5-HT, and 5-HT receptor antagonists reduce
pulmonary (Malik and Johnson, 1989). Clot embolism in dogs leads
to release of 5-HT, and 5-HT receptor antagonists reduce
pulmonary hypertension during embolism (Utsunomiya
et al., 1981). Similarly, glass bead or clot embolism in
d (Tucker et al., 1976b) and TxB₂ (Utsunomiya et al., 1981). Similarly, glass bead or clot embolism in dogs, rabbits, and sheep induce the release of histamine (Tucker et al., 1976b) and TxB_2 (Utsunomiya et al., 1982; G et al., 1981). Similarly, glass bead or clot embolism in dogs, rabbits, and sheep induce the release of histamine (Tucker et al., 1976b) and TxB_2 (Utsunomiya et al., 1982; Garcia-Szabo et al., 1983). The increase in pul dogs, rabbits, and sheep induce the release of histamine (Tucker et al., 1976b) and TxB_2 (Utsunomiya et al., 1982; Garcia-Szabo et al., 1983). The increase in pulmonary vascular resistance is reduced by histamine antago (Tucker et al., 1976b) and Tx B_2 (Utsunomiya et al., 1982; Garcia-Szabo et al., 1983). The increase in pulmonary vascular resistance is reduced by histamine antagonists (Tucker et al., 1976b) and inhibition of Tx A_2 s nary vascular resistance is reduced by histamine antagonists (Tucker et al., 1976b) and inhibition of TxA_2 synthesis (Utsunomiya et al., 1982). The role of 5-HT in pulmonary embolism has been questioned, inasmuch as

REGULATION **OF PULMONARY** VASCULAR **TONE** ¹⁰⁵

REGULATION OF PULMONAR
the normal human pulmonary vascular bed seems to be
unresponsive to this agent in vivo (Harris and Heath, (Sa REGULATION OF PULM
the normal human pulmonary vascular bed seems to be
unresponsive to this agent in vivo (Harris and Heath,
1986). However, 5-HT constricts human pulmonary ar-REGULATION OF PULMON

1986). However, 5-HT constricts human pulmonary ar-

1986). However, 5-HT constricts human pulmonary ar-

1986). However, 5-HT constricts human pulmonary ar-

1985). Moreover, pulmothe normal human pulmonary vascular bed seems to
unresponsive to this agent in vivo (Harris and Heat
1986). However, 5-HT constricts human pulmonary
teries in vitro (Raffestin et al., 1985). Moreover, pulm
nary vascular re unresponsive to this agent in vivo (Harris and Heath, 1986). However, 5-HT constricts human pulmonary ar-
teries in vitro (Raffestin et al., 1985). Moreover, pulmo-
nary vascular reactivity may alter under pathological
con unresponsive to this agent in vivo (Harris and Heath, 1986). However, 5-HT constricts human pulmonary arteries in vitro (Raffestin et al., 1985). Moreover, pulmonary vascular reactivity may alter under pathological conditi teries in vitro (Raffestin et al., 1985). Moreover, pulm
nary vascular reactivity may alter under pathologic
conditions. For example, endogenous 5-HT increas
PPA in patients with PPH (Herve et al., 1990). Vaso
lators with nary vascular reactivity may alter under pathological
conditions. For example, endogenous 5-HT increases
PPA in patients with PPH (Herve et al., 1990). Vasodi-
lators with diverse mechanisms of action reduce pulmo-
nary va conditions. For example, endogenous 5-HT increasers PPA in patients with PPH (Herve et al., 1990). Vasod lators with diverse mechanisms of action reduce pulmonary vascular resistance in patients with pulmonary embo-
hypert PPA in patients with PPH (Herve et al., 1990). Vasodi-
lators with diverse mechanisms of action reduce pulmo-
nary vascular resistance in patients with pulmonary
hypertension secondary to recurrent pulmonary embo-
lism, su lators with diverse mechanisms of action reduce pulmonary
nary vascular resistance in patients with pulmonary
hypertension secondary to recurrent pulmonary embo-
lism, suggesting that in addition to pulmonary vascular
obst mary vascular resistance in patients with pulmonary
hypertension secondary to recurrent pulmonary embo-
lism, suggesting that in addition to pulmonary vascular
obstruction, there is a vasoconstrictor component
(Dantzker an hypertension secondary to recurrent pulmonary emblism, suggesting that in addition to pulmonary vascula
obstruction, there is a vasoconstrictor component
(Dantzker and Bower, 1981). Additionally, activate
neutrophil- or m lism, suggesting that in addition to pulmonary vascular

obstruction, there is a vasoconstrictor component

(Dantzker and Bower, 1981). Additionally, activated

incurrephil- or macrophage-derived inflammatory medi-

ators obstruction, there is a vasoconstrictor compone
(Dantzker and Bower, 1981). Additionally, activat
neutrophil- or macrophage-derived inflammatory me
ators such as PAF, LTB₄, TNF- α , interleukin-1 β , a
reactive oxygen (Dantzker and Bower, 1981). Additionally, activated
neutrophil- or macrophage-derived inflammatory medi-
ators such as PAF, LTB₄, TNF- α , interleukin-1 β , and
reactive oxygen species may be important in the pulmo-
n neutrophil- or macrophage-derived inflammatory medi-
ators such as PAF, LTB₄, TNF- α , interleukin-1 β , and
reactive oxygen species may be important in the pulmo-
nary vascular injury after pulmonary embolism (Malik
 ors such as PAF, LTB₄, TNF- α , interleukin-1 β , and active oxygen species may be important in the pulmo-
hy vascular injury after pulmonary embolism (Malik d Johnson, 1989).
4. Ad*ult respiratory distress syndrome*.

reactive oxygen species may be important in the pulmo-
nary vascular injury after pulmonary embolism (Malik
and Johnson, 1989).
4. Adult respiratory distress syndrome. Pulmonary hy-
pertension associated with an increase i pertension associated with an increase in pulmonary
vascular resistance is frequently observed in animal and Johnson, 1989).

4. Adult respiratory distress syndrome. Pulmonary hypertension associated with an increase in pulmonary

1. Vascular resistance is frequently observed in animal

models and patients with ARDS (Rounds, 4. Adult respiratory distress syndrome. Pulmonary hypertension associated with an increase in pulmonary vascular resistance is frequently observed in animal models and patients with ARDS (Rounds, 1989). The labormal pulmon pertension associated with an increase in pulmonary
vascular resistance is frequently observed in animal
models and patients with ARDS (Rounds, 1989). The
abnormal pulmonary circulatory control can influence
both the exten models and patients with ARDS (Rounds, 1989). The abnormal pulmonary circulatory control can influence both the extent of pulmonary edema and the systemic hypoxemia that characterize ARDS. Two main mechanisms responsible f modella and patients with ARDS (Roumas, 1989). The biddhormal pulmonary circulatory control can influence mist
both the extent of pulmonary edema and the systemic may
hypoxemia that characterize ARDS. Two main mecha-
nisms both the extent of pulmonary edema and the system
hypoxemia that characterize ARDS. Two main mech
nisms responsible for pulmonary hypertension in ARI
are pulmonary vasoconstriction and vascular obstri
tion. Humoral mediato hypoxemia that characterize ARDS. Two main mechanisms responsible for pulmonary hypertension in ARD
are pulmonary vasoconstriction and vascular obstruction. Humoral mediators are important in the pulmonary hypertension see are pulmonary vasoconstriction and vascular obstruction. Humoral mediators are important in the pulmonary hypertension seen ARDS. Cyclo-oxygenase products, particularly TxA₂, are likely to be the mediators conducts, part mary hypertension seen ARDS. Cyclo-oxygenase products, particularly TxA_2 , are likely to be the mediators opulmonary hypertension in endotoxin, PAF, thrombing and clot-induced lung injury, but not in oleic acid-induced l ucts, particularly TxA_2 , are likely to be the mediators of responsive pulmonary hypertension in endotoxin, PAF, thrombin, na and clot-induced lung injury, but not in oleic acid-in-sponsive dured lung injury (Rounds, 198 pulmonary hypertension in endotoxin, PAF, thrombin,
and clot-induced lung injury, but not in oleic acid-in-
duced lung injury (Rounds, 1989). Lipoxygenase prod-
ucts of arachidonic acid may also play an important role
in t and clot-induced lung injury, but not in oleic acid-in-
duced lung injury (Rounds, 1989). Lipoxygenase prod-
and
ucts of arachidonic acid may also play an important role (197
in the pulmonary hypertension seen with endoxem duced lung injury (Rounds, 1989). Lipoxygenase products of arachidonic acid may also play an important role
in the pulmonary hypertension seen with endoxemia
(Ahmed et al., 1986; Rounds, 1989). There is evidence to ucts of arachidonic acid may also play an important role
in the pulmonary hypertension seen with endoxemia
(Ahmed et al., 1986; Rounds, 1989). There is evidence to
indicate that 5-HT may mediate the pulmonary hyper-
tensio in the pulmonary hypertension seen with endoxen
(Ahmed et al., 1986; Rounds, 1989). There is evidence
indicate that 5-HT may mediate the pulmonary hyp
tension after autologous clot infusion (Hechtman et 1
1984; Rounds, 198 (Ahmed et al., 1986; Rounds, 1989). There is evidence to indicate that 5-HT may mediate the pulmonary hypertension after autologous clot infusion (Hechtman et al., 1984; Rounds, 1989). Another important factor contributing tension after autologous clot infusion (Hechtman et al., 1984; Rounds, 1989). Another important factor contributing to the pulmonary hypertension seen in lung injury, particularly that induced by endotoxin, is down-regulat tension after autologous clot infusion (Hechtman et al., hydroget). Another important factor contributing to the pulmonary hypertension seen in lung in-
jury, particularly that induced by endotoxin, is down-
regulation of 1984; Rounds, 1989). Another important factor contributing to the pulmonary hypertension seen in lung in-
jury, particularly that induced by endotoxin, is down-
regulation of the eNOS (Yoshizumi et al., 1993). Loss of
endo uting to the pulmonary hypertension seen in lung i
jury, particularly that induced by endotoxin, is dow
regulation of the eNOS (Yoshizumi et al., 1993). Loss
endothelium-derived NO will predispose vascul
smooth muscle to v jury, particularly that induced by endotoxin, is down-
regulation of the eNOS (Yoshizumi et al., 1993). Loss of
endothelium-derived NO will predispose vascular
smooth muscle to vasoconstriction and enhance pulmo-
nary vaso regulation of the eNOS (Yoshizumi et al., 1993). Loss of endothelium-derived NO will predispose vascula smooth muscle to vasoconstriction and enhance pulmonary vasoconstrictor responses (Liu et al., 1992c; Stanens et al., endothelium-derived NO will predispose vascular
smooth muscle to vasoconstriction and enhance pulmo-
nary vasoconstrictor responses (Liu et al., 1992c; Ste-
nens et al., 1992). Lung injury involves complex endo-
thelial an smooth muscle to vasoconstriction and enhance pulmo-
nary vasoconstrictor responses (Liu et al., 1992c; Ste-
nens et al., 1992). Lung injury involves complex endo-
thelial and inflammatory cell interactions (Rounds,
1989), mary vasoconstrictor responses

nens et al., 1992). Lung injury

ithelial and inflammatory cell

1989), and multiple inflammato

kines are undoubtedly involved.

5. Pulmonary edema. Substano ms et al., 1992). Lung injury involves complex endo-

elial and inflammatory cell interactions (Rounds, §

189), and multiple inflammatory mediators and cyto-

nes are undoubtedly involved.

5. *Pulmonary edema*. Substance the ial and inflammatory cell interactions (Rounds, 1989), and multiple inflammatory mediators and cyto-
kines are undoubtedly involved.
5. Pulmonary edema. Substances such as BK (Pang et al., 1982), ET-1 (Rodman et al., 1

5. Pulmonary edema. Substances such as BK (Pang et al., 1982), ET-1 (Rodman et al., 1992; Simmet et al., 1993), histamine (Raud et al., 1991; Yuan et al., 1993c), 5-HT (Sumita et al., 1989; Raud et al., 1991), LTB₄ kines are undoubtedly involved. motion is a motion of the sum (1992), histamine (Raud et al., 1991; Yuan et al., 1993c), (Vo
5-HT (Sumita et al., 1989; Raud et al., 19 5. Pulmonary edema. Substances such as BK (Pang et 1.
al., 1982), ET-1 (Rodman et al., 1992; Simmet et al., inver
1992), histamine (Raud et al., 1991; Yuan et al., 1993c), (Voe
5-HT (Sumita et al., 1989; Raud et al., 1991 al., 1982), ET-1 (Rodman et al., 1992; Simmet et al., 1992), histamine (Raud et al., 1991; Yuan et al., 1993c), 5-HT (Sumita et al., 1989; Raud et al., 1991), LTB₄ (Raud et al., 1991), PAF (Chan et al., 1994) and SP (Bra 1992), histamine (Raud et al., 1991; Yuan et al., 1993c), 5-HT (Sumita et al., 1989; Raud et al., 1991), LTB_4 (Raud et al., 1991), PAF (Chan et al., 1994) and SP (Brain and Williams, 1985) are edema-forming or promotin 5-HT (Sumita et al., 1989; Raud et al., 1991), LTB₄ i
(Raud et al., 1991), PAF (Chan et al., 1994) and SP
(Brain and Williams, 1985) are edema-forming or pro-
moting agents and may therefore participate in the for-
mati

REGULATION OF PULMONARY VASCULAR TONE
ular bed seems to be edema. By contrast, CGRP (Raud et al., 1991) and VIP
(Harris and Heath, (Said, 1990) have anti-inflammatory properties and (Said, 1990) have anti-inflammatory properties and
therefore may be protective against the development of
therefore may be protective against the development of 105
edema. By contrast, CGRP (Raud et al., 1991) and VIP
(Said, 1990) have anti-inflammatory properties and
therefore may be protective against the development of
pulmonary edema. Adenosine has also been reported to edema. By contrast, CGRP (Raud et al., 1991) and VIP
(Said, 1990) have anti-inflammatory properties and
therefore may be protective against the development of
pulmonary edema. Adenosine has also been reported to
contribute edema. By contrast, CGRP (Raud et al., 1991) and VI (Said, 1990) have anti-inflammatory properties an therefore may be protective against the development opulmonary edema. Adenosine has also been reported to contribute to (Said, 1990) have anti-inflammatory properties
therefore may be protective against the developm
pulmonary edema. Adenosine has also been repor
contribute to the platelet-mediated reduction of
thelial albumin permeability (pulmonary edema. Adenosine has also been reported to
contribute to the platelet-mediated reduction of endo-
thelial albumin permeability (Paty et al., 1992).
IV. Respiratory Gases
Pulmonary vascular tone is under the act

Pulmonary vascular tone is under the active influence
Pulmonary vascular tone is under the active influence
respiratory gases. Both hypoxia and hypercapnia in-IV. Respiratory Gases.
IV. Respiratory Gases.
Pulmonary vascular tone is under the active influence
of respiratory gases. Both hypoxia and hypercapnia in-
duce pulmonary vasoconstriction (Fishman, 1961), but **IV. Respiratory Gases**
Pulmonary vascular tone is under the active influence
of respiratory gases. Both hypoxia and hypercapnia in-
duce pulmonary vasoconstriction (Fishman, 1961), but
increases in mixed venous CO_2 is increases in mixed venous CO2 is the main stimulus for Pulmonary vascular tone is under the active influence
of respiratory gases. Both hypoxia and hypercapnia in-
duce pulmonary vasoconstriction (Fishman, 1961), but
increases in mixed venous CO_2 is the main stimulus for
th of respiratory gases. Both hypoxia and hypercaphia in-
duce pulmonary vasoconstriction (Fishman, 1961), but
increases in mixed venous CO_2 is the main stimulus for
the hypercapnic response, whereas decreased mixed ve-
no increases in mixed venous CO_2 is the main stimulus for
the hypercapnic response, whereas decreased mixed ve-
nous PO_2 is only a contributory factor in the hypoxic
response (Duke, 1954; Marshall and Marshall, 1983).
Th the hypercapnic response, whereas decreased
nous PO₂ is only a contributory factor in th
response (Duke, 1954; Marshall and Marsha
The principal stimulus for HPV is alveola
(Duke, 1954; Marshall and Marshall, 1983). response (Duke, 1954; Marshall and Marshall, 1983).
 The principal stimulus for HPV is alveolar hypoxia

(Duke, 1954; Marshall and Marshall, 1983).
 A. Hypoxic Pulmonary Vasoconstriction
 HPV is a physiological respon

tion. Humoral mediators are important in the pulmo-
nary hypertension seen ARDS. Cyclo-oxygenase prod-
Von Euler and Liljestrand initially suggested that HPV
ucts, particularly TxA₂, are likely to be the mediators of re de principal stimulus for HTV is alveolar hypoxiated
uke, 1954; Marshall and Marshall, 1983).
Hypoxic Pulmonary Vasoconstriction
HPV is a physiological response whereby circulating
ood is diverted away from hypoxic alveoli blood is diverted away from hypoxic pulmonary Vasoconstriction
HPV is a physiological response whereby circulating
blood is diverted away from hypoxic alveoli, thus opti-
mizing the matching of perfusion and ventilation an A. Hypoxic Pulmonary Vasoconstriction

HPV is a physiological response whereby circulating

blood is diverted away from hypoxic alveoli, thus opti-

mizing the matching of perfusion and ventilation and

maximizing arterial HPV is a physiological response whereby circulating
blood is diverted away from hypoxic alveoli, thus opti-
mizing the matching of perfusion and ventilation and
maximizing arterial oxygenation. Because it is unique
and per maximizing arterial oxygenation. Because it is unique and perhaps the most powerful active control mechanism in the pulmonary circulation, HPV has been an nism in the pulmonary from hypoxic aiveon, thus opu-
mizing the matching of perfusion and ventilation and
maximizing arterial oxygenation. Because it is unique
and perhaps the most powerful active control mecha-
nism in th maximizing arterial oxygenation. Because it is unique
and perhaps the most powerful active control mecha-
nism in the pulmonary circulation, HPV has been an
area of intensive investigation and much debate since it
was fir mism in the pulmonary circulation, HPV has been
area of intensive investigation and much debate since
was first described by Von Euler and Liljestrand (194
Von Euler and Liljestrand initially suggested that HI
resulted fr area of intensive investigation and much debate since it
was first described by Von Euler and Liljestrand (1947).
Von Euler and Liljestrand initially suggested that HPV
resulted from the constriction of small muscular pul sponse to alveolar phorious are the injetical confirmed in the interpretation of response (Duke, 1954; Marshall and Marshall, 1983). The principal stimulus for HPV is alveolar hypoxia (Duke, 1954; Marshall and Marshall, 1 Von Euler and Liljestrand initially suggested that HPV
resulted from the constriction of small muscular pulmo-
nary arteries (several hundred μ m in diameter) in re-
sponse to alveolar hypoxia. This was confirmed by Kat resulted from the constriction of sinal muscular pumo-
nary arteries (several hundred μ m in diameter) in re-
sponse to alveolar hypoxia. This was confirmed by Kato
and Staub (1966). Subsequently, Glazier and Murray
(19 mary arteries (several hundred μ m in diameter) in response to alveolar hypoxia. This was confirmed by Kato and Staub (1966). Subsequently, Glazier and Murray (1971) found, using rapid freezing techniques, that hypoxia sponse w arveolar hypoxia. This was committed by K
and Staub (1966). Subsequently, Glazier and Mur
(1971) found, using rapid freezing techniques, that
poxia primarily constricted small pulmonary arter
This site was further poxia primarily constricted small pulmonary arteries.
This site was further confirmed by pulmonary arteriograms (Shirai et al., 1986) and by the demonstration of hypoxic constriction primarily in pulmonary arteries (30) (1971) found, using rapid freezing techniques, that hypoxia primarily constricted small pulmonary arteries.
This site was further confirmed by pulmonary arteriograms (Shirai et al., 1986) and by the demonstration of hypox poxia primarily constricted small pulmonary arteries.
This site was further confirmed by pulmonary arteriograms (Shirai et al., 1986) and by the demonstration of
hypoxic constriction primarily in pulmonary arteries (30
to This site was further confirmed by pulmonary arte
grams (Shirai et al., 1986) and by the demonstratio
hypoxic constriction primarily in pulmonary arteries
to 200 μ m) in bullfrog lungs (Koyama and Horim
1983). Direct mi grams (Shirai et al., 1986) and by the demonstration
hypoxic constriction primarily in pulmonary arteries (
to 200 μ m) in bullfrog lungs (Koyama and Horimo
1983). Direct micropuncture measurements of intrap
monary vasc mypoxic constriction primarity in putinolary arteries (50
to 200 μ m) in bullfrog lungs (Koyama and Horimoto,
1983). Direct micropuncture measurements of intrapul-
monary vascular pressure further supported this concluto 200 μ m) in bullfrog lungs (Koyama and Horimoto, 1983). Direct micropuncture measurements of intrapulmonary vascular pressure further supported this conclusion by showing that the predominant site of HPV is the preca 1983). Direct micropuncture measurements of intrapulmonary vascular pressure further supported this conclusion by showing that the predominant site of HPV is the precapillary arteries (Nagasaka et al., 1984). On the other monary vascular pressure further supported this concrudion
sion by showing that the predominant site of HPV is the
precapillary arteries (Nagasaka et al., 1984). On the
other hand, measurements by means of dimensio
transdu precapillary arteries (Nagasaka et al., 1984). On the other hand, measurements by means of dimension
transducers and functional approaches have also den
onstrated venoconstriction in response to hypoxia (Mo
gan et al., 196 other nand, measurements by means of dimension
transducers and functional approaches have also dem-
onstrated venoconstriction in response to hypoxia (Mor-
gan et al., 1968; Dawson et al., 1979). Nevertheless,
most investi *1.* attracted venoconstriction in response to hypoxia (Mornet al., 1968; Dawson et al., 1979). Nevertheless, bost investigators have concluded that the small pul-
party arteries are the major site of HPV.
1. Mechanisms.

gan et al., 1968; Dawson et al., 1979). Nevertheless, most investigators have concluded that the small pulmonary arteries are the major site of HPV.

1. Mechanisms. Despite more than four decades of investigation, the mech most investigators have concluded that the small pul-
monary arteries are the major site of HPV.
1. Mechanisms. Despite more than four decades of
investigation, the mechanism of HPV remains unclear
(Voelkel, 1986). Early w monary arteries are the major site of HPV.

1. Mechanisms. Despite more than four decades of

investigation, the mechanism of HPV remains unclea

(Voelkel, 1986). Early work established that autonomi

innervation does not 1. *Mechanisms*. Despite more than four decades of investigation, the mechanism of HPV remains unclear (Voelkel, 1986). Early work established that autonomic innervation does not seem to be necessary for the pressor respon (Voelkel, 1986). Early work established that autonomic
innervation does not seem to be necessary for the pres-
sor response of the adult lung to hypoxia (Fishman,
1976; Szidon and Flint, 1977; Hales and Westphal,
1979), ba sor response of the adult lung to hypoxia (Fishman, 1976; Szidon and Flint, 1977; Hales and Westphal, 1979), based on several lines of evidence. Firstly, HPV persists in isolated lung preparations (Hauge, 1968;

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Hauge and Melmon, 1968) and in human transplanted Failure to
lungs (Robin et al., 1987). Secondly, HPV is unaffected moted the al lungs (Robin et al., 1968) and in human transplanted
Hauge and Melmon, 1968) and in human transplanted
lungs (Robin et al., 1987). Secondly, HPV is unaffected
by adrenoceptor blockade (Malik and Kidd, 1973), cate-BARNE
Hauge and Melmon, 1968) and in human transplanted
hungs (Robin et al., 1987). Secondly, HPV is unaffected
by adrenoceptor blockade (Malik and Kidd, 1973), cate
cholamine depletion (Goldering et al., 1962; Silove and Hauge and Melmon, 1968) and in human transplanted
lungs (Robin et al., 1987). Secondly, HPV is unaffected mo
by adrenoceptor blockade (Malik and Kidd, 1973), cate-
cholamine depletion (Goldering et al., 1962; Silove and In Hauge and Melmon, 1968) and in human transplanted
lungs (Robin et al., 1987). Secondly, HPV is unaffected
by adrenoceptor blockade (Malik and Kidd, 1973), cate-
cholamine depletion (Goldering et al., 1962; Silove and
Grove by adrenoceptor blockade (Malik and Kidd, 1973), cate-
cholamine depletion (Goldering et al., 1962; Silove and
Grover, 1968), sympathectomy (Fishman, 1961), or de-
pletion of sensory neuropeptides with capsaicin (McCor-
ma by adrenoceptor blockade (Malik and Kidd, 1973), cate-
cholamine depletion (Goldering et al., 1962; Silove and In
Grover, 1968), sympathectomy (Fishman, 1961), or de-
pletion of sensory neuropeptides with capsaicin (McCorcholamine depletion (Goldering et al., 1962; Silove and In Grover, 1968), sympathectomy (Fishman, 1961), or de-
pletion of sensory neuropeptides with capsaicin (McCor-19 mack et al., 1993). Thus, intrinsic mechanisms withi Grover, 1968), sympathectomy (Fishman, 1961), or depletion of sensory neuropeptides with capsaicin (McCormack et al., 1993). Thus, intrinsic mechanisms within the lung seem to be responsible for HPV. Two main hypotheses ha pletion of sensory neuropeptides with capsaicin (McCormack et al., 1993). Thus, intrinsic mechanisms within the lung seem to be responsible for HPV. Two main hypotheses have been proposed. One is the mediator hypothesis, i mack et al., 1993). Thus, intrinsic mechanisms within pox
the lung seem to be responsible for HPV. Two main in c
hypotheses have been proposed. One is the mediator anis
hypothesis, in which endogenous vasoconstrictors or v the lung seem to be responsible for HPV. Two main
hypotheses have been proposed. One is the mediator
hypothesis, in which endogenous vasoconstrictors or va-
sodilators are believed to be released or suppressed by
hypoxia, hypotheses have been proposed. One is the mediat
hypothesis, in which endogenous vasoconstrictors or v
sodilators are believed to be released or suppressed
hypoxia, thus initiating HPV. The other hypothesis p
poses a direc hypothesis, in which endogenous vasoconstrictors of sodilators are believed to be released or suppresse
hypoxia, thus initiating HPV. The other hypothesis
poses a direct effect of hypoxia on the pulmonary valar smooth musc

hypoxia, thus initiating HPV. The other hypothesis p
poses a direct effect of hypoxia on the pulmonary vase
lar smooth muscle, inducing contraction (fig. 2).
In the search for chemical mediators, many vasoacti
substances h poses a direct effect of hypoxia on the pulmonary vascular smooth muscle, inducing contraction (fig. 2).
In the search for chemical mediators, many vasoactive
substances have been considered as candidates, includ-
ing cate lar smooth muscle, inducing contraction (fig. 2).
In the search for chemical mediators, many vasoactive
substances have been considered as candidates, includ-
ing catecholamines (Fishman, 1976), histamine (Hauge,
1968; Hau In the search for chemical mediators, many vasoactive smost substances have been considered as candidates, including catecholamines (Fishman, 1976), histamine (Hauge, scriber 1968; Hauge and Melmon, 1968), A-II (Berkov, 19 substances have been considered as candidates, includ-
ing catecholamines (Fishman, 1976), histamine (Hauge, scri
1968; Hauge and Melmon, 1968), A-II (Berkov, 1974), VI.I
vasoconstrictor prostaglandins (Weir et al., 1976), ing catecholamines (Fishman, 1976), histamine (Hauge, scription 1968; Hauge and Melmon, 1968), A-II (Berkov, 1974), VI.I vasoconstrictor prostaglandins (Weir et al., 1976), 5-HT actifican. 1976), PAF (McCormack et al., 198 1968; Hauge and Melmon, 1968), A-II (Berkov, 1974), vasoconstrictor prostaglandins (Weir et al., 1976), 5-HT (Fishman, 1976), PAF (McCormack et al., 1989a), ATP (McCormack et al., 1989b), and others. As discussed in III.A. vasoconstrictor prostaglandins (Weir et al., 1976), 5-HT ac (Fishman, 1976), PAF (McCormack et al., 1989a), ATP pu
(McCormack et al., 1989b), and others. As discussed in modulator, none of these has proved to be essential (Fishman, 1976), PAF (McCormack et al., 1989a), ATP
(McCormack et al., 1989b), and others. As discussed in
III.A., none of these has proved to be essential for HPV,
although these substances may have a modulatory role
or (McCormack et al., 1989b), and others. As discussed in me III.A., none of these has proved to be essential for HPV, Yualthough these substances may have a modulatory role evident or might play a role in setting up the bac III.A., none of these has proved to be essential for HPV,
although these substances may have a modulatory role
or might play a role in setting up the background con-
ditions that are necessary for HPV to occur. LTC_4 although these substances may have a modulatory row might play a role in setting up the background conditions that are necessary for HPV to occur. LTC_4 at LTD_4 are still under consideration (Morganroth et a 1984 or might play a role in setting up the background conditions that are necessary for HPV to occur. LTC_4 and LTD_4 are still under consideration (Morganroth et al., 1984; Lonigro et al., 1988; McDonnell et al., 1990; Ric ditions that are necessary for HPV to occur. LTC₄ and pu
LTD₄ are still under consideration (Morganroth et al., va
1984; Lonigro et al., 1988; McDonnell et al., 1990; Richa-
let et al., 1991), but their definitive rol LTD₄ are still under consideration (Morganroth et al., 1984; Lonigro et al., 1988; McDonnell et al., 1990; Richalet et al., 1991), but their definitive role in HPV still remains to be confirmed. ET-1 may play a role in 1984; Lonigro et al., 1988; McDonnell et al., 1990; Richa-
let et al., 1991), but their definitive role in HPV still ha
remains to be confirmed. ET-1 may play a role in the ra
development of chronic hypoxic pulmonary hyper let et al., 1991), but their definitive role in HPV still have remains to be confirmed. ET-1 may play a role in the radevelopment of chronic hypoxic pulmonary hypertension (We but is unlikely to mediate acute HPV, as the o remains to be confirmed. ET-1 may play a development of chronic hypoxic pulmonary hypotic is unlikely to mediate acute HPV, as the contractile response and recovery after we much slower than the time course of HPV.
The ide welopment of chronic hypoxic pulmonary hypertension
it is unlikely to mediate acute HPV, as the onset of the
ntractile response and recovery after washout are
uch slower than the time course of HPV.
The idea that suppressi

but is unlikely to mediate acute HPV, as the onset of the contractile response and recovery after washout are much slower than the time course of HPV.
The idea that suppression of vasodilator production, such as BK, by hyp contractile response and recovery after washout are
much slower than the time course of HPV.
The idea that suppression of vasodilator production,
such as BK, by hypoxia could mediate HPV was first
proposed by Weir (1978). much slower than the time course of HPV.
The idea that suppression of vasodilator productions as BK, by hypoxia could mediate HPV was forpposed by Weir (1978). Although BK has been elimated as a candidate, many other endog The idea that suppression of vasodilator production,
such as BK, by hypoxia could mediate HPV was first
proposed by Weir (1978). Although BK has been elimi-
nated as a candidate, many other endogenous vasodila-
tors, such such as BK, by hypoxia could mediate HF
proposed by Weir (1978). Although BK has
nated as a candidate, many other endogeno
tors, such as NO and PGI₂, remain possible.
will be discussed later, in the next section.

Afferent nerve
FIG. 2. Mechanisms of hypoxic pulmonary vasoconstriction. Pul-
monary vascular tone may increase with hypoxia because of reduced
release of relaxants from endothelial cells, via release of mediators
from o FIG. 2. Mechanisms of hypoxic pulmonary vasoconstriction. Pulmonary vascular tone may increase with hypoxia because of reduced release of nediators from other cells, or by a direct effect of hypoxia on the smooth muscle ce cell.

hypoxia, thus initiating HPV. The other hypothesis pro-
poses a direct effect of hypoxia on the pulmonary vascu-
 1989 , which has led to the suggestion that hypoxia may
lar smooth muscle, inducing contraction (fig. 2).
I Failure to identify conclusive mediator(s) has pro-
Failure to identify conclusive mediator(s) has pro-
oted the alternative proposal that HPV is caused by a ND LIU
Failure to identify conclusive mediator(s) has pro-
moted the alternative proposal that HPV is caused by a
direct effect on pulmonary vascular smooth muscle cells. BARNES AND LIU

lanted Failure to identify conclusive mediator(s) has pro-

ffected moted the alternative proposal that HPV is caused by a

), cate- direct effect on pulmonary vascular smooth muscle cells.

ve and In suppo Failure to identify conclusive mediator(s) has pro-
moted the alternative proposal that HPV is caused by a
direct effect on pulmonary vascular smooth muscle cells.
In support of this hypothesis, small pulmonary arteries,
o Failure to identify conclusive mediator(s) has promoted the alternative proposal that HPV is caused by a direct effect on pulmonary vascular smooth muscle cells.
In support of this hypothesis, small pulmonary arteries, of moted the alternative proposal that HPV is caused by a
direct effect on pulmonary vascular smooth muscle cells.
In support of this hypothesis, small pulmonary arteries,
of cat (Madden et al., 1985) and human (Hoshino et al direct effect on pulmonary vascular smooth muscle cells.
In support of this hypothesis, small pulmonary arteries,
of cat (Madden et al., 1985) and human (Hoshino et al.,
1988) contracts pulmonary vascular smooth muscle cel In support of this hypothesis, small pulmonary arteri
of cat (Madden et al., 1985) and human (Hoshino et a
1988) contract in response to hypoxia in vitro, and h
poxia contracts pulmonary vascular smooth muscle ce
in cultur 1988) contract in response to hypoxia in vitro, and hypoxia contracts pulmonary vascular smooth muscle cells in culture (Murray et al., 1990). Several possible mechanisms have been proposed to explain how hypoxia directly closes a K^+ channel and causes membrane depolarizapoxia contracts pulmonary vascular smooth muscle
in culture (Murray et al., 1990). Several possible m
anisms have been proposed to explain how hypoxic
rectly causes pulmonary vasoconstriction. Hyp
closes a K^+ channel a in culture (Murray et al., 1990). Several possible mechanisms have been proposed to explain how hypoxia directly causes pulmonary vasoconstriction. Hypoxia closes a K^+ channel and causes membrane depolarization of the anisms have been proposed to explain how hypoxia directly causes pulmonary vasoconstriction. Hypoxia closes a K^+ channel and causes membrane depolarization of the carotid body type I cells (Lopez-Lopez et al., 1989), w rectly causes pulmonary vasoconstriction. Hypoxia
closes a K^+ channel and causes membrane depolariza-
tion of the carotid body type I cells (Lopez-Lopez et al.,
1989), which has led to the suggestion that hypoxia may
c closes a K⁺ channel and causes membrane depolarization of the carotid body type I cells (Lopez-Lopez et al., 1989), which has led to the suggestion that hypoxia may close oxygen-sensitive K⁺ channels, which leads to s tion of the carotid body type I cells (Lopez-Lopez et al., 1989), which has led to the suggestion that hypoxia may close oxygen-sensitive K^+ channels, which leads to smooth muscle depolarization and Ca^{2+} entry, thus 1989), which has led to the suggestion that hypoxia may
close oxygen-sensitive K^+ channels, which leads to
smooth muscle depolarization and Ca^{2+} entry, thus in-
ducing contraction. Several K^+ channels have been d smooth muscle depolarization and Ca^{2+} entry, thus inducing contraction. Several K^+ channels have been described in pulmonary vascular smooth muscle cells (see VI.E.). Hypoxia inhibits both voltage-gated and Ca^{2+} -activated K^+ channels, and induces depolarization of ducing contraction. Several K^+ channels have been described in pulmonary vascular smooth muscle cells (see VI.E.). Hypoxia inhibits both voltage-gated and Ca^{2+} -activated K^+ channels, and induces depolarization of scribed in pulmonary vascular smooth muscle cells (see VI.E.). Hypoxia inhibits both voltage-gated and Ca^{2+} -activated K^+ channels, and induces depolarization of pulmonary artery smooth muscle cells, but not renal or activated K^+ channels, and induces depolarization of pulmonary artery smooth muscle cells, but not renal or mesenteric artery smooth muscle cells (Post et al., 1992; Yuan et al., 1993b; Cornfield et al., 1994). Additio activated K^+ channels, and induces depolarization
pulmonary artery smooth muscle cells, but not renal
mesenteric artery smooth muscle cells (Post et al., 19.
Yuan et al., 1993b; Cornfield et al., 1994). Addition
eviden pulmonary artery smooth muscle cells, but not renal or
mesenteric artery smooth muscle cells (Post et al., 1992;
Yuan et al., 1993b; Cornfield et al., 1994). Additional
evidence supporting this suggestion is the the demonmesenteric artery smooth muscle cells (Post et al., 1992
Yuan et al., 1993b; Cornfield et al., 1994). Additiona
evidence supporting this suggestion is the the demon
stration that hypoxia causes Ca^{2+} influx into culture Yuan et al., 1993b; Cornfield et al., 1994). Additional
evidence supporting this suggestion is the the demon-
stration that hypoxia causes Ca^{2+} influx into cultured
pulmonary artery smooth muscle cells of adult rats (S evidence supporting this suggestion is the the demon-
stration that hypoxia causes Ca^{2+} influx into cultured
pulmonary artery smooth muscle cells of adult rats (Sal-
vaterra and Goldman, 1993) and fetal lambs (Cornfiel stration that hypoxia causes Ca^{2+} influx into cultured
pulmonary artery smooth muscle cells of adult rats (Sal-
vaterra and Goldman, 1993) and fetal lambs (Cornfield
et al., 1994). However, ATP-dependent K^+ channels pulmonary artery smooth muscle cells of adult rats (Salvaterra and Goldman, 1993) and fetal lambs (Cornfield
et al., 1994). However, ATP-dependent K⁺ channels
have been shown to mediate secondary vasodilation
rather than et al., 1994). However, ATP-dependent K⁺ channels
have been shown to mediate secondary vasodilation
rather than the initial constriction to severe hypoxia
(Wiener et al., 1991). The energy state hypothesis sug-
gests tha have been shown to mediate secondary vasodilation and McMurtry, 1983). The cytochrome P_{450} hypothesis rather than the initial constriction to severe hypoxia
(Wiener et al., 1991). The energy state hypothesis suggests that HPV is initiated by decreased oxidative phos-
phorylation (Rounds and McMurtry, 1981; Stanbrook
and M (Wiener et al., 1991). The energy state hypothesis suggests that HPV is initiated by decreased oxidative phosphorylation (Rounds and McMurtry, 1981; Stanbrook and McMurtry, 1983). The cytochrome P_{450} hypothesis propos gests that HPV is initiated by decreased oxidative ph
phorylation (Rounds and McMurtry, 1981; Stanbrand McMurtry, 1983). The cytochrome P_{450} hypothe
proposes that cytochrome P_{450} acts a sensor that i
tiates HPV (M phorylation (Kounds and McMurtry, 1981; Standrook
and McMurtry, 1983). The cytochrome P_{450} hypothesis
proposes that cytochrome P_{450} acts a sensor that ini-
tiates HPV (Miller and Hales, 1979). The redox hypoth-
es and McMurtry, 1983). The cytochrome P_{450} hypothesis proposes that cytochrome P_{450} acts a sensor that initiates HPV (Miller and Hales, 1979). The redox hypothesis states that oxygen tension regulates the production proposes that cytochrome P_{450} acts a sensor that initiates HPV (Miller and Hales, 1979). The redox hypothesis states that oxygen tension regulates the production of reactive oxygen species or peroxide, which control t tiates HPV (Miller and Hales, 1979). The redox hypothesis states that oxygen tension regulates the production of reactive oxygen species or peroxide, which control transmembrane Ca^{2+} flux and hence vascular tone throug esis states that oxygen tension regulates the production
of reactive oxygen species or peroxide, which control
transmembrane Ca^{2+} flux and hence vascular tone
through a direct action on sulfhydryl groups in the Ca^{2+} of reactive oxygen species or peroxide, which control
transmembrane Ca^{2+} flux and hence vascular tone
through a direct action on sulfhydryl groups in the Ca^{2+} -
channel protein of vascular smooth muscle (Archer et
al transmembrane Ca^{2+} flux and hence vascular tone
through a direct action on sulfhydryl groups in the Ca^{2+} -
channel protein of vascular smooth muscle (Archer et
al., 1986b, 1993). All these hypotheses are still being
 through a direct action on sulfhydryl groups in the Ca^{2+} -
channel protein of vascular smooth muscle (Archer et
al., 1986b, 1993). All these hypotheses are still being
explored, but any hypothesis needs to account for t channel protein of vascular smooth muscle (Arch
al., 1986b, 1993). All these hypotheses are still l
explored, but any hypothesis needs to account for
difference in response to hypoxia of vascular sm
muscle in the pulmonary Partias, 1986b, 1993). All these hypotheses are still bein, plored, but any hypothesis needs to account for the fference in response to hypoxia of vascular smoother in the pulmonary and systemic circulations.
2. Abnormalit

explored, but any hypothesis needs to account for the difference in response to hypoxia of vascular smooth muscle in the pulmonary and systemic circulations.
2. Abnormalities in pulmonary vascular disease. Alterations in t difference in response to hypoxia of vascular smooth
muscle in the pulmonary and systemic circulations.
2. Abnormalities in pulmonary vascular disease. Al-
terations in the HPV response may occur in several
clinical condit muscle in the pulmonary and systemic circulations.

2. Abnormalities in pulmonary vascular disease. Alterations in the HPV response may occur in several

clinical conditions. HPV is lost or greatly diminished in

various t 2. Abnormalities in pulmonary vascular disease.
terations in the HPV response may occur in sever-
clinical conditions. HPV is lost or greatly diminished
various types of lung injuries. Loss or diminished HI
response has be terations in the HPV response may occur in severational conditions. HPV is lost or greatly diminished various types of lung injuries. Loss or diminished H response has been observed in lungs treated with hydrogia (Newman e clinical conditions. HPV is lost or greatly diminished in
various types of lung injuries. Loss or diminished HPV
response has been observed in lungs treated with hyper-
oxia (Newman et al., 1981), hydrogen peroxide (Burghu various types of lung injuries. Loss or diminished HPV
response has been observed in lungs treated with hyper-
oxia (Newman et al., 1981), hydrogen peroxide (Burghu-
ber et al., 1984), endotoxin (Reeves et al., 1974; Hales response has been observed in lungs treated with hyperoxia (Newman et al., 1981), hydrogen peroxide (Burghuber et al., 1984), endotoxin (Reeves et al., 1974; Hales et al., 1981), and bleomycin (McCormack et al., 1992). Eit oxia (Newman et al., 1981), hydrogen peroxide (Burgnu-
ber et al., 1984), endotoxin (Reeves et al., 1974; Hales et
al., 1981), and bleomycin (McCormack et al., 1992). Ei-
ther blunted (Leeman et al., 1992) or unchanged
(Jo ber et al., 1984), endotoxin (Reeves et al., 1974; Hales et al., 1981), and bleomycin (McCormack et al., 1992). Either blunted (Leeman et al., 1992) or unchanged (Johnston et al., 1989) HPV responses have also been report ther blunted (Leeman et al., 1992) or unchanged
(Johnston et al., 1989) HPV responses have also been
reported in the oleic acid-induced lung injuries of dogs.
In contrast, lung injury induced by α -napthylthyiourea
or m

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REGULATION OF PULMONAR
Rounds, 1983; Gillespie et al., 1986). Lungs treated with of
TNF- α also show an increased HPV response without wh REGULATION OF PULM
Rounds, 1983; Gillespie et al., 1986). Lungs treated with
TNF- α also show an increased HPV response without
obvious lung injury (Liu et al., 1992c). The differing REGULATION OF PULMONA

Rounds, 1983; Gillespie et al., 1986). Lungs treated with

TNF- α also show an increased HPV response without

which who differing

vascular reactivities in these lung injury models may re Rounds, 1983; Gillespie et al., 1986). Lungs treated with of TNF- α also show an increased HPV response without who by obvious lung injury (Liu et al., 1992c). The differing reactivities in these lung injury models may TNF- α also show an increased HPV response without when using these agents.

obvious lung injury (Liu et al., 1992c). The differing The mechanisms responsible for the alteration in HPV vascular reactivities in these lun TNF- α also show an increased HPV response without whe
obvious lung injury (Liu et al., 1992c). The differing T
vascular reactivities in these lung injury models may resp
relate to differences in the extent or site of i vascular reactivities in these lung injury models may
relate to differences in the extent or site of injury or may
reflect different stages of lung injury. The alterations in
pulmonary vascular reactivity during lung inju reflect different stages of lung injury. The alterations in pulmonary vascular reactivity during lung injury induced by endotoxin, α -napthylthyiourea, or monocrotaline is not specific to hypoxia, inasmuch as the reacti relate to differences in the extent or site of injury or may conserve the reflect different stages of lung injury. The alterations in common pulmonary vascular reactivity during lung injury induced by endotoxin, α -napt reflect different stages of lung injury. The alterations in pulmonary vascular reactivity during lung injury induced by endotoxin, α -napthylthyiourea, or monocrotal-
ine is not specific to hypoxia, inasmuch as the reac pulmonary vascular reactivity during lung injury in-
duced by endotoxin, α -napthylthyiourea, or monocrotal-
ine is not specific to hypoxia, inasmuch as the reactivity
to other pharmacological stimuli is also altered (H duced by endotoxin, α -napthylthyiourea, or monocrotal-
ine is not specific to hypoxia, inasmuch as the reactivity
to other pharmacological stimuli is also altered (Hales et
al., 1981; Hill and Rounds, 1983; Gillespie e ine is not specific to hypoxia, inasmuch as the reactivity
to other pharmacological stimuli is also altered (Hales et
al., 1981; Hill and Rounds, 1983; Gillespie et al., 1986).
On the other hand, bleomycin-induced lung inj to other pharmacological stimuli is also altered (Hales et emia (Hales et al., 1981). It is now clear that induction of al., 1981; Hill and Rounds, 1983; Gillespie et al., 1986). an inducible NO synthase and increased for al., 1981; Hill and Rounds, 1983; Gillespie et al., 1986).
On the other hand, bleomycin-induced lung injury di-
minishes the HPV response, without affecting the con-
strictor response to A-II (McCormack et al., 1992). The
 On the other hand, bleomycin-induced lung injury diminishes the HPV response, without affecting the constrictor response to A-II (McCormack et al., 1992). The HPV response is absent or diminished in an animal model of *Pse* HPV response is absent or diminished in an animal model of *Pseudomonas aeruginosa* pneumonia (Hanly et al., 1987), in atelectasis (Thomas and Garrett, 1982), and in some, but not all, patients with hepatic cirrhosis strictor response to A-II (McCormack et al., 1992). The
HPV response is absent or diminished in an animal
model of *Pseudomonas aeruginosa* pneumonia (Hanly et
al., 1987), in atelectasis (Thomas and Garrett, 1982),
and in HPV response is absent or diminished in an animal
model of *Pseudomonas aeruginosa* pneumonia (Hanly et
al., 1987), in atelectasis (Thomas and Garrett, 1982),
and in some, but not all, patients with hepatic cirrhosis
(Dao model of *Pseudomonas aeruginosa* pneumonia (Hanly et al., 1987), in atelectasis (Thomas and Garrett, 1982), and in some, but not all, patients with hepatic cirrhosis (Daoud et al., 1972; Rodriguez-Roisin et al., 1987). Th al., 1987), in atelectasis (Thomas and Garrett, 1982),
and in some, but not all, patients with hepatic cirrhosis
(Daoud et al., 1972; Rodriguez-Roisin et al., 1987). This
could at least partially account for the severe hyp and in some, but not all, patients with hepatic cirrhosis
(Daoud et al., 1972; Rodriguez-Roisin et al., 1987). This
could at least partially account for the severe hypoxemia
seen in these conditions. Elevations in pulmonar (Daoud et al., 1972; Rodriguez-Roisin et al., 1987). This

could at least partially account for the severe hypoxemia

seen in these conditions. Elevations in pulmonary and

left atrial pressure blunt HPV, which may partia could at least partially account for the severe hypoxemia
seen in these conditions. Elevations in pulmonary and
left atrial pressure blunt HPV, which may partially ex-
plain the abnormal ventilation/perfusion matching and
 seen in these conditions. Elevations in pulmonary and
left atrial pressure blunt HPV, which may partially ex-
plain the abnormal ventilation/perfusion matching and
hypoxemia associated with severe congestive or mitral
hea ent atrial pressure blunt III v, which may partially ex-
plain the abnormal ventilation/perfusion matching and
hypoxemia associated with severe congestive or mitral
heart disease and volume overload (Benumoff and
Wahrenbro plain the abnormal ventilation/perfusion matching and
hypoxemia associated with severe congestive or mitral
heart disease and volume overload (Benumoff and
Wahrenbrock, 1975). There are also reports that the
HPV response hypoxemia associated with severe congestive or mitral
heart disease and volume overload (Benumoff and
Wahrenbrock, 1975). There are also reports that the
HPV response is blunted in some patients with chronic
bronchitis (W heart disease and volume overload (Benumoff and Wahrenbrock, 1975). There are also reports that the obser
HPV response is blunted in some patients with chronic cludi
bronchitis (Weitzenblum et al., 1988), asthma (Corte
an Wahrenbrock, 1975). There are also reports that the HPV response is blunted in some patients with chronic bronchitis (Weitzenblum et al., 1988), asthma (Corte and Young, 1985), and suspected pulmonary embolism (Sostman et HPV response is blunted in some patients with chronic bronchitis (Weitzenblum et al., 1988), asthma (Corte and Young, 1985), and suspected pulmonary embolism (Sostman et al., 1983). The mechanism and significance of the al bronchitis (We
and Young, 19
(Sostman et al.
of the altered I
are not clear.
The effects o d Young, 1985), and suspected pulmonary embolism
ostman et al., 1983). The mechanism and significance
the altered HPV response in these clinical conditions
e not clear.
The effects of chronic hypoxia on the HPV response
e

of the altered HPV response in these clinical conditions
are not clear.
The effects of chronic hypoxia on the HPV response
are somewhat conflicting. In rats exposed to chronic
hypoxia, some investigators reported a decreas are not clear.
The effects of chronic hypoxia on the HPV response
are somewhat conflicting. In rats exposed to chronic
hypoxia, some investigators reported a decreased re-
sponse (McMurtry et al., 1980; Hill and Ou, 1984), The effects of chronic hypoxia on the HPV response
are somewhat conflicting. In rats exposed to chronic
hypoxia, some investigators reported a decreased re-
sponse (McMurtry et al., 1980; Hill and Ou, 1984),
whereas others are somewhat conflicting. In rats exposed to chronic hypoxia, some investigators reported a decreased response (McMurtry et al., 1980; Hill and Ou, 1984), whereas others demonstrated an increased pressor response (Emery et hypoxia, some investigators reported a decreased response (McMurtry et al., 1980; Hill and Ou, 1984), whereas others demonstrated an increased pressor response (Emery et al., 1981; Park et al., 1977). Variations fin age o sponse (McMurtry et al., 1980; Hill and Ou, 1984),
whereas others demonstrated an increased pressor re-
sponse (Emery et al., 1981; Park et al., 1977). Variations
in age or strain of animals and the duration of hypoxic
ex whereas others demonstrated an increased pressor response (Emery et al., 1981; Park et al., 1977). Variations for in age or strain of animals and the duration of hypoxic dexposure may explain these contradictory results. sponse (Emery et al., 1981; Park et al., 1977). Variations
in age or strain of animals and the duration of hypoxic
exposure may explain these contradictory results. It has
recently been reported that rats exposed to hypoxi in age or strain of animals and the duration of hypoxic dilation exposure may explain these contradictory results. It has as L-N recently been reported that rats exposed to hypoxia for ited (*i* 15 h or 2 days exhibit a m exposure may explain these contradictory results. It has
recently been reported that rats exposed to hypoxia for
15 h or 2 days exhibit a markedly reduced HPV re-
sponse, whereas rats exposed to hypoxia for 7 days show
an recently been reported that rats exposed to hypoxia for
15 h or 2 days exhibit a markedly reduced HPV response, whereas rats exposed to hypoxia for 7 days show
an HPV response similar to that in control rats (Zhao et
al., 15 h or 2 days exhibit a markedly reduced HPV response, whereas rats exposed to hypoxia for 7 days show p an HPV response similar to that in control rats (Zhao et al., 1993). The decreased or increased HPV response n afte sponse, whereas rats exposed to hypoxia for 7 days show an HPV response similar to that in control rats (Zhao al., 1993). The decreased or increased HPV response for chronic hypoxia is associated with a decreased increased an HPV response similar to that in control rats (Zhao et al., 1993). The decreased or increased HPV response after chronic hypoxia is associated with a decreased or increased pressor response to other pharmacological stimu al., 1993). The decreased or increased HPV response
after chronic hypoxia is associated with a decreased or
increased pressor response to other pharmacological
stimuli, suggesting an alteration in pulmonary vascular
reacti after chronic hypoxia is associated with a decreased or \exp
increased pressor response to other pharmacological the
stimuli, suggesting an alteration in pulmonary vascular ED
reactivity. An enhanced HPV response has been increased pressor response to other pharmacological
stimuli, suggesting an alteration in pulmonary vascular
reactivity. An enhanced HPV response has been ob-
served during lung hyperinflation (Quebbeman and
Dawson, 1977) i stimuli, suggesting an alteration in pulmonary vascular
reactivity. An enhanced HPV response has been ob-
served during lung hyperinflation (Quebbeman and
Dawson, 1977) in dogs with hypothermia (Fan et al.,
1992) and in pa reactivity. An enhanced HPV response has been ob-
served during lung hyperinflation (Quebbeman and
Dawson, 1977) in dogs with hypothermia (Fan et al., of
1992) and in patients with systemic hypertension ev
(Guazzi et al., served during lung hyperinflation (Quebbeman and Dawson, 1977) in dogs with hypothermia (Fan et al., 1992) and in patients with systemic hypertension (Guazzi et al., 1989). The clinical significance of the increased HPV re Dawson, 1977) in dogs with hypothermia (Fan et al., or
1992) and in patients with systemic hypertension e
(Guazzi et al., 1989). The clinical significance of the ta-
increased HPV response is unclear. The HPV response the
 1992) and in patients with systemic hypertension (Guazzi et al., 1989). The clinical significance of the increased HPV response is unclear. The HPV response can be inhibited by multiple vasodilator mediators or drugs (see

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of assessing gas exchange as well as hemodynamics

when using these agents. WARY VASCULAR TONE
of assessing gas exchang
when using these agents.
The mechanisms respone

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assessing gas exchange as well as hemodynamics

inen using these agents.

The mechanisms responsible for the alteration in HPV

sponse in disease are largely unknown. Endothelial of assessing gas exchange as well as hemodynamics
when using these agents.
The mechanisms responsible for the alteration in HPV
response in disease are largely unknown. Endothelia
damage may account for the hyperreactivity of assessing gas exchange as well as hemodynamics
when using these agents.
The mechanisms responsible for the alteration in HPV
response in disease are largely unknown. Endothelial
damage may account for the hyperreactivi when using these agents.
The mechanisms responsible for the alteration in HPV
response in disease are largely unknown. Endothelial
damage may account for the hyperreactivity seen after
 α -napthylthyiourea- or monocrotal The mechanisms responsible for the alteration in HPV
response in disease are largely unknown. Endothelial
damage may account for the hyperreactivity seen after
 α -napthylthyiourea- or monocrotaline-induced lung in-
jury response in disease are largely unknown. Endothelial
damage may account for the hyperreactivity seen after
 α -napthylthyiourea- or monocrotaline-induced lung in-
jury (Hill and Rounds, 1983; Gillespie et al., 1986). Pro damage may account for the hyperreactivity seen aft α -napthylthyiourea- or monocrotaline-induced lung i
jury (Hill and Rounds, 1983; Gillespie et al., 1986). Pr
duction of vasodilator prostaglandins may contribute
the α -napthylthyiourea- or monocrotaline-induced lung in-
jury (Hill and Rounds, 1983; Gillespie et al., 1986). Pro-
duction of vasodilator prostaglandins may contribute to
the pulmonary vascular hyporeactivity seen in end jury (Hill and Rounds, 1983; Gillespie et al., 1986). Production of vasodilator prostaglandins may contribute to
the pulmonary vascular hyporeactivity seen in endox-
emia (Hales et al., 1981). It is now clear that inductio duction of vasodilator prostaglandins may contribute
the pulmonary vascular hyporeactivity seen in endo
emia (Hales et al., 1981). It is now clear that induction
an inducible NO synthase and increased formation
NO are larg the pulmonary vascular hyporeactivity seen in
emia (Hales et al., 1981). It is now clear that indu
an inducible NO synthase and increased forms
NO are largely responsible for endotoxin-induced
nary vascular hyporeactivity **VO synthase and increased form**
responsible for endotoxin-induce
hyporeactivity (Liu et al., 1993).
V. Role of Endothelium
n-Derived Relaxing Factor A. Endothelium-Derived Relaxing Factor
A. Endothelium-Derived Relaxing Factor

(Sostman et al., 1983). The mechanism and significance
of the altered HPV response in these clinical conditions
are not clear.
The effects of chronic hypoxia on the HPV response
are somewhat conflicting. In rats exposed t V. Role of Endothelium
Endothelium-Derived Relaxing Factor
In 1980, Furchgott and Zawadzki demonstrated that
e vascular relaxation induced by ACh was dependent **V. Role of Endothelium**
A. *Endothelium-Derived Relaxing Factor*
In 1980, Furchgott and Zawadzki demonstrated that
the vascular relaxation induced by ACh was dependent
on the presence of an intact vascular endothelium. Th A. *Endothelium-Derived Relaxing Factor*
In 1980, Furchgott and Zawadzki demonstrated that
the vascular relaxation induced by ACh was dependent
on the presence of an intact vascular endothelium. They
also demonstrated that A. *Endothetium-Derived Relaxing ractor*
In 1980, Furchgott and Zawadzki demonstrated that
the vascular relaxation induced by ACh was dependent
on the presence of an intact vascular endothelium. They
also demonstrated that In 1980, Furchgott and Zawadzki demonstrated that
the vascular relaxation induced by ACh was dependen
on the presence of an intact vascular endothelium. The
also demonstrated that ACh-induced smooth muscle re
laxation resu the vascular relaxation induced by ACh was dependent
on the presence of an intact vascular endothelium. They
also demonstrated that ACh-induced smooth muscle re-
laxation resulted from the endothelium-mediated re-
lease of on the presence of an intact vascular endothelium. They
also demonstrated that ACh-induced smooth muscle re-
laxation resulted from the endothelium-mediated re-
lease of a nonprostanoid, labile relaxing substance later
ter also demonstrated that ACh-induced smooth muscle re-
laxation resulted from the endothelium-mediated re-
lease of a nonprostanoid, labile relaxing substance later
termed EDRF (Cherry et al., 1982). The phenomenon of
endoth laxation resulted from the endothelium-mediated re-
lease of a nonprostanoid, labile relaxing substance later
termed EDRF (Cherry et al., 1982). The phenomenon of
endothelium-dependent relaxation was subsequently
observed lease of a nonprostanoid, labile relaxing substance later
termed EDRF (Cherry et al., 1982). The phenomenon of
endothelium-dependent relaxation was subsequently
observed in a wide range of vascular preparations in-
cluding gions in response to a diverse range of pharmacological
choosing arteries, veins, and microvessels of various re-
gions in response to a diverse range of pharmacological
and physiological stimuli (Furchgott, 1984; Furchgot observed in a wide range of vascular preparations in-
cluding arteries, veins, and microvessels of various re-
gions in response to a diverse range of pharmacological
and physiological stimuli (Furchgott, 1984; Furchgott
a gions in response to a diverse range of pharmacological
and physiological stimuli (Furchgott, 1984; Furchgott gions in response to a diverse range of pharmacological
and physiological stimuli (Furchgott, 1984; Furchgot
and Vanhoutte, 1989). Furchgott (1988) and Ignarr
(Ignarro et al., 1988b) independently suggested tha
EDRF may be and physiological stimuli (Furchgott, 1984; Furchgott
and Vanhoutte, 1989). Furchgott (1988) and Ignarro
(Ignarro et al., 1988b) independently suggested that
EDRF may be NO, based on the pharmacological simi-
larities bet and Vanhoutte, 1989). Furchgott (1988) and Ignarro (Ignarro et al., 1988b) independently suggested that EDRF may be NO, based on the pharmacological similarities between EDRF and NO generated from either acidified NO_2^- (Ignarro et al., 1988b) independently suggested that
EDRF may be NO, based on the pharmacological simi-
larities between EDRF and NO generated from either
acidified NO_2^- or NO gas, and evidence now strongly
supports the EDRF may be NO, based on the pharmacological is
larities between EDRF and NO generated from e
acidified NO_2^- or NO gas, and evidence now stro
supports the identification of EDRF as NO (Monca
al., 1991; Nathan, 1992). An larities between EDRF and NO generated from either
acidified NO_2^- or NO gas, and evidence now strongly
supports the identification of EDRF as NO (Moncada et
al., 1991; Nathan, 1992). Another proposed nonprostan-
oid EDR acidified NO_2^- or NO gas, and evidence now strongly
supports the identification of EDRF as NO (Moncada et
al., 1991; Nathan, 1992). Another proposed nonprostan-
oid EDRF that differs from NO is EDHF (Komori and
Vanhoutt supports the identification of EDRF as NO (Moncada e
al., 1991; Nathan, 1992). Another proposed nonprostar
oid EDRF that differs from NO is EDHF (Komori an
Vanhoutte, 1990). In the physiological salt solution per
fused pul al., 1991; Nathan, 1992). Another proposed nonprostan-
oid EDRF that differs from NO is EDHF (Komori and
Vanhoutte, 1990). In the physiological salt solution per-
fused pulmonary vascular bed of rat, ACh-induced vaso-
dila oid EDRF that differs from NO is EDHF (Komori and Vanhoutte, 1990). In the physiological salt solution per fused pulmonary vascular bed of rat, ACh-induced vasa dilation is not inhibited by NO synthase inhibitors sue as L-Vanhoutte, 1990). In the physiological salt solution per-
fused pulmonary vascular bed of rat, ACh-induced vaso-
dilation is not inhibited by NO synthase inhibitors such
as L-NMMA, although BK-induced relaxation is inhib-
 fused pulmonary vascular bed of rat, ACh-induced vaso-
dilation is not inhibited by NO synthase inhibitors such
as L-NMMA, although BK-induced relaxation is inhib-
ited (Archer et al., 1989). ACh-induced vasodilation is
co dilation is not inhibited by NO synthase inhibitors such
as L-NMMA, although BK-induced relaxation is inhib-
ited (Archer et al., 1989). ACh-induced vasodilation is
consistently inhibited by NO synthase inhibitors in the
p as L-NMMA, although BK-induced relaxation is inhibited (Archer et al., 1989). ACh-induced vasodilation is consistently inhibited by NO synthase inhibitors in the pulmonary vascular beds of cat and lamb (Fineman et al., 199 consistently inhibited by NO synthase inhibitors in the pulmonary vascular beds of cat and lamb (Fineman et al., 1991a; McMahon et al., 1991a). Differences in agonist efficacy in the receptor system being studied might exp consistently inhibited by NO synthase inhibitors in the pulmonary vascular beds of cat and lamb (Fineman et al., 1991a; McMahon et al., 1991a). Differences in agonist efficacy in the receptor system being studied might exp pulmonary vascular beds of cat and lamb (Fineman et al., 1991a; McMahon et al., 1991a). Differences in agonist efficacy in the receptor system being studied might explain the agonist- and tissue-dependent variation in the al., 1991a; McMahon et al., 1991a). Differences in ago-
mist efficacy in the receptor system being studied might
explain the agonist- and tissue-dependent variation in
the L-NMMA effect (Martin et al., 1992). Whether
EDRF, mist efficacy in
explain the at
the L-NMMA
EDRF, in add
be determined
1. Role of ba plain the agonist- and tissue-dependent variation in
 i e L-NMMA effect (Martin et al., 1992). Whether
 DRF, in addition to NO and EDHF, exists remains to
 determined.
 1. Role of basally released nitric oxide. The the L-NMMA effect (Martin et al., 1992). Whether
EDRF, in addition to NO and EDHF, exists remains to
be determined.
1. Role of basally released nitric oxide. The importance
of NO in the regulation of pulmonary vascular ton

EDRF, in addition to NO and EDHF, exists remains to
be determined.
1. Role of basally released nitric oxide. The importance
of NO in the regulation of pulmonary vascular tone is
evident by the demonstration that many humor be determined.

1. Role of basally released nitric oxide. The importance

of NO in the regulation of pulmonary vascular tone is

evident by the demonstration that many humoral fac-

tors and autacoids induce pulmonary vaso 1. Role of oasally released nuric oxide. The importance
of NO in the regulation of pulmonary vascular tone is
evident by the demonstration that many humoral fac-
tors and autacoids induce pulmonary vasodilation
through the or NO in the regulation or pulmonary vascular tone is
evident by the demonstration that many humoral fac-
tors and autacoids induce pulmonary vasodilation
through the release of NO. Substances that have been
reported to in

BARNES AND LIU
et al., 1991a, 1992), norepinephrine (Liu et al., 1991a), 1994),
BK (Ignarro et al., 1987a), SP (Maggi et al., 1990; Mc- PVR is BARNES
et al., 1991a, 1992), norepinephrine (Liu et al., 1991a),
BK (Ignarro et al., 1987a), SP (Maggi et al., 1990; Mc-
Mahon and Kadowitz, 1993), ATP (Liu et al., 1992a), BARNES
et al., 1991a, 1992), norepinephrine (Liu et al., 1991a),
BK (Ignarro et al., 1987a), SP (Maggi et al., 1990; Mc-
Mahon and Kadowitz, 1993), ATP (Liu et al., 1992a),
histamine (Szarek et al., 1992; Ortiz et al., 199 et al., 1991a, 1992), norepinephrine (Liu et al., 1991a), 1994
BK (Ignarro et al., 1987a), SP (Maggi et al., 1990; Mc- PVR
Mahon and Kadowitz, 1993), ATP (Liu et al., 1992a), (Sta:
histamine (Szarek et al., 1992; Ortiz et et al., 1991a, 1992), norepinephrine (Liu et al., 1991a),
BK (Ignarro et al., 1987a), SP (Maggi et al., 1990; Mc-
Mahon and Kadowitz, 1993), ATP (Liu et al., 1992a), (
histamine (Szarek et al., 1992; Ortiz et al., 1992), 5 BK (Ignarro
Mahon and
histamine (S
(Glusa and .
al., 1992a).
Acute infi

(Glusa and Richter, 1993), ET-1 and ET-3 (Crawley et al., 1992a).

Acute infusion of L-NMMA or oral administration of L-NAME for periods of 4 weeks causes a dose-dependent increase in systemic arterial blood pressure that increase in systemic arterial blood pressure that is asal., 1992a).

Acute infusion of L-NMMA or oral administration of a

L-NAME for periods of 4 weeks causes a dose-dependent

increase in systemic arterial blood pressure that is as-

sociated with a reduction in aortic cGMP Acute infusion of L-NMMA or oral administration of and L-NAME for periods of 4 weeks causes a dose-dependent land increase in systemic arterial blood pressure that is ased sociated with a reduction in aortic cGMP content (L-NAME for periods of 4 weeks causes a dose-dependent la
increase in systemic arterial blood pressure that is as-
sociated with a reduction in aortic cGMP content (Rees
et al., 1989; Arnal et al., 1992), indicating that b increase in systemic arterial blood pressure that is as-
sociated with a reduction in aortic cGMP content (Rees cular r
et al., 1989; Arnal et al., 1992), indicating that basally onism
released NO plays an important role sociated with a reduction in aortic cGMP content (Rees culled at al., 1989; Arnal et al., 1992), indicating that basally oniveleased NO plays an important role in the regulation of averagement blood pressure. The role of et al., 1989; Arnal et al., 1992), indicating that basally
released NO plays an important role in the regulation of
systemic blood pressure. The role of basal levels of NO
released into the pulmonary circulation seems to b released NO plays an important role in the regulation of a
systemic blood pressure. The role of basal levels of NO
released into the pulmonary circulation seems to be
variable between species. L-NMMA or L-NA increase
base systemic blood pressure. The role of basal levels of NO
released into the pulmonary circulation seems to be
variable between species. L-NMMA or L-NA increase
baseline PPA in pulmonary vascular beds of guinea pigs
(Davidson released into the pulmonary circulation seems to be
variable between species. L-NMMA or L-NA increase
baseline PPA in pulmonary vascular beds of guinea pigs
(Davidson and Eldemerdash, 1991), rabbits (Wiklund et K^+
al., variable between species. L-NMMA or L-NA increadured baseline PPA in pulmonary vascular beds of guinea p
(Davidson and Eldemerdash, 1991), rabbits (Wiklund
al., 1990), and lambs (Fineman et al., 1991a; Gordon a
Tod, 1993). baseline PPA in pulmonary vascular beds of guinea p
(Davidson and Eldemerdash, 1991), rabbits (Wiklund
al., 1990), and lambs (Fineman et al., 1991a; Gordon a
Tod, 1993). L-NA reduces pulmonary vascular cond
tance with no c (Davidson and Eldemerdash, 1991), rabbits (Wiklund et Kal., 1990), and lambs (Fineman et al., 1991a; Gordon and tion, 1993). L-NA reduces pulmonary vascular conducations with no change in PPA in the pigs in vivo, suggest-
 al., 1990), and lambs (Fineman et al., 1991a; Gordon and Tod, 1993). L-NA reduces pulmonary vascular conductance with no change in Pra in the pigs in vivo, suggesting an increase in pulmonary vascular resistance during L-N Tod, 1993). L-NA reduces pulmonary vascular conduc-
tance with no change in PPA in the pigs in vivo, suggest-
ing an increase in pulmonary vascular resistance during (
L-NA infusion (van Gelderen et al., 1993). Methylene s tance with no change in PPA in the pigs in vivo, suggesting an increase in pulmonary vascular resistance during L-NA infusion (van Gelderen et al., 1993). Methylene blue also increases PPA in the pulmonary vascular beds of L-NA infusion (van Gelderen et al., 1993). Methylene
blue also increases PPA in the pulmonary vascular beds
of cats (Hyman et al., 1989). By contrast, L-NA or L-
NAME have no effect on pulmonary vascular resistance
in dogs blue also increases PPA in the pulmonary vascular beds cof cats (Hyman et al., 1989). By contrast, L-NA or L- ('NAME have no effect on pulmonary vascular resistance cin dogs, either under basal conditions or when the pulmo of cats (Hyman et al., 1989). By contrast, L-NA or NAME have no effect on pulmonary vascular resistan
in dogs, either under basal conditions or when the p
monary venous pressure is slightly elevated to ensu
that the circul monary venous pressure is signtly elevated to ensure
that the circulation is under zone 3 conditions (Nishi-
waki et al., 1992; Barnard et al., 1993). L-NMMA or
hemoglobin increase baseline vascular tone in isolated
pulmon waki et al., 1992; Barnard et al., 1993). L-NMMA or network in the in solated repulmonary artery rings of pigs and guinea pigs (Liu et pulmonary artery rings of pigs and guinea pigs (Liu et pal., 1992a, d) or lambs (Abman hemoglobin increase baseline vascular tone in isolated rel
pulmonary artery rings of pigs and guinea pigs (Liu et ph
al., 1992a, d) or lambs (Abman et al., 1991) but not rats see
(Crawley et al., 1990). L-NMMA or L-NA have pulmonary artery rings of pigs and guinea pigs (End et al., 1992a, d) or lambs (Abman et al., 1991) but not rats (Crawley et al., 1990). L-NMMA or L-NA have no effects or slightly increase pulmonary perfusion pressure in t (Crawley et al., 1990). L-NMMA or L-NA have no effects or slightly increase pulmonary perfusion pressure in the perfused pulmonary vascular bed under basal conditions (Archer et al., 1989; Hasunuma et al., 1991a; Liu et al or slightly increase pulmonary perfusion pressure in the perfused pulmonary vascular bed under basal conditions perfused pulmonary vascular bed under basal conditions

(Archer et al., 1989; Hasunuma et al., 1991a; Liu et al.,

1991b) but increase PPA or vascular resistance in hyper-

tensive pulmonary vascular beds (Oka et al., 1993 (Archer et al., 1989; Hasunuma et al., 1991a; Liu et al., 1991b) but increase PPA or vascular resistance in hypertensive pulmonary vascular beds (Oka et al., 1993; Barer et al., 1993) or when the venous pressure is slight tensive pulmonary vascular beds (Oka et al., 1993; modulatory role on the adrenergic response. Pulmonary Barer et al., 1993) or when the venous pressure is endothelial cells take up and degrade norepinephrine, slightly ele tensive pulmonary vascular beds (Oka et al., 1
Barer et al., 1993) or when the venous pressur
slightly elevated to ensure that the pulmonary vasc
beds are under zone 3 conditions in the rats (Barnai
al., 1993). Under the s Barer et al., 1993) or when the venous pressure is
slightly elevated to ensure that the pulmonary vascular
beds are under zone 3 conditions in the rats (Barnard et
al., 1993). Under the same conditions, the cyclo-oxygen-
a beds are under zone 3 conditions in the rats (Barnard et al., 1993). Under the same conditions, the cyclo-oxygenase inhibitor, indomethacin, has no effect on the basal pulmonary vascular resistance of rats but increases pu beds are under zone 3 conduons in the rats (Barnard et al., 1993). Under the same conditions, the cyclo-oxygenase inhibitor, indomethacin, has no effect on the basal pulmonary vascular resistance of rats but increases pulm 1993). Thus, vasodilator prostaglandins regulate basal pulmonary vascular tone in the dogs, whereas NO regulates the basal pulmonary vascular tone in rats, cats, pulmonary vascular resistance of rats but increases pul-
monary vascular resistance in dogs (Barnard et al.,
1993). Thus, vasodilator prostaglandins regulate basal
pulmonary vascular tone in the dogs, whereas NO reg-
ulate monary vascular resistance in dogs (Barnard et al., tan 1993). Thus, vasodilator prostaglandins regulate basal end
pulmonary vascular tone in the dogs, whereas NO reg-
ulates the basal pulmonary vascular tone in rats, cats 1993). Thus, vasodilator prostaglandins regulate basal pulmonary vascular tone in the dogs, whereas NO regulates the basal pulmonary vascular tone in rats, cats, guinea pigs, pigs, and sheep. Basally released NO also plays pulmonary vascular tone in the dogs, whereas NO regulates the basal pulmonary vascular tone in rats, cats, guinea pigs, pigs, and sheep. Basally released NO also plays an important role in the maintenance of low pulmonary ulates the basal pulmonary vascular tone in rats, cats, conguinea pigs, pigs, and sheep. Basally released NO also after plays an important role in the maintenance of low pul-
pig monary vascular tone in humans (Celermajer guinea pigs, pigs, and sheep. Basally released NO also
plays an important role in the maintenance of low pul-
monary vascular tone in humans (Celermajer et al.,
1994; Stamler et al., 1994). Infusion of L-NMMA into
healthy plays an important role in the maintenance of low pul-
monary vascular tone in humans (Celermajer et al.,
1994; Stamler et al., 1994). Infusion of L-NMMA into
healthy volunteers or children with congenital heart
disease bu monary vascular tone in humans (Celermajer et al., 1994; Stamler et al., 1994). Infusion of L-NMMA into healthy volunteers or children with congenital heart disease but with normal pulmonary blood flow, pressure, and resis resistance (Stamler et al., 1994). Infusion of L-NMMA into the disease but with normal pulmonary blood flow, pressure, and resistance, causes a dose-dependent increase in pulmonary vascular resistance (Stamler et al., 1994

Mahon and Kadowitz, 1993), ATP (Liu et al., 1992a), (Stamler et al., 1994). Taken together with the demon-
histamine (Szarek et al., 1992; Ortiz et al., 1992), 5-HT strations that basally released NO inhibits the contrac-
 ND LIU
1994), with no change in PPA. Moreover, the increased
PVR is associated with a reduction in plasma NO₃ Ievel ND LIU
1994), with no change in PPA. Moreover, the increased
PVR is associated with a reduction in plasma NO_3^- level
(Stamler et al., 1994). Taken together with the demon-ND LIU
1994), with no change in PPA. Moreover, the increase
PVR is associated with a reduction in plasma NO_3^- le
(Stamler et al., 1994). Taken together with the demon-
strations that basally released NO inhibits the con 1994), with no change in PPA. Moreover, the increase PVR is associated with a reduction in plasma NO_3^- le (Stamler et al., 1994). Taken together with the demostrations that basally released NO inhibits the contractie r 1994), with no change in PPA. Moreover, the increase PVR is associated with a reduction in plasma $NO₃^-$ leve (Stamler et al., 1994). Taken together with the demonstrations that basally released NO inhibits the contr PVR is associated with a reduction in plasma NO_3^- level
(Stamler et al., 1994). Taken together with the demon-
strations that basally released NO inhibits the contrac-
tile responses to adrenergic stimulation and other (Stamler et al., 1994). Taken together with the demostrations that basally released NO inhibits the contri
tile responses to adrenergic stimulation and other vas
constrictors, these results indicate that basal NO pla
an im strations that basally released NO inhibits the contractile responses to adrenergic stimulation and other vaso-
constrictors, these results indicate that basal NO plays
an important role in the regulation of pulmonary vasc tile responses to adrenergic stimulation and other vaso-
constrictors, these results indicate that basal NO plays
an important role in the regulation of pulmonary vascu-
lar tone, both under basal conditions, and when tone an important role in the regulation of pulmonary vascular tone, both under basal conditions, and when tone is elevated. Basal NO release increases when PPA or vascular resistance is higher, thus providing a tonic antag-
on an important role in the regulation of pulmonary vascular tone, both under basal conditions, and when tone is
elevated. Basal NO release increases when PPA or vas-
cular resistance is higher, thus providing a tonic antag-
 lar tone, both under basal conditions, and when tone is
elevated. Basal NO release increases when PPA or vas-
cular resistance is higher, thus providing a tonic antag-
onism to the elevation in pulmonary vascular tone and
 Franchism to the elevation in pulmonary vascular tone and avoidance of any overshoot in pulmonary blood pressure.
 B. Endothelium-Derived Hyperpolarizing Factor
 EDHF may be another EDRF distinct from NO (Na-

in dogs, either under basal conditions or when the pul-
monary venous pressure is slightly elevated to ensure (Bolotina et al., 1994). Additionally, a specific inhibitor
that the circulation is under zone 3 conditions (Ni monary venous pressure is slightly elevated to ensure (Bolotina et al., 1994). Additionally, a specific inhibitor
that the circulation is under zone 3 conditions (Nishi-of K⁺_{Ca} channels, charybdotoxin, virtually aboli ism to the elevation in pulmonary vascular tone and
oidance of any overshoot in pulmonary blood pressure
Endothelium-Derived Hyperpolarizing Factor
EDHF may be another EDRF distinct from NO (Na-
o and Vanhoutte, 1993) that avoidance of any overshoot in pulmonary blood pressure.

B. Endothelium-Derived Hyperpolarizing Factor

EDHF may be another EDRF distinct from NO (Na-

gao and Vanhoutte, 1993) that causes the opening of a

K⁺ channel, l B. Endothelium-Derived Hyperpolarizing Factor
EDHF may be another EDRF distinct from NO
gao and Vanhoutte, 1993) that causes the opening
K⁺ channel, leading to smooth muscle hyperpolition. The nature of EDHF remains unkn EDHF may be another EDRF distinct from NO (Nagao and Vanhoutte, 1993) that causes the opening of a
K⁺ channel, leading to smooth muscle hyperpolariza-
tion. The nature of EDHF remains unknown, but its
action is not inhib EDHF may be another EDRF distinct from NO (Nagao and Vanhoutte, 1993) that causes the opening of a K^+ channel, leading to smooth muscle hyperpolarization. The nature of EDHF remains unknown, but its action is not inhib gao and Vanhoutte, 1993) that causes the opening of a K⁺ channel, leading to smooth muscle hyperpolarization. The nature of EDHF remains unknown, but its action is not inhibited by hemoglobin and methylene blue. EDHF has K^+ channel, leading to smooth muscle hyperpolariion. The nature of EDHF remains unknown, but action is not inhibited by hemoglobin and methyle blue. EDHF has been reported in pulmonary arts (Chen et al., 1988). One com tion. The nature of EDHF remains unknown, but its
action is not inhibited by hemoglobin and methylene
blue. EDHF has been reported in pulmonary artery
(Chen et al., 1988). One complication for the under-
standing of EDHF action is not inhibited by hemoglobin and methylene
blue. EDHF has been reported in pulmonary artery
(Chen et al., 1988). One complication for the under-
standing of EDHF is the demonstration that NO itself
can open K^+ blue. EDHF has been reported in pulmonary artery
(Chen et al., 1988). One complication for the under-
standing of EDHF is the demonstration that NO itself
can open K⁺ channels and causes hyperpolarization
(Tare et al., (Chen et al., 1988). One complication for the under-
standing of EDHF is the demonstration that NO itself
can open K^+ channels and causes hyperpolarization
(Tare et al., 1990). Both exogenous NO and native EDRF
can dir standing of EDHF is the demonstration that NO itself
can open K^+ channels and causes hyperpolarization
(Tare et al., 1990). Both exogenous NO and native EDRF
can directly activate single Ca^{2+} -activated K^+ channel can open K^+ channels and causes hyperpolarization
(Tare et al., 1990). Both exogenous NO and native EDRF
can directly activate single Ca^{2+} -activated K^+ channels
in cell-free membrane patches without requiring cGM can directly activate single Ca^{2+} -activated K^+ channels
in cell-free membrane patches without requiring cGMP
(Bolotina et al., 1994). Additionally, a specific inhibitor
of K^+_{Ca} channels, charybdotoxin, virtually in cell-free membrane patches without requiring cGMP
(Bolotina et al., 1994). Additionally, a specific inhibitor
of K^+_{Ca} channels, charybdotoxin, virtually abolishes the
methylene blue-resistant component in the NO-in of K^+_{Ca} channels, charybdotoxin, virtually abolishes the
methylene blue-resistant component in the NO-induced
relaxation of rabbit aorta (Bolotina et al., 1994). The
physiological role of EDHF is largely unexplored, b of K^+_{Ca} channels, charybdotoxin, virtually abolishes t
methylene blue-resistant component in the NO-induc
relaxation of rabbit aorta (Bolotina et al., 1994). T
physiological role of EDHF is largely unexplored, but
see methylene blue-resistant component in the NO-induced
relaxation of rabbit aorta (Bolotina et al., 1994). The
physiological role of EDHF is largely unexplored, but it
seems to contribute to the endothelium-dependent relax-
 relaxation of rabbit aorta (Bolotina et al., 1994). The physiological role of EDHF is largely unexplored, but it seems to contribute to the endothelium-dependent relaxant responses to some vasodilators, such as ACh (Nagao EDHF may be another EDRF distinct from NO (Na-
gao and Vanhoutte, 1993) that causes the opening of a
K⁺ channel, leading to smooth muscle hyperpolariza-
tion. The nature of EDHF remains unknown, but its
action is not in

C. Endothelium and Adrenergic Responses

Pulmonary vascular endothelium has an important and Vanhoutte, 1993).

C. Endothelium and Adrenergic Responses

Pulmonary vascular endothelium has an important

modulatory role on the adrenergic response. Pulmonary

endothelial cells take up and degrade norepinephrine, C. Endothelium and Adrenergic Responses

Pulmonary vascular endothelium has an imports

modulatory role on the adrenergic response. Pulmons

endothelial cells take up and degrade norepinephrine

serotonin, and ATP, the pri C. *Endothelium and Adrenergic Responses*
Pulmonary vascular endothelium has an important
modulatory role on the adrenergic response. Pulmonary
endothelial cells take up and degrade norepinephrine,
serotonin, and ATP, the rumonary vascular endothelium has an important
modulatory role on the adrenergic response. Pulmonary
endothelial cells take up and degrade norepinephrine,
serotonin, and ATP, the principal transmitters and co-
transmitters serotonin, and ATP, the principal transmitters and duransmitters of adrenergic nerves, thereby diminishi
the adrenergic contraction (Said, 1982). Endothel
cells activate and release vasoconstrictors, which m
act synergisti transmitters of adrenergic nerves, thereby diminishing
the adrenergic contraction (Said, 1982). Endothelial
cells activate and release vasoconstrictors, which may
act synergistically with norepinephrine. More impor-
tantly cells activate and release vasoconstrictors, which may act synergistically with norepinephrine. More importantly, complex (a) endothelium-smooth muscle and (b) endothelium-adrenergic nerve interactions exist. Cocks cells activate and release vasoconstrictors, which may
act synergistically with norepinephrine. More impor-
tantly, complex (a) endothelium-smooth muscle and (b)
endothelium-adrenergic nerve interactions exist. Cocks
and A act synergistically with norepinephrine. More importantly, complex (a) endothelium-smooth muscle and (b) endothelium-adrenergic nerve interactions exist. Cocks and Angus (1983) observed a marked potentiation of the cont tantly, complex (a) endothelium-smooth muscle and (b)
endothelium-adrenergic nerve interactions exist. Cocks
and Angus (1983) observed a marked potentiation of the
contractile response to norepinephrine and serotonin
af endothelium-adrenergic nerve interactions exist. Cock
and Angus (1983) observed a marked potentiation of th
contractile response to norepinephrine and serotoni
after removal of the vascular endothelium in canine an
pig cor and Angus (1983) observed a marked potentiation of contractile response to norepinephrine and seroto after removal of the vascular endothelium in canine ε pig coronary arteries. Early studies showed that enthelium rem contractile response to norepinephrine and serotonin
after removal of the vascular endothelium in canine and
pig coronary arteries. Early studies showed that endo-
thelium removal had no effect on the adrenergic contrac-
t after removal of the vascular endothelium in canine and
pig coronary arteries. Early studies showed that endo-
thelium removal had no effect on the adrenergic contrac-
tion to either nerve stimulation (Loiacono and Story,
 pig coronary arteries. Early studies showed that endo-
thelium removal had no effect on the adrenergic contrac-
tion to either nerve stimulation (Loiacono and Story,
1984) or to exogenous norepinephrine in pulmonary ves-
s thelium removal had no effect on the adrenergic contration to either nerve stimulation (Loiacono and Std 1984) or to exogenous norepinephrine in pulmonary v
sels (de Mey and Vanhoutte, 1982), but more rec
studies demonstra tion to either nerve stimulation (Loiacono and Story, 1984) or to exogenous norepinephrine in pulmonary vessels (de Mey and Vanhoutte, 1982), but more recent studies demonstrate a clear enhancement of the contractile respo 1984) or to exogenous norepinephrine in pulmonary vessels (de Mey and Vanhoutte, 1982), but more recent
studies demonstrate a clear enhancement of the contractile response to adrenergic agonists (Greenberg et al.,
1989; Cr

PHARMACOLOGICAL REVIEWS

REGULATION OF PULMON
to adrenergic nerve stimulation (Greenberg et al., 1989)
in these vessels. to adrenergic ner
in these vessels.
Several mecha

REGULATION OF I

adrenergic nerve stimulation (Greenberg et al., 19

Several mechanisms have been explored. Endother

in-derived vasodilator prostaglandins are unlikely to adrenergic nerve stimulation (Greenberg et al., 1989) chol
in these vessels. vess
Several mechanisms have been explored. Endotheli-
nerven-derived vasodilator prostaglandins are unlikely to ergi
be involved (Miller et a to adrenergic nerve stimulation (Greenberg et al., 1989)
in these vessels.
Several mechanisms have been explored. Endotheli-
um-derived vasodilator prostaglandins are unlikely to
be involved (Miller et al., 1984; Greenberg in these vessels.

Several mechanisms have been explored. Endoth

um-derived vasodilator prostaglandins are unlikely

be involved (Miller et al., 1984; Greenberg et al., 19

Liu et al., 1991a). Reduction of norepinephrine Several mechanisms have been explored. Endotheli-
um-derived vasodilator prostaglandins are unlikely to
be involved (Miller et al., 1984; Greenberg et al., 1989;
Liu et al., 1991a). Reduction of norepinephrine degrada-
tio um-derived vasodilator prostaglandins are unlikely to
be involved (Miller et al., 1984; Greenberg et al., 1989;
Liu et al., 1991a). Reduction of norepinephrine degrada-
tion may play a role, but is unlikely to be important be involved (Miller et al., 1984; Greenberg et al., 1989;
Liu et al., 1991a). Reduction of norepinephrine degrada-
tion may play a role, but is unlikely to be important
(Greenberg et al., 1989). In the isolated guinea pig tion may play a role, but is unlikely to be important (Greenberg et al., 1989). In the isolated guinea pig pul-
monary artery, electrical field stimulation (EFS) of in-
tramural adrenergic nerves caused a frequency-depen-
 (Greenberg et al., 1989). In the isolated guinea p
monary artery, electrical field stimulation (EFS)
tramural adrenergic nerves caused a frequency-
dent contraction, which was markedly enhanced
NO synthase inhibitor L-NMMA monary artery, electrical field stimulation (EFS) of in-
tramural adrenergic nerves caused a frequency-depen-
dent contraction, which was markedly enhanced by the
NO synthase inhibitor L-NMMA in a concentration-de-
pendent tramural adrenergic nerves caused a frequency-
dent contraction, which was markedly enhanced
NO synthase inhibitor L-NMMA in a concentrati
pendent and L-arginine reversible manner, indi
endogenous NO is responsible for the dent contraction, which was markedly enhanced by the
NO synthase inhibitor L-NMMA in a concentration-de-
pendent and L-arginine reversible manner, indicating
endogenous NO is responsible for the endothelium-me-
diated inhi Income Synthiase inhibitor L-INMIA in a concentration-de-
pendent and L-arginine reversible manner, indicating
endogenous NO is responsible for the endothelium-me-
diated inhibition (Liu et al., 1991a). An NO synthase
inhi endogenous NO is responsible for the endothelium-me-
diated inhibition (Liu et al., 1991a). An NO synthase not
inhibitor also augments the pressor response to sympa-
thetic nerve stimulation in vivo (Tabrizchi and Triggle, diated inhibition (Liu et al., 1991a). An NO synthase not yet been confirmed in pulmonary vessels but pre-
inhibitor also augments the pressor response to sympa-
thetic nerve stimulation in vivo (Tabrizchi and Triggle, Alt 1991). An NO-adrenergic nerve interaction has also been thetic nerve stimulation in vivo (Tabrizchi and Triggle,
1991). An NO-adrenergic nerve interaction has also been
suggested (Greenberg et al., 1989, 1990). In isolated dog
intrapulmonary arteries and veins, endothelium re-
 1991). An NO-adrenergic nerve interaction has also b
suggested (Greenberg et al., 1989, 1990). In isolated
intrapulmonary arteries and veins, endothelium
moval enhances EFS-induced norepinephrine rele
(Greenberg et al., 19 suggested (Greenberg et al., 1969, 1990). In isolated dog
intrapulmonary arteries and veins, endothelium re-
moval enhances EFS-induced norepinephrine release
(Greenberg et al., 1989). Basal effluent from endotheli-
um-int moval enhances EFS-ind
(Greenberg et al., 1989). I
um-intact donor aorta inhi
rine release from denuded
(Greenberg et al., 1989).
NO-releasing compound um-intact donor aorta inhibits EFS-induced norepinephrine release from denuded recipient pulmonary arteries
(Greenberg et al., 1989).
NO-releasing compounds such as 3-morpholinosyd-
nonime and nitroprusside inhibit norepin

um-intact donor aorta inhibits EFS-induced norepinephrine release from denuded recipient pulmonary arteries
(Greenberg et al., 1989).
NO-releasing compounds such as 3-morpholinosyd-
nonime and nitroprusside inhibit norepin rine release from denuded recipient pulmonary arter
(Greenberg et al., 1989).
NO-releasing compounds such as 3-morpholinosy
nonime and nitroprusside inhibit norepinephrine
lease from perivascular adrenergic nerves of dog m (Greenberg et al., 1989). The recent NO-releasing compounds such as 3-morpholinosyd-
nonime and nitroprusside inhibit norepinephrine re-
lease from perivascular adrenergic nerves of dog mesen-
teric arteries (Greenberg et NO-releasing compounds such as 3-morpholinosyd-
nonime and nitroprusside inhibit norepinephrine re-
lease from perivascular adrenergic nerves of dog mesen-
teric arteries (Greenberg et al., 1990). However, NO
synthase inhi nonime and nitroprusside inhibit norepinephrine re-
lease from perivascular adrenergic nerves of dog mesen-
teric arteries (Greenberg et al., 1990). However, NO
synthase inhibitors have been consistently found to in-
hibit lease from perivascular adrenergic nerves of dog mesen-
teric arteries (Greenberg et al., 1990). However, NO
synthase inhibitors have been consistently found to in-
hibit norepinephrine release in systemic vascular beds,
s teric arteries (Greenberg et al., 1990). However, NO
synthase inhibitors have been consistently found to in-
hibit norepinephrine release in systemic vascular beds,
suggesting that endogenous NO does not inhibit but
rather synthase inhibitors have been consistently found to inhibit norepinephrine release in systemic vascular beds, suggesting that endogenous NO does not inhibit but rather facilitates norepinephrine release (Halbrugge et al., hibit norepinephrine release in systemic vascular beds
suggesting that endogenous NO does not inhibit bu
rather facilitates norepinephrine release (Halbrugge e
al., 1991; Yamamoto et al., 1993). The NO synthas
inhibitor Lrather facilitates norepinephrine release (Halbrugge et al., 1991; Yamamoto et al., 1993). The NO synthase inhibitor L-NMMA has no significant effect on EFS-
induced norepinephrine release in guinea pig pulmo-., 1991; Yamamoto et al., 1993). The NO synthas
hibitor L-NMMA has no significant effect on EFS
duced norepinephrine release in guinea pig pulmo
ry arteries (Cederqvist et al., 1991).
Activation of endothelial α_2 -adre

nary arteries (Cederqvist et al., 1991).
Activation of endothelial α_2 -adrenergic receptors leading to the release of NO from endothelial cells has been inhibitor L-NMMA has no significant effect on EFS-
induced norepinephrine release in guinea pig pulmo-
hary arteries (Cederqvist et al., 1991). and
Activation of endothelial α_2 -adrenergic receptors lead-
ing to the re mauced norepmephrine release in guinea pig p
nary arteries (Cederqvist et al., 1991).
Activation of endothelial α_2 -adrenergic receptors
ing to the release of NO from endothelial cells has
reported to be mainly respons mary arteries (Cederqvist et al., 1991). an adressed and a analytic expected in the release of NO from endothelial cells has been to reported to be mainly responsible for the endothelium-
mediated inhibition on adrenergic Activation of endothelial a_2 -adrenergic receptors lead-
ing to the release of NO from endothelial cells has been
reported to be mainly responsible for the endothelium-
mediated inhibition on adrenergic contraction in t reported to be mainly responsible for the endothermin-
mediated inhibition on adrenergic contraction in the
vascular bed of skeletal muscles (Nakamura and Pre-
witt, 1991). Endothelial α_2 -adrenoceptors exist in pul-
m vascular bed of skeletal muscles (Nakamura and Pre-
witt, 1991). Endothelial α_2 -adrenoceptors exist in pul-
monary vessels (Liu et al., 1991a). NO mediates α_2 -
adrenoceptor agonist-induced pulmonary vasodilation t witt, 1991). Endothelial α_2 -adrenoceptors exist in pul-
monary vessels (Liu et al., 1991a). NO mediates α_2 -
boradrenoceptor-agonist-induced pulmonary vasodilation thi
(Liu et al., 1991a; Pepke-Zaba et al., 1993). monary vessels (Liu et al., 1991a). NO mediates α_2 -
adrenoceptor agonist-induced pulmonary vasodilation
(Liu et al., 1991a; Pepke-Zaba et al., 1993). However, the
 α_2 -adrenoceptor-mediated NO release is unlikely to (Liu et al., 1991a; Pepke-Zaba et al., 1993). However, th α_2 -adrenoceptor-mediated NO release is unlikely to b important in mediating the inhibitory effects of endothe lium on adrenergic contraction in pulmonary vesse α_2 -adrenoceptor-mediated NO release is unlikely to be region
important in mediating the inhibitory effects of endothe-spot-
lium on adrenergic contraction in pulmonary vessels hibi-
under physiological conditions (Liu important in mediating the inhibitory effects of endothe-

lium on adrenergic contraction in pulmonary vessels

under physiological conditions (Liu et al., 1991a), inas-

much as norepinephrine has little relaxant effect o lium on adrenergic contraction in pulmonary vessels
under physiological conditions (Liu et al., 1991a), inas-
much as norepinephrine has little relaxant effect on
these vessels, even when the vascular tone was elevated
(Li

Under in vitro conditions, application of EFS activates
intramural adrenergic, cholinergic, and NANC nerves
simultaneously. NO is a transmitter of i-NANC nerves much as norepinephrine has little relaxant effect on
these vessels, even when the vascular tone was elevated
(Liu et al., 1991a).
Under in vitro conditions, application of EFS activates
intramural adrenergic, cholinergic, these vessels, even when the vascular tone was elevated
(Liu et al., 1991a).
Under in vitro conditions, application of EFS activates
intramural adrenergic, cholinergic, and NANC nerves
simultaneously. NO is a transmitter o (Liu et al., 1991a). si
Under in vitro conditions, application of EFS activates pl
intramural adrenergic, cholinergic, and NANC nerves rasimultaneously. NO is a transmitter of i-NANC nerves the
(Liu et al., 1992b) and a se

vary vascular tone
cholinergic nerves (McMahon et al., 1992) in pulmonary
vessels. NO released during the activation of these variantly vertex in the matrix of the activation of these
coldinergic nerves (McMahon et al., 1992) in pulmonary
vessels. NO released during the activation of these
nerves could provide a functional antagonism to adren-
er cholinergic nerves (McMahon et al., 1992) in pulmona
vessels. NO released during the activation of the
nerves could provide a functional antagonism to adre
ergic contraction (Liu et al., 1992b). However, this mec
anism may vessels. NO released during the activation of these
nerves could provide a functional antagonism to adren-
ergic contraction (Liu et al., 1992b). However, this mech-
anism may not be important under in vivo conditions, ergic contraction (Liu et al., 1992b). However, this mechtaneously. gic contraction (Liu et al., 1992b). However, this mech-
ism may not be important under in vivo conditions,
asmuch as these nerves may not be activated simul-
neously.
Both endothelial shear stress, caused by changes in
rf inasmuch as these nerves may not be activated simul-

(Greenberg et al., 1989). In the isolated guinea pig pul-
monary artery, electrical field stimulation (EFS) of in-
perfusate velocity and viscosity, and mechanical defor-
tramural adrenergic nerves caused a frequency-depen inasmuch as these nerves may not be activated simul-
taneously.
Both endothelial shear stress, caused by changes in
perfusate velocity and viscosity, and mechanical defor-
mation of vascular wall have been demonstrated to taneously.
Both endothelial shear stress, caused by changes if perfusate velocity and viscosity, and mechanical deformation of vascular wall have been demonstrated to release EDRF/NO (Tesfamariam and Cohen, 1988; Lamontagn bout endothelial shear stress, caused by changes in
perfusate velocity and viscosity, and mechanical defor-
mation of vascular wall have been demonstrated to re-
lease EDRF/NO (Tesfamariam and Cohen, 1988; Lam-
ontagne et mation of vascular wan have been demonstrated to re-
lease EDRF/NO (Tesfamariam and Cohen, 1988; Lam-
ontagne et al., 1992), and this NO also inhibits
adrenergic contractions to EFS in systemic arteries
(Tesfamariam and Co ontagne et al., 1992), and this NO also inhibits sumably should be operative. (Tesfamariam and Cohen, 1988). This mechanism has

(Tesfamariam and Cohen, 1988). This mechanism has
not yet been confirmed in pulmonary vessels but pre-
sumably should be operative.
Although several factors contribute to the endotheli-
um-mediated inhibition of adrenergic not yet been confirmed in pulmonary vessels but pre-
sumably should be operative.
Although several factors contribute to the endotheli-
um-mediated inhibition of adrenergic contraction, the
basal and mechanically stimulat sumably should be operative.

Although several factors contribute to the endotheli-

um-mediated inhibition of adrenergic contraction, the

basal and mechanically stimulated release of NO from

endothelial cells are likely Although several factors contribute to the endotheli-
um-mediated inhibition of adrenergic contraction, the
basal and mechanically stimulated release of NO from
endothelial cells are likely to be mainly responsible for
the um-mediated inhibition of adrenergic contraction, the basal and mechanically stimulated release of NO from endothelial cells are likely to be mainly responsible f
the inhibition of adrenergic contraction. This could e
plai basal and mechanically stimulated release of NO from
endothelial cells are likely to be mainly responsible for
the inhibition of adrenergic contraction. This could ex-
plain the uniform augmentation by NO synthase inhib-
i endothelial cells are likely to be mainly responsible for
the inhibition of adrenergic contraction. This could ex-
plain the uniform augmentation by NO synthase inhib-
itors of the contractile responses to vasoconstrictors the inhibition of adrenergic contraction. This could ex-
plain the uniform augmentation by NO synthase inhib-
itors of the contractile responses to vasoconstrictors with
diverse mechanisms of action (Liu et al., 1991a). M plain the uniform augmentation by NO synthase inhibitors of the contractile responses to vasoconstrictors with diverse mechanisms of action (Liu et al., 1991a). Morecently, it was suggested that enhanced release of EDRF m diverse mechanisms of action (Liu et al., 1991a). More recently, it was suggested that enhanced release of EDRF may contribute to the long-term α -adrenoceptor agonist exposure-induced desensitization of vascular smooth EDRF may contribute to the long-term α -adrenoceptor

D. Endothelium and Cholinergic Responses Nooth muscle to these agonists (Hu et al., 1994).

Endothelium and Cholinergic Responses

NO mediates ACh-induced vasodilation in the pulmo-

In the pulmo-

In the precedency circulation (McMahon et al., 1992). In the prec D. Endothelium and Cholinergic Responses
NO mediates ACh-induced vasodilation in the puln
nary circulation (McMahon et al., 1992). In the preco
tracted cat pulmonary vascular bed, vagal stimulati D. Endothelium and Cholinergic Responses
NO mediates ACh-induced vasodilation in the pulmo-
nary circulation (McMahon et al., 1992). In the precon-
tracted cat pulmonary vascular bed, vagal stimulation
elicits a frequency-D. Endothetium and Chothergic Responses
NO mediates ACh-induced vasodilation in the pulmo-
nary circulation (McMahon et al., 1992). In the precon-
tracted cat pulmonary vascular bed, vagal stimulation
elicits a frequency-d NO mediates ACh-induced vasodilation in the pulmo-
nary circulation (McMahon et al., 1992). In the precon-
tracted cat pulmonary vascular bed, vagal stimulation
elicits a frequency-dependent relaxation, which is
blocked by nary circulation (McMahon et al., 1992). In the precontracted cat pulmonary vascular bed, vagal stimulation elicits a frequency-dependent relaxation, which is blocked by atropine and greatly inhibited by L-NAME and by inhi elicits a frequency-dependent relaxation, which is
blocked by atropine and greatly inhibited by L-NAME
and by inhibition of guanylyl cyclase. By contrast, L-
NAME has no inhibitory effects on the dilator response
to drugs blocked by atropine and greatly inhibited by L-NA
and by inhibition of guanylyl cyclase. By contrast
NAME has no inhibitory effects on the dilator respo
to drugs with diverse mechanisms of action, inclue
adenosine, nicoran and by inhibition of guanylyl cyclase. By contrast, $NAME$ has no inhibitory effects on the dilator respons to drugs with diverse mechanisms of action, includin adenosine, nicorandil, isoproterenol, sodium nitropruside, P NAME has no inhibitory effects on the dilator response
to drugs with diverse mechanisms of action, including
adenosine, nicorandil, isoproterenol, sodium nitroprus-
side, PGE₁, or 8-bromo-cGMP in the same preparation.
T to drugs with diverse mechanisms of action, including
adenosine, nicorandil, isoproterenol, sodium nitroprus-
side, PGE_1 , or 8-bromo-cGMP in the same preparation.
There is still uncertainty about how ACh released from
c adenosine, nicorandil, isoproterenol, sodium nitroprusside, PGE_1 , or 8-bromo-cGMP in the same preparation.
There is still uncertainty about how ACh released from cholinergic nerve terminals at the adventitio-medial bord side, FGE_1 , or σ -oromo-convir- in the same preparation.
There is still uncertainty about how ACh released from
cholinergic nerve terminals at the adventitio-medial
border exerts its action on endothelial cells, inasm cholinergic nerve terminals at the adventitio-medial
border exerts its action on endothelial cells, inasmuch as
this presumably involves diffusion through the smooth
muscle layer. Inconsistent results have been reported
re border exerts its action on endothelial cells, inasmuch as
this presumably involves diffusion through the smooth
muscle layer. Inconsistent results have been reported
regarding the role of NO in mediating the relaxant re-
 this presumably involves diffusion through the smooth
muscle layer. Inconsistent results have been reported
regarding the role of NO in mediating the relaxant re-
sponse to exogenous ACh. NO synthase inhibitors in-
hibit t muscle layer. Inconsistent results have been reported
regarding the role of NO in mediating the relaxant re-
sponse to exogenous ACh. NO synthase inhibitors in-
hibit the pulmonary vasodilator response to ACh in the
cat an regarding the role of NO in mediating the relaxant sponse to exogenous ACh. NO synthase inhibitors is
hibit the pulmonary vasodilator response to ACh in t
cat and lamb in vivo (Fineman et al., 1991a; McMahon
al., 1991a, 19 sponse to exogenous ACh. NO synthase inhibitors in-
hibit the pulmonary vasodilator response to ACh in the
cat and lamb in vivo (Fineman et al., 1991a; McMahon et
al., 1991a, 1992) and in the blood-perfused rat pulmo-
nary molt the pulmonary vasodinator response to ACh in the cat and lamb in vivo (Fineman et al., 1991a; McMahon et al., 1991a, 1992) and in the blood-perfused rat pulmonary vascular bed in situ (Liu et al., 1991a) but do not si al., 1991a, 1992) and in the blood-perfused rat pulmo-
nary vascular bed in situ (Liu et al., 1991a) but do not
significantly inhibit ACh-induced vasodilation in the
physiological salt perfused pulmonary vascular bed of
ra nary vascular bed in situ (Liu et al., 1991a) but do not
significantly inhibit ACh-induced vasodilation in the
physiological salt perfused pulmonary vascular bed of
rat, although BK-induced relaxation was inhibited by
the reason ficantly inhibit ACh-induced vasodilation in
physiological salt perfused pulmonary vascular l
rat, although BK-induced relaxation was inhibit
the NO synthase inhibitor (Archer et al., 1989)
reason for this discrepan

PHARMACOLOGICAL REVIEWS

¹¹⁰ BARNES AND LIU *E. Endothelium and Nonadrenergic, Noncholinergic Responses*

BARNES ANI
 Endothelium and Nonadrenergic, Noncholinergic G.

sponses

The i-NANC vasodilator response in guinea pig is

rtially endothelium-dependent (Liu et al., 1992a). to: E. Endothelium and Nonadrenergic, Noncholinergic
Responses
The i-NANC vasodilator response in guinea pig is
partially endothelium-dependent (Liu et al., 1992a).
ATP, the possible i-NANC mediator, is an endothelium-E. Endothelium and Nonadrenergic, Noncholinergic
Responses
The i-NANC vasodilator response in guinea pig is
partially endothelium-dependent (Liu et al., 1992a).
ATP, the possible i-NANC mediator, is an endothelium-
depende The i-NANC vasodilator response in guinea pig is
partially endothelium-dependent (Liu et al., 1992a).
ATP, the possible i-NANC mediator, is an endothelium-
dependent pulmonary vasodilator (Greenberg et al.,
1987a; Liu et a The i-NANC vasodilator response in guinea pig i
partially endothelium-dependent (Liu et al., 1992a
ATP, the possible i-NANC mediator, is an endothelium
dependent pulmonary vasodilator (Greenberg et al
1987a; Liu et al., 19 partially endothelium-dependent (Liu et al., 1992a).
ATP, the possible i-NANC mediator, is an endothelium-
dependent pulmonary vasodilator (Greenberg et al.,
1987a; Liu et al., 1989a) and induces pulmonary vaso-
dilation v ATP, the possible i-NANC mediator, is an endothelium-
dependent pulmonary vasodilator (Greenberg et al.,
1987a; Liu et al., 1989a) and induces pulmonary vaso-
dilation via stimulation of NO release from vascular
endotheliu dependent pulmonary vasodilator (Greenberg et al., 1987a; Liu et al., 1989a) and induces pulmonary vasodilation via stimulation of NO release from vascular endothelium (Liu et al., 1992a). As discussed in II.C.3, NO is lik 1987a, End et al., 1989a) and muddilation via stimulation of NO reendothelium (Liu et al., 1992a). As
NO is likely to be an i-NANC neumonary vessels (Liu et al., 1992b). *F. Endothelium (Lid et al., 1992a).* As discusses

NO is likely to be an i-NANC neurotransm

monary vessels (Liu et al., 1992b).
 F. Endothelium and Humoral Mechanisms

Endothelial cells play an important role is

monary vessels (Liu et al., 1992b).

F. Endothelium and Humoral Mechanisms

Endothelial cells play an important role in the gener-

ation, metabolism, and degradation of many vasoactive F. Endothelium and Humoral Mechanisms
Endothelial cells play an important role in the gener-
ation, metabolism, and degradation of many vasoactive
substances. Pulmonary vascular endothelial cells take F. Endothelium and Humoral Mechanisms

Endothelial cells play an important role in the gener-

ation, metabolism, and degradation of many vasoactive

substances. Pulmonary vascular endothelial cells take

up and degrade va r. Endothelial cells play an important role in the general Endothelial cells play an important role in the general substances. Pulmonary vascular endothelial cells up and degrade vasoactive amines such as norepin rine and Endothelial cells play an important role in the generation, metabolism, and degradation of many vasoactive substances. Pulmonary vascular endothelial cells take up and degrade vasoactive amines such as norepinephrine and s ation, metabolism, and degradation of many vasoactive
substances. Pulmonary vascular endothelial cells take
up and degrade vasoactive amines such as norepineph-
rine and serotonin (Alabaster and Bakhle, 1970; Said,
1982) a substances. I unholary vascular endothelial cells cate
up and degrade vasoactive amines such as norepineph-
rine and serotonin (Alabaster and Bakhle, 1970; Said,
1978). Pulmonary endothelial cells contain angiotensin-
conv rine and serotonin (Alabaster and Bakhle, 1970; Said, 1982) and metabolize ATP to adenosine (Dieterle et al., 1978). Pulmonary endothelial cells contain angiotensinconverting enzyme, which catalyzes formation of A-II and d 1982) and metabolize ATP to adenosine (Dieterle et al., 1978). Pulmonary endothelial cells contain angiotensin-
converting enzyme, which catalyzes formation of A-II and degrades BK (Johnson and Erdös, 1977; Said, 1982) an 1978). Pulmonary endothelial cells contain angioten
converting enzyme, which catalyzes formation of λ
and degrades BK (Johnson and Erdös, 1977; Said, 19
and tachykinins (Barnes et al., 1991). Endothelial c
also contain and degrades BK (Johnson and Erdös, 1977; Said, 1982)
and tachykinins (Barnes et al., 1991). Endothelial cells
also contain neutral endopeptidase to degrade enkepha-
lin and other short peptides, including tachykinins (Erand degrades BK (Johnson and Erdös, 1977; Said, 1982)
and tachykinins (Barnes et al., 1991). Endothelial cells
also contain neutral endopeptidase to degrade enkepha-
lin and other short peptides, including tachykinins (Erand tachykinins (Barnes et al., 1991). Endothelial cells
also contain neutral endopeptidase to degrade enkepha-
lin and other short peptides, including tachykinins (Er-
dös et al., 1978). Pulmonary endothelial cells parti also contain neutral endopeptidase to degrade enkephalin and other short peptides, including tachykinins (Erdös et al., 1978). Pulmonary endothelial cells participate in the metabolism of arachidonic acids (Said, 1982), an lin and other short peptides, including tachykinins (Erdös et al., 1978). Pulmonary endothelial cells participate
in the metabolism of arachidonic acids (Said, 1982), and
synthesize prostacyclin, a potent vasodilator and dös et al., 1978). Pulmonary endothelial cells participate
in the metabolism of arachidonic acids (Said, 1982), and
synthesize prostacyclin, a potent vasodilator and an in-
hibitor of platelet aggregation (Frangos et al., in the metabolism of arachidonic acids (Said, 1982), and synthesize prostacyclin, a potent vasodilator and an inhibitor of platelet aggregation (Frangos et al., 1985). discussed in V.A., endothelial cells also release NEDH synthesize prostacyclin, a potent vasodilator and an inhibitor of platelet aggregation (Frangos et al., 1985). As discussed in V.A., endothelial cells also release NO, EDHF, and ET-1. These metabolic and secretory activiti hibitor of platelet aggregation (Frangos et al., 1985). As hidiscussed in V.A., endothelial cells also release NO, St EDHF, and ET-1. These metabolic and secretory activities help to maintain homeostasis in the pulmonary s EDHF, and ET-1. These metabolic and secretory activities help to maintain homeostasis in the pulmonary circulation and to regulate pulmonary vascular smooth muscle tone.
Many vasoactive substances exert their pulmonary DHF, and ET-1. These metabolic and secretory activises help to maintain homeostasis in the pulmonary reculation and to regulate pulmonary vascular smooth usele tone.
Many vasoactive substances exert their pulmonary isodila ties help to maintain homeostasis in the pulmona
circulation and to regulate pulmonary vascular smot
muscle tone.
Many vasoactive substances exert their pulmona
vasodilator actions via endothelium-dependent mech
nisms, inc

vasodilator actions via endothelium-dependent mechanisms, including histamine (Abacioglu et al., 1987), 5-HT (Glusa and Richter, 1993), BK (Ignarro et al., muscle tone.

Many vasoactive substances exert their pulmonary

vasodilator actions via endothelium-dependent mecha-

nisms, including histamine (Abacioglu et al., 1987),

5-HT (Glusa and Richter, 1993), BK (Ignarro et al. Many vasoactive substances exert their pulmonary
vasodilator actions via endothelium-dependent mecha-
nisms, including histamine (Abacioglu et al., 1987),
5-HT (Glusa and Richter, 1993), BK (Ignarro et al.,
1987a), ATP, AD vasodilator actions via endothelium-dependent mechanisms, including histamine (Abacioglu et al., 1987),
5-HT (Glusa and Richter, 1993), BK (Ignarro et al., 1987a), ATP, ADP (Greenberg et al., 1987a; Liu et al., 1989a), sub nisms, including histamine (Abacioglu et al., 1987), 199
5-HT (Glusa and Richter, 1993), BK (Ignarro et al., HP
1987a), ATP, ADP (Greenberg et al., 1987a; Liu et al., zap
1989a), substance P (Bolton and Clapp, 1986; Maggi 5-HT (Glusa and Richter, 1993), BK (Ignarro et al., 1987a), ATP, ADP (Greenberg et al., 1987a; Liu et al., 1989a), substance P (Bolton and Clapp, 1986; Maggi et al., 1990), thrombin (De Mey and Vanhoutte, 1982) and arachid 1989a), substance P (Bolton and Clapp, 1986; Maggi et al., 1990), thrombin (De Mey and Vanhoutte, 1982) and arachidonic acid (De Mey and Vanhoutte, 1982). Another important mechanism for endothelium-dependent regulation of 1989a), substance P (Bolton and Clapp, 1986; Maggi
al., 1990), thrombin (De Mey and Vanhoutte, 1982) a
arachidonic acid (De Mey and Vanhoutte, 1982). A
other important mechanism for endothelium-depende
regulation of pulmo al., 1990), thrombin (De Mey and Vanhoutte, 1982) and mid-
arachidonic acid (De Mey and Vanhoutte, 1982). An-
other important mechanism for endothelium-dependent The
regulation of pulmonary vascular tone is shear stress-
 arachidonic acid (De Mey and Vanhoutte, 1982). An-
other important mechanism for endothelium-dependent The
regulation of pulmonary vascular tone is shear stress-
induced release of PGI_2 (Frangos et al., 1985). Both tis
 other important mechanism for endothelium-depend
regulation of pulmonary vascular tone is shear stre
induced release of PGI_2 (Frangos et al., 1985). B
blood flow changes and mechanical deformation of
vascular wall impos regulation of pulmonary vascular tone is shear stress-
induced release of PGI_2 (Frangos et al., 1985). Both
blood flow changes and mechanical deformation of the
vascular wall impose shear stress on vascular endothe-
lia blood flow changes and mechanical deformation of the vascular wall impose shear stress on vascular endothe-
lial cells and induce release of NO (Rubanyi et al., 1986;
Lamontagne et al., 1992). Thus, an increase in pulmo-
n lial cells and induce release of NO (Rubanyi et al., 1986; NO synthase activity (Rengasamy and Johns, 1991) and Lamontagne et al., 1992). Thus, an increase in pulmo-
nary blood flow and possibly endothelium deformation na vascular wall impose shear stress on vascular endothe-
lial cells and induce release of NO (Rubanyi et al., 1986; N
Lamontagne et al., 1992). Thus, an increase in pulmo-
nary blood flow and possibly endothelium deformatio lial cells and induce release of NO (Rubanyi et al., 194
Lamontagne et al., 1992). Thus, an increase in puln
nary blood flow and possibly endothelium deformati
due to pulmonary vasoconstriction will cause release
NO and P Lamontagne et al., 1992). Thus, an increase in pulmo-
nary blood flow and possibly endothelium deformation
due to pulmonary vasoconstriction will cause release of
NO and PGI₂, which counteract the increase in pulmo-
nar mary blood now and possibly endothelium deformation hary
due to pulmonary vasoconstriction will cause release of ren e
NO and PGI_2 , which counteract the increase in pulmo-
mmH
nary blood pressure. Activation of Ca^{2+} -

G. *Endothelium and Hypoxic Pulmonary Vasoconstriction*

LIU
Endothelium and Hypoxic Pulmonary
Isoconstriction
The pulmonary endothelium is an important modu
r of HPV. Endothelial injury has been demonstrated G. Endothelium and Hypoxic Pulmonary
Vasoconstriction
The pulmonary endothelium is an important modula-
tor of HPV. Endothelial injury has been demonstrated to
enhance HPV (Hill and Rounds, 1983; Rosenberg et al., tor of HPV. Endothelial injury has been demonstrated to
enhance HPV (Hill and Rounds, 1983; Rosenberg et al.,
1985; Liu et al., 1992c) and hypoxic contractions (Tracey Vasoconstriction

The pulmonary endothelium is an important modula-

tor of HPV. Endothelial injury has been demonstrated to

enhance HPV (Hill and Rounds, 1983; Rosenberg et al.,

1985; Liu et al., 1992c) and hypoxic cont The pulmonary endothelium is an important modulator of HPV. Endothelial injury has been demonstrated the enhance HPV (Hill and Rounds, 1983; Rosenberg et al. 1985; Liu et al., 1992c) and hypoxic contractions (Trace et al., tor of HPV. Endothelial injury has been demonstrated to
enhance HPV (Hill and Rounds, 1983; Rosenberg et al.,
1985; Liu et al., 1992c) and hypoxic contractions (Tracey
et al., 1989). Structural alterations in pulmonary end emance in v (film and flounds, 1985, flosenberg et al., 1985; Liu et al., 1992c) and hypoxic contractions (Tracey et al., 1989). Structural alterations in pulmonary endothelial cells may also contribute to the development 1989, Lid et al., 1992c) and hypoxic contractions (Tracey
et al., 1989). Structural alterations in pulmonary endo-
thelial cells may also contribute to the development of
hypoxic pulmonary hypertension (Magee et al., 1988; et al., 1989). Structural alterations in pulmonary endo-
the ial cells may also contribute to the development of
hypoxic pulmonary hypertension (Magee et al., 1988;
Wilkinson et al., 1988). The pulmonary endothelium
could thelial cells may also contribute to the development
hypoxic pulmonary hypertension (Magee et al., 193
Wilkinson et al., 1988). The pulmonary endothelit
could modulate HPV by two mechanisms. Firstly, it n
tabolizes and cle hypoxic pulmonary hypertension (Magee et al., 1988; Wilkinson et al., 1988). The pulmonary endothelium could modulate HPV by two mechanisms. Firstly, it metabolizes and clears several circulating vasoconstrictors, thereby Wilkinson et al., 1988). The pulmonary endothelium
could modulate HPV by two mechanisms. Firstly, it me-
tabolizes and clears several circulating vasoconstrictors,
thereby reducing their synergistic action with hypoxia.
Se could modulate HPV by two mechanisms. Firstly, it me-
tabolizes and clears several circulating vasoconstrictors,
thereby reducing their synergistic action with hypoxia.
Secondly, and more importantly, endothelial cells retabolizes and clears several circulating vasoconstrictor
thereby reducing their synergistic action with hypoxi
Secondly, and more importantly, endothelial cells r
lease potent vasodilators such as NO and PGI_2 , whic
can thereby reducing their synergistic action with hypoxia.
Secondly, and more importantly, endothelial cells release potent vasodilators such as NO and PGI_2 , which can inhibit the contractile response to hypoxia. Moreover, Secondly, and more importantly, endothelial cells rease potent vasodilators such as NO and $PGI₂$, whice can inhibit the contractile response to hypoxia. More over, $PGI₂$ release is increased during HPV (Voelke lease potent vasodilators such as NO and PGI_2 , which
can inhibit the contractile response to hypoxia. More-
over, PGI_2 release is increased during HPV (Voelkel et
al., 1981) and inhibition of PGI_2 synthesis by cyclo can inhibit the contractile response to hypoxia. More-
over, PGI_2 release is increased during HPV (Voelkel et
al., 1981) and inhibition of PGI_2 synthesis by cyclo-
oxygenase inhibitors enhances the pulmonary pressor
r over, PGI_2 release is increased during HPV (Voelkel et al., 1981) and inhibition of PGI_2 synthesis by cyclo-
oxygenase inhibitors enhances the pulmonary pressor
response to hypoxia (Weir et al., 1976; Voelkel et al., oxygenase inhibitors enhances the pulmonary pressor
response to hypoxia (Weir et al., 1976; Voelkel et al.,
1981) and reduces blood flow perfusing hypoxic alveoli in
a canine unilateral alveolar hypoxia model (Sprauge et
a oxygenase inhibitors enhances the pulmonary pressor
response to hypoxia (Weir et al., 1976; Voelkel et al.,
1981) and reduces blood flow perfusing hypoxic alveoli in
a canine unilateral alveolar hypoxia model (Sprauge et
a response to hypoxia (Weir et al., 1976; Voelkel et al., 1981) and reduces blood flow perfusing hypoxic alveoli in
a canine unilateral alveolar hypoxia model (Sprauge et
al., 1984). Additionally, pulmonary arteries from ra 1981) and reduces blood flow perfusing hypoxic alveoli in
a canine unilateral alveolar hypoxia model (Sprauge et
al., 1984). Additionally, pulmonary arteries from rats
exposed to hypoxia for 7 days have an almost three-fo a canine unila
al., 1984). Ad
exposed to hypelevation of P(
et al., 1991). The modula ., 1984). Additionally, pulmonary arteries from rat posed to hypoxia for 7 days have an almost three-fole evation of PGI_2 compared with control animals (Shau al., 1991).
The modulatory role of EDRF on HPV was first dem-

exposed to hypoxia for 7 days have an almost three-fold
elevation of PGI_2 compared with control animals (Shaul
et al., 1991).
The modulatory role of EDRF on HPV was first dem-
onstrated by Brashers et al. (1988), who sh elevation of PGI_2 compared with control animals (Shaul
et al., 1991).
The modulatory role of EDRF on HPV was first dem-
onstrated by Brashers et al. (1988), who showed a
marked potentiation of HPV by nonselective EDR et al., 1991).
The modulatory role of EDRF on HPV was first demonstrated by Brashers et al. (1988), who showed a
marked potentiation of HPV by nonselective EDRF in-
hibitors in perfused pulmonary vascular bed of rats.
Subs The modulatory role of EDRF on HPV was first donstrated by Brashers et al. (1988), who showed marked potentiation of HPV by nonselective EDRF hibitors in perfused pulmonary vascular bed of rs. Subsequently, several groups onstrated by Brashers et al. (1988), who showed a
marked potentiation of HPV by nonselective EDRF in-
hibitors in perfused pulmonary vascular bed of rats.
Subsequently, several groups reported marked augmen-
tation of HPV marked potentiation of HPV by nonselective EDRF in-
hibitors in perfused pulmonary vascular bed of rats.
Subsequently, several groups reported marked augmen-
tation of HPV to inhibit NO action, either by use of
selective N hibitors in perfused pulmonary vascular bed of ra
Subsequently, several groups reported marked augmetation of HPV to inhibit NO action, either by use
selective NO inhibitors (Archer et al., 1989; Liu et a
1991b; Sprague et Subsequently, several groups reported marked augmentation of HPV to inhibit NO action, either by use of selective NO inhibitors (Archer et al., 1989; Liu et al., 1991b; Sprague et al., 1992) or guanylyl cyclase inhibitors Lation of HPV to finition (Archer et al., 1989; Liu et a
selective NO inhibitors (Archer et al., 1989; Liu et a
1991b; Sprague et al., 1992) or guanylyl cyclase inhi
tors (Mazmanian et al., 1989). The precursor of N
L-argi selective NO inhibitors (Archer et al., 1989; Liu et al., 1991b; Sprague et al., 1992) or guanylyl cyclase inhibitors (Mazmanian et al., 1989). The precursor of NO, L-arginine, has no effect on baseline pulmonary hemodynam 1991b; Sprague et al., 1992) or guanylyl cyclase inhibitors (Mazmanian et al., 1989). The precursor of NO,
L-arginine, has no effect on baseline pulmonary hemo-
dynamics but inhibits and reverses HPV (Liu et al., 1991b; F tors (Mazmanian et al., 1989). The precursor of NO,

L-arginine, has no effect on baseline pulmonary hemo-

dynamics but inhibits and reverses HPV (Liu et al.,

1991b; Fineman et al., 1991c). The effect of L-arginine on
 L-arginine, has no effect on baseline pulmonary hen
dynamics but inhibits and reverses HPV (Liu et a
1991b; Fineman et al., 1991c). The effect of L-arginine
HPV is inhibited by methylene blue and potentiated
zaprinast, a P dynamics but inhibits and reverses HPV (Liu et al., 1991b; Fineman et al., 1991c). The effect of L-arginine on HPV is inhibited by methylene blue and potentiated by zaprinast, a PDE V inhibitor that inhibits cGMP degradati 1991b; Fineman et al., 1991c). The effect of L-arginine on HPV is inhibited by methylene blue and potentiated by zaprinast, a PDE V inhibitor that inhibits cGMP degradation (Fineman et al., 1991c). Moreover, exogenous admi HPV is inhibited by methylene blue and potentiated by zaprinast, a PDE V inhibitor that inhibits cGMP degradation (Fineman et al., 1991c). Moreover, exogenous administration of NO and cGMP inhibits HPV (Frostell et al., 19 zaprinast, a PDE V inhibitor that inhibits cGMP degradation (Fineman et al., 1991c). Moreover, exogenous administration of NO and cGMP inhibits HPV (Frostell et al., 1991; Fujimoto et al., 1990; Roberts et al., 1993a).
Th dation (Fineman et al., 1991c). Moreover, exogenous a
ministration of NO and cGMP inhibits HPV (Frostell
al., 1991; Fujimoto et al., 1990; Roberts et al., 1993;
Thus, NO and PGI₂ act as functional antagonists
HPV, and l ministration of NO and cGMP in
al., 1991; Fujimoto et al., 1990;
Thus, NO and PGI_2 act as fun
HPV, and loss of this feedback me
tiate hypoxia-induced contraction
The role of suppression of EDR Thus, NO and PGI_2 act as functional antagonists to
HPV, and loss of this feedback mechanism would poten-
tiate hypoxia-induced contraction.
The role of suppression of EDRF activity in the medi-

Thus, NO and $PGI₂$ act as functional antagonists to
HPV, and loss of this feedback mechanism would poten-
tiate hypoxia-induced contraction.
The role of suppression of EDRF activity in the medi-
ation of HPV is unce HPV, and loss of this feedback mechanism would potentiate hypoxia-induced contraction.
The role of suppression of EDRF activity in the mediation of HPV is uncertain. Low oxygen tension reduces NO synthase activity (Rengasa tiate hypoxia-induced contraction.
The role of suppression of EDRF activity in the me
ation of HPV is uncertain. Low oxygen tension reduc
NO synthase activity (Rengasamy and Johns, 1991) a
reduces EDRF production from cult The role of suppression of EDRF activity in the medation of HPV is uncertain. Low oxygen tension reduce
NO synthase activity (Rengasamy and Johns, 1991) areduces EDRF production from cultured bovine pulm
nary vascular end ation of HPV is uncertain. Low oxygen tension reduces
NO synthase activity (Rengasamy and Johns, 1991) and
reduces EDRF production from cultured bovine pulmo-
nary vascular endothelial cells in response to BK (War-
ren et NO synthase activity (Rengasamy and Johns, 1991) and
reduces EDRF production from cultured bovine pulmo-
nary vascular endothelial cells in response to BK (War-
ren et al., 1989). In addition, moderate (PO₂ = 40
mmHg) o reduces EDRF production from cultured bovine pulm
nary vascular endothelial cells in response to BK (Wa
ren et al., 1989). In addition, moderate (PO₂ = \cdot
mmHg) or severe (PO₂ = 4 to 17 mmHg) hypoxia inhibi
endothel nary vascular endothelial cells in response to BK (War
ren et al., 1989). In addition, moderate ($PO_2 = 4$
mmHg) or severe ($PO_2 = 4$ to 17 mmHg) hypoxia inhibit
endothelium-dependent relaxation to methacholine
ACh, ATP, an ren et al., 1989). In addition, moderate $(PO_2 = 40$ mmHg) or severe $(PO_2 = 4 \text{ to } 17 \text{ mmHg})$ hypoxia inhibits endothelium-dependent relaxation to methacholine, ACh, ATP, and A23187 and the associated cGMP accumulation in

PHARMACOLOGICAL REVIEW!

REGULATION OF PULMONARY VASCULAR TONE
(Johns et al., 1989; Rodman et al., 1990) and in small Barer et al., 1993).
pulmonary artery rings of sheep (Demiryurek et al., poxic rats show an i REGULATION OF PULMOI
(Johns et al., 1989; Rodman et al., 1990) and in small
pulmonary artery rings of sheep (Demiryurek et al.,
1991), although this is not seen in isolated canine in-REGULATION OF PULMON COMET ALL, 1989; Rodman et al., 1990) and in small

pulmonary artery rings of sheep (Demiryurek et al.,

1991), although this is not seen in isolated canine in-

trapulmonary arteries (Chand and Altura (Johns et al., 1989; Rodman et al., 1990) and in small Ba
pulmonary artery rings of sheep (Demiryurek et al., po:
1991), although this is not seen in isolated canine in-
trapulmonary arteries (Chand and Altura, 1981). In p pulmonary artery rings of sheep (Demiryurek et al., 1991), although this is not seen in isolated canine in-
trapulmonary arteries (Chand and Altura, 1981). In pig
small pulmonary artery rings, hypoxia inhibits the re-
laxa 1991), although this is not seen in isolated canine
trapulmonary arteries (Chand and Altura, 1981). In
small pulmonary artery rings, hypoxia inhibits the
laxant response to ACh, reduces basal cGMP cont
and augments the con trapulmonary arteries (Chand and Altura, 1981). In pig
small pulmonary artery rings, hypoxia inhibits the re-
laxant response to ACh, reduces basal cGMP content,
and augments the contractile response to phenyleph-
rine, an small pulmonary arte
laxant response to A
and augments the corner, an effect that is
(Ogata et al., 1992).
Hypoxic contraction xant response to ACh, reduces basal cGMP conten
id augments the contractile response to phenylepl
ne, an effect that is abolished by endothelium remova
gata et al., 1992).
Hypoxic contraction is enhanced by removal of endo and augments the contractile response to phenylep
rine, an effect that is abolished by endothelium remov
(Ogata et al., 1992).
Hypoxic contraction is enhanced by removal of end
thelium and by inhibition of NO using L-NMMA,

rine, an effect that is abolished by endothelium removal
(Ogata et al., 1992).
Hypoxic contraction is enhanced by removal of endo-
thelium and by inhibition of NO using L-NMMA, hemo-
globin, and methylene blue (Ogata et al (Ogata et al., 1992). calculated by removal of endo-

Hypoxic contraction is enhanced by removal of endo-

the lium and by inhibition of NO using L-NMMA, hemo-

globin, and methylene blue (Ogata et al., 1992). In iso-

la Hypoxic contraction is enhanced by removal of endo-
the lium and by inhibition of NO using L-NMMA, hemo-
globin, and methylene blue (Ogata et al., 1992). In iso-
lated perfused bovine pulmonary artery and vein, both
the ac globin, and methylene blue (Ogata et al., 1992). In isolated perfused bovine pulmonary artery and vein, both the activity and half-life of EDRF are *increased* by reduction in oxygen tension in the perfusate (Ignarro et al lated perfused bovine pulmonary artery and vein, bot
the activity and half-life of EDRF are *increased* by r
duction in oxygen tension in the perfusate (Ignarro
al., 1988a). Differences in duration and severity of h
poxia the activity and half-life of EDRF are *increased* by re-
duction in oxygen tension in the perfusate (Ignarro et 194
al., 1988a). Differences in duration and severity of hy-
poxia or preconditions may explain these discrep duction in oxygen tension in the perfusate (Ignarro et 198
al., 1988a). Differences in duration and severity of hy-
poxia or preconditions may explain these discrepancies. rele
Nevertheless, these in vitro experiments may al., 1988a). Differences in duration and severity of hy-
poxia or preconditions may explain these discrepancies. rele
Nevertheless, these in vitro experiments may not be et a
relevant to the physiological HPV response. The poxia or preconditions may explain these discrepancies.
Nevertheless, these in vitro experiments may not be
relevant to the physiological HPV response. These in
vitro hypoxic contraction studies are conducted either on
lar relevant to the physiological HPV response. These in vitro hypoxic contraction studies are conducted either on large conduit pulmonary arteries (Rodman et al., 1989; Johns et al., 1989; Rodman et al., 1990) or under condit relevant to the physiological HPV response. These in d
vitro hypoxic contraction studies are conducted either on T
large conduit pulmonary arteries (Rodman et al., 1989; m
Johns et al., 1989; Rodman et al., 1990) or under vitro hypoxic contraction studies are conducted either
large conduit pulmonary arteries (Rodman et al., 19
Johns et al., 1989; Rodman et al., 1990) or under cor
tions of severe hypoxia (Demiryurek et al., 1991; Og
et al., large conduit pulmonary arteries (Rodman et al., 198
Johns et al., 1989; Rodman et al., 1990) or under contions of severe hypoxia (Demiryurek et al., 1991; Oge
et al., 1992). Furthermore, this in vitro hypoxic contration h Johns et al., 1989; Rodman et al., 1990) or under conditions of severe hypoxia (Demiryurek et al., 1991; Ogata
et al., 1992). Furthermore, this in vitro hypoxic contraction has been demonstrated in systemic arteries, inclu tions of severe hypoxia (Demiryurek et al., 1991; Ogata
et al., 1992). Furthermore, this in vitro hypoxic contrac-
tion has been demonstrated in systemic arteries, includ-
ing aorta (Furchgott and Zawadzki, 1980; Rodman et et al., 1992). Furthermore, this in vitro hypoxic contraction has been demonstrated in systemic arteries, including aorta (Furchgott and Zawadzki, 1980; Rodman et al., and 1989), coronary arteries, (Graser and Vanhoutte, 1 tion has been demonstrated in systemic arteries, including aorta (Furchgott and Zawadzki, 1980; Rodman et al., 1989), coronary arteries, (Graser and Vanhoutte, 1991; Muramatsu et al., 1992) and femoral arteries (de Mey and 1989), coronary arteries, (Graser and Vanhoutte, 1991; 19
Muramatsu et al., 1992) and femoral arteries (de Mey peand Vanhoutte, 1982), whereas HPV is unique to pul-
monary vessels. The duration and degree of hypoxic ex-
e Muramatsu et al., 1992) and femoral arteries (de Mey
and Vanhoutte, 1982), whereas HPV is unique to pul-
monary vessels. The duration and degree of hypoxic
exposure needed for elicitation of HPV (usually less than
10 minu and Vanhoutte, 1982), whereas HPV is unique to pul-
monary vessels. The duration and degree of hypoxic exist
exposure needed for elicitation of HPV (usually less than Eld
10 minutes and PO_2 above 40 mmHg) are much short monary vessels. The duration and degree of hypoxic exposure needed for elicitation of HPV (usually less than IO minutes and PO_2 above 40 mmHg) are much shorter and of a lesser magnitude than those used in these in notic exposure needed for elicitation of HPV (usually less than 10 minutes and PO_2 above 40 mmHg) are much shorter and of a lesser magnitude than those used in these in vitro studies. NO synthase activity may not be inhibited 10 minutes and PO_2 above 40 mmHg) are much shorter
and of a lesser magnitude than those used in these in
witro studies. NO synthase activity may not be inhibited
by moderate hypoxia. Additionally, even though the en-
is and of a lesser magnitude than those used in these in
vitro studies. NO synthase activity may not be inhibited
by moderate hypoxia. Additionally, even though the en-
zyme activity is inhibited to some extent, its activity vitro studies. NO synthase activity may not be immorted
by moderate hypoxia. Additionally, even though the en-
zyme activity is inhibited to some extent, its activity
may increase in response to strong stimuli. For example zyme activity is inhibited to some extent, its activity and may increase in response to strong stimuli. For example, dhypoxia inhibits cyclo-oxygenase activity and PGI_2 pro-
duction in rat pulmonary arteries in vitro (S may increase in response to strong stimuli. For example,
hypoxia inhibits cyclo-oxygenase activity and $PGI₂$ pro-
duction in rat pulmonary arteries in vitro (Shaul et al.,
1992), whereas in vivo hypoxia results in a hypoxia inhibits cyclo-oxygenase activity and PGI_2 pro-
duction in rat pulmonary arteries in vitro (Shaul et al.,
1992), whereas in vivo hypoxia results in a marked
increase in tissue PGI_2 production (Shaul et al., 19 duction in rat pulmonary arteries in vitro (Shaul et al., 2
1992), whereas in vivo hypoxia results in a marked is
increase in tissue PGI_2 production (Shaul et al., 1991). h
During HPV, several factors, including endothe 1992), whereas in vivo hypoxia results in a marked is
increase in tissue PGI_2 production (Shaul et al., 1991). h
During HPV, several factors, including endothelial B
shear stress resulting from changes in blood flow pro shear stress resulting from changes in blood flow profile contraction (Lamontagne et al., 1992), could stimulate
EDRF release during acute HPV.
The effects of *chronic* hypoxia on endothelium-depen-
dent responses are also controversial. Adnot et al. and endothelial deformation induced by smooth muscle
contraction (Lamontagne et al., 1992), could stimulate
EDRF release during acute HPV.
The effects of *chronic* hypoxia on endothelium-depen-
dent responses are also cont

contraction (Lamontagne et al., 1992), could stimulate
EDRF release during acute HPV.
The effects of *chronic* hypoxia on endothelium-dependent responses are also controversial. Adnot et al.
(1991b) reported that endotheli EDRF release during acute HPV.
The effects of *chronic* hypoxia on endothelium-dependent responses are also controversial. Adnot et al
(1991b) reported that endothelium-dependent relaxan
responses to ACh and A-23187 were d The effects of *chronic* hypoxia on endothelium-depen-
dent responses are also controversial. Adnot et al. or I
(1991b) reported that endothelium-dependent relaxant unli
responses to ACh and A-23187 were diminished or abol dent responses are also controversial. Adnot et al. or (1991b) reported that endothelium-dependent relaxant university responses to ACh and A-23187 were diminished or abolicies in the pulmonary vascular beds of rats expose ished in the pulmonary vascular beds of rats exposed to ished in the pulmonary vascular beds of rats exposed to
hypoxia for 1 or 3 weeks. However, others observed
enhanced dilator responses to ACh, BK, or A-23187 in
the pulmonary vascular beds of rats and calves after
exposure hypoxia for 1 or 3 weeks. However, others observed aduenhanced dilator responses to ACh, BK, or A-23187 in al., the pulmonary vascular beds of rats and calves after greexposure to chronic hypoxia (Barer et al., 1988; Orton enhanced dilator responses to ACh, BK, or A-23187 in
the pulmonary vascular beds of rats and calves after
exposure to chronic hypoxia (Barer et al., 1988; Orton et
al., 1988; Russ and Walker, 1993); chronic hypoxia also
do

111
Barer et al., 1993). Large pulmonary arteries from hy-
poxic rats show an impaired relaxant response to ACh FRIM VASCULAR TONE 111

111 Barer et al., 1993). Large pulmonary arteries from hy-

poxic rats show an impaired relaxant response to ACh

(Crawley et al., 1992c), although the relaxant response 111

Barer et al., 1993). Large pulmonary arteries from hy-

poxic rats show an impaired relaxant response to ACh

(Crawley et al., 1992c), although the relaxant response

of the pulmonary vascular bed to sodium nitropruss Barer et al., 1993). Large pulmonary arteries from hypoxic rats show an impaired relaxant response to ACh (Crawley et al., 1992c), although the relaxant response of the pulmonary vascular bed to sodium nitroprusside is unc poxic rats show an impaired relaxant response to ACh
(Crawley et al., 1992c), although the relaxant response
of the pulmonary vascular bed to sodium nitroprusside
is unchanged by chronic hypoxia (Orton et al., 1988;
Adnot (Crawley et al., 1992c), although the relaxant response
of the pulmonary vascular bed to sodium nitroprusside
is unchanged by chronic hypoxia (Orton et al., 1988;
Adnot et al., 1991b). Both unchanged and impaired re-
laxan of the pulmonary vascular bed to sodium nitroprusside
is unchanged by chronic hypoxia (Orton et al., 1988;
Adnot et al., 1991b). Both unchanged and impaired re-
laxant responses to sodium nitroprusside have been re-
ported is unchanged by chronic hypoxia (Orton et al., 1988;
Adnot et al., 1991b). Both unchanged and impaired re-
laxant responses to sodium nitroprusside have been re-
ported in isolated large pulmonary rings from hypoxic
calves Adnot et al., 1991b). Both unchanged a
laxant responses to sodium nitroprussid
ported in isolated large pulmonary ring
calves (Orton et al., 1988) and rats (1992).
1992c; Wanstall and O'Donnell, 1992). laxant responses to sodium nitroprusside have been reported in isolated large pulmonary rings from hypoxic calves (Orton et al., 1988) and rats (Crawley et al., 1992c; Wanstall and O'Donnell, 1992).
H. Endothelium in Imma

ing aorta (Furchgott and Zawadzki, 1980; Rodman et al., and becomes even lower in mature adults (Liu et al., 1989), coronary arteries, (Graser and Vanhoutte, 1991; 1992d; Zellers and Vanhoutte, 1991). Endothelium-de-
Muram Endothelial cells may regulate fetal pulmonary vascular tone through the release of PGI₂ (Frangos et al., 1992c; Wanstall and O'Donnell, 1992).
 H. Endothelium in Immature Pulmonary Vessels

Endothelial cells may regulate fetal pulmonary vascular

tone through the release of PGI₂ (Frangos et al.,

1985). PGI₂ is a poten H. Endothelium in Immature Pulmonary Vessels
Endothelial cells may regulate fetal pulmonary vascu-
lar tone through the release of PGI_2 (Frangos et al.,
1985). PGI₂ is a potent dilator of the fetal and perinatal
pulmo Fr. Endothelial cells may regulate fetal pulmonary vascu-
lar tone through the release of $PGI₂$ (Frangos et al., 1985). $PGI₂$ is a potent dilator of the fetal and perinatal
pulmonary circulations (Leffler et a Endothelial cells may regulate fetal pulmonary vascular tone through the release of PGI_2 (Frangos et al., 1985). PGI_2 is a potent dilator of the fetal and perinatal pulmonary circulations (Leffler et al., 1979, 1980) lar tone through the release of PGI_2 (Frangos et al., 1985). PGI_2 is a potent dilator of the fetal and perinatal pulmonary circulations (Leffler et al., 1979, 1980) and is released into the pulmonary circulation at bi 1985). PGI₂ is a potent dilator of the fetal and perinatal pulmonary circulations (Leffler et al., 1979, 1980) and is released into the pulmonary circulation at birth (Leffler et al., 1980, 1984). Inhibition of PGI_2 s pulmonary circulations (Leffler et al., 1979, 1980) and is
released into the pulmonary circulation at birth (Leffler
et al., 1980, 1984). Inhibition of PGI_2 synthesis slows
down the reduction in PPA at birth (Leffler et released into the pulmonary circulation at birth (Leiner
et al., 1980, 1984). Inhibition of PGI₂ synthesis slows
down the reduction in PPA at birth (Leffler et al., 1978).
The role of endothelium in the modulation of fet et an., 1960, 1964). Inmolution of FG1_2 synthesis slows
down the reduction in PPA at birth (Leffler et al., 1978).
The role of endothelium in the modulation of fetal pul-
monary vascular tone has also been investiga The role of endothelium in the modulation of fetal pulmonary vascular tone has also been investigated. In pig
pulmonary arteries, the relaxant response to ACh is
negligible at birth (5 min to 2 h) but develops rapidly
ther monary vascular tone has also been investigated. In pig
pulmonary arteries, the relaxant response to ACh is
negligible at birth (5 min to 2 h) but develops rapidly
thereafter, becoming maximal at 3 to 10 days; the re-
spon pulmonary arteries, the relaxant response to ACh is
negligible at birth (5 min to 2 h) but develops rapidly
thereafter, becoming maximal at 3 to 10 days; the re-
sponse decreases gradually, decreasing at 3 to 8 weeks,
and negligible at birth (5 min to 2 h) but develops r
thereafter, becoming maximal at 3 to 10 days; t
sponse decreases gradually, decreasing at 3 to 8
and becomes even lower in mature adults (Liu
1992d; Zellers and Vanhoutte, thereafter, becoming maximal at 3 to 10 days; the response decreases gradually, decreasing at 3 to 8 weeks,
and becomes even lower in mature adults (Liu et al.,
1992d; Zellers and Vanhoutte, 1991). Endothelium-de-
pendent sponse decreases gradually, decreasing at 3 to 8 weeks,
and becomes even lower in mature adults (Liu et al.,
1992d; Zellers and Vanhoutte, 1991). Endothelium-de-
pendent relaxant response to ACh and BK is absent in
fetal r and becomes even lower in mature addits (Lid et al., 1992d; Zellers and Vanhoutte, 1991). Endothelium-dependent relaxant response to ACh and BK is absent in fetal rabbit pulmonary arteries (Zubrow et al., 1989) but exists pendent relaxant response to ACh and BK is absent in
fetal rabbit pulmonary arteries (Zubrow et al., 1989) but
exists in guinea pigs at age 1 to 3 days (Davidson and
Eldemerdash, 1990).
In sheep, the relaxant responses to fetal rabbit pulmonary arteries (Zubrow et al., 1989) but
exists in guinea pigs at age 1 to 3 days (Davidson and
Eldemerdash, 1990).
In sheep, the relaxant responses to ACh or ATP are
minimal in the fetus, increased in the

increase in tissue PGI_2 production (Shaul et al., 1991). horn et al., 1993). The vasodilator response to ACh or
During HPV, several factors, including endothelial BK is probably mediated predominantly by NO, inas-
sh responses to ACh and A-23187 were diminished or abol-
inasmuch as these vessels relax in response to sodium
ished in the pulmonary vascular beds of rats exposed to
hypoxia for 1 or 3 weeks. However, others observed adult p fetal rabbit pulmonary arteries (Zubrow et al., 1989) but
exists in guinea pigs at age 1 to 3 days (Davidson and
Eldemerdash, 1990).
In sheep, the relaxant responses to ACh or ATP are
minimal in the fetus, increased in th exists in guinea pigs at age 1 to 3 days (Davidson ar
Eldemerdash, 1990).
In sheep, the relaxant responses to ACh or ATP a
minimal in the fetus, increased in the newborn (1 to
weeks), and even greater in the adult pulmonar In sheep, the relaxant responses to ACh or ATP are
minimal in the fetus, increased in the newborn (1 to 4
weeks), and even greater in the adult pulmonary arter-
ies (Abman et al., 1991). Using tissue cGMP content as
an ind minimal in the fetus, increased in the newborn (1 to 4 weeks), and even greater in the adult pulmonary arteries (Abman et al., 1991). Using tissue cGMP content as an indicator of NO activity, Shaul et al. (1993) also demon weeks), and even greater in the adult pulmonary arter-
ies (Abman et al., 1991). Using tissue cGMP content as
an indicator of NO activity, Shaul et al. (1993) also
demonstrated the existence of NO activity in the fetus,
in ies (Abman et al., 1991). Using tissue cGMP content as
an indicator of NO activity, Shaul et al. (1993) also
demonstrated the existence of NO activity in the fetus,
increased activity at 1 week, and even greater activity a all indicator of NO activity, Shati et al. (1993) also
demonstrated the existence of NO activity in the fetus,
increased activity at 1 week, and even greater activity at
2 weeks. Maturational change in the sensitivity to A 2 weeks. Maturational change in the sensitivity to ACh is also observed in the pulmonary veins of sheep (Stein-2 weeks. Maturational change in the sensitivity to AC
is also observed in the pulmonary veins of sheep (Stein
horn et al., 1993). The vasodilator response to ACh
BK is probably mediated predominantly by NO, ina
much as L-N is also observed in the pulmonary veins of sheep (Steinhorn et al., 1993). The vasodilator response to ACh c BK is probably mediated predominantly by NO, inas much as L-NMMA and L-NA inhibit most of the relaxion (Liu et al horn et al., 1993). The vasodilator response to ACh or BK is probably mediated predominantly by NO, inasmuch as L-NMMA and L-NA inhibit most of the relaxation (Liu et al., 1992d; Steinhorn et al., 1993). AChinduced cGMP ac BK is probably mediated predominantly by NO, inasmuch as L-NMMA and L-NA inhibit most of the relaxation (Liu et al., 1992d; Steinhorn et al., 1993). AChinduced cGMP accumulation in fetal and neonatal pulmonary artery rings much as L-NMMA and L-NA inhibit most of the relax-
ation (Liu et al., 1992d; Steinhorn et al., 1993). ACh-
induced cGMP accumulation in fetal and neonatal
pulmonary artery rings is also inhibited by L-NA (Shaul
et al., 199 ation (Liu et al., 1992d; Steinhorn et al., 1993). AChinduced cGMP accumulation in fetal and neonatal pulmonary artery rings is also inhibited by L-NA (Shaul et al., 1993). However, the diminished response to ACh or BK in induced cGMP accumulation in fetal and neonatal
pulmonary artery rings is also inhibited by L-NA (Shaul
et al., 1993). However, the diminished response to ACh
or BK in the fetal or neonatal pulmonary arteries is
unlikely t pulmonary artery rings is also inhibited by L-NA (Shaul
et al., 1993). However, the diminished response to ACh
or BK in the fetal or neonatal pulmonary arteries is
unlikely to be caused by a lack of sensitivity to NO,
inas et al., 1993). However, the diminished response to ACh
or BK in the fetal or neonatal pulmonary arteries is
unlikely to be caused by a lack of sensitivity to NO,
inasmuch as these vessels relax in response to sodium
nitrop or BK in the fetal or neonatal pulmonary arteries is
unlikely to be caused by a lack of sensitivity to NO,
inasmuch as these vessels relax in response to sodium
nitroprusside or NO to a similar extent as in neonatal or
adu unlikely to be caused by a lack of sensitivity to NO, inasmuch as these vessels relax in response to sodium nitroprusside or NO to a similar extent as in neonatal or adult pulmonary arteries (Liu et al., 1992d; Steinhorn e inasmuch as these vessels relax in response to sodium
nitroprusside or NO to a similar extent as in neonatal or
adult pulmonary arteries (Liu et al., 1992d; Steinhorn et
al., 1993). Basal NO release in pulmonary vessels is nitroprusside or NO
adult pulmonary art
al., 1993). Basal N
greater at 1 day po
and Marte, 1993).
The greater EDR ult pulmonary arteries (Liu et al., 1992d; Steinhorn et

., 1993). Basal NO release in pulmonary vessels is

eater at 1 day postnatally than at 7 days (Perreault

d Marte, 1993).

The greater EDRF activity in neonates indi al., 1993). Basal NO release in pulmonary vessels is greater at 1 day postnatally than at 7 days (Perreault and Marte, 1993). The greater EDRF activity in neonates indicates that EDRF may be important in the second phase o

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nary vascular adaptation. The role of EDRF in the first

phase of pulmonary vascular adaptation remains un-BARNES

phase of pulmonary vascular adaptation. The role of EDRF in the first

phase of pulmonary vascular adaptation remains un-

clear. Endothelium-mediated relaxation to ACh and BK BARNES AND LIU
nary vascular adaptation. The role of EDRF in the first of endo
phase of pulmonary vascular adaptation remains un-
clear. Endothelium-mediated relaxation to ACh and BK dent v
is absent in pulmonary arteries nary vascular adaptation. The role of EDRF in the first chase of pulmonary vascular adaptation remains unclear. Endothelium-mediated relaxation to ACh and BK is absent in pulmonary arteries from fetal or early neo-
natal p phase of pulmonary vascular adaptation remains unclear. Endothelium-mediated relaxation to ACh and BK is absent in pulmonary arteries from fetal or early neonatal pigs and guinea pigs (Liu et al., 1992d; Zubrow et lal., 19 clear. Endotherium-mediated relaxation to ACh and BK den
is absent in pulmonary arteries from fetal or early neo-
natal pigs and guinea pigs (Liu et al., 1992d; Zubrow et be
al., 1993) but is present, albeit small, in pulm natal pigs and guinea pigs (Liu et al., 1992d; Zubrow et be al., 1989) but is present, albeit small, in pulmonary the arteries from fetal lambs (Abman et al., 1991; Shaul et nardl., 1993). In late gestational lambs, ACh ca al., 1989) but is present, albeit small, in pulmonary
arteries from fetal lambs (Abman et al., 1991; Shaul et
al., 1993). In late gestational lambs, ACh causes an
increase in pulmonary blood flow, which is inhibited by
L-N arteries from fetal lambs (Abman et al., 1991; Shaul et al., 1993). In late gestational lambs, ACh causes an pincrease in pulmonary blood flow, which is inhibited by c
L-NA. L-NA elevates basal PPA and reduces the increase al., 1993). In late gestational lambs, ACh causes an pen
increase in pulmonary blood flow, which is inhibited by or a
L-NA L-NA elevates basal PPA and reduces the increase thel
in pulmonary blood flow that occurs at birth increase in pulmonary blood flow, which is inhibited by
L-NA. L-NA elevates basal PPA and reduces the increase
in pulmonary blood flow that occurs at birth (Abman et
al., 1990); L-NA also inhibits the vasodilation induced in pulmonary blood flow that occurs at birth (Abman et al., 1990); L-NA also inhibits the vasodilation induced by ventilation and increased oxygen tension in the lambs (Cornfield et al., 1992; Tiktinsky and Morin, 1993). W al., 1990); L-NA also inhibits the vasodilation induced by al., 1990); L-NA also inhibits the vasodilation induced by
ventilation and increased oxygen tension in the lambs
(Cornfield et al., 1992; Tiktinsky and Morin, 1993).
Whether the difference between lamb and other species
re ventilation and increased oxygen tension in the lamb
(Cornfield et al., 1992; Tiktinsky and Morin, 1993
Whether the difference between lamb and other specie
represents a species variation or reflects a difference
between i (Cornfield et al., 1992; Tiktinsky and Morin, 1993)
Whether the difference between lamb and other species
represents a species variation or reflects a difference
between in vivo and in vitro studies is unclear. Add
tional Whether the difference between lamb and other species m
represents a species variation or reflects a difference
between in vivo and in vitro studies is unclear. Addi-
stional in vivo studies to compare the maturational $\$ question.

Inasmuch as endothelium represents one of the most
important structures in the regulation of pulmonary
vascular tone and vascular cellular functions, there has I. Role of Endothelium in Pulmonary Vascular Disease

Inasmuch as endothelium represents one of the most

Emportant structures in the regulation of pulmonary

vascular tone and vascular cellular functions, there has

metal between considerable interest in the function of the most
important structures in the regulation of pulmonary
vascular tone and vascular cellular functions, there has
been considerable interest in the function and role of
 Inasmuch as endothelium represents one of the most
important structures in the regulation of pulmonary
vascular tone and vascular cellular functions, there has
been considerable interest in the function and role of
endothe important structures in the regulation of pulmonary prol
vascular tone and vascular cellular functions, there has mus
been considerable interest in the function and role of end
endothelial cells in pulmonary vascular disea vascular tone and vascular cellular functions, there has
been considerable interest in the function and role of
endothelial cells in pulmonary vascular diseases. Dys-
function and injury of pulmonary vascular endothelium
m monary hypertension (Loscalzo, 1992; Dinh-Xuan, 1993). Morphological changes of the intima have been showserved in animal models of pulmonary hypertension (Loscalzo, 1992; Dinh-Xuan, 1993). Morphological changes of the int function and injury of pulmonary vascular endothelium
ay play an important role in the development of pu
monary hypertension (Loscalzo, 1992; Dinh-Xua
1993). Morphological changes of the intima have bee
observed in animal may play an important role in the development of pu
monary hypertension (Loscalzo, 1992; Dinh-Xuan
1993). Morphological changes of the intima have bee
observed in animal models of pulmonary hypertension
induced by adminis monary hypertension (Loscalzo, 1992; Dinh-Xuan, 1993). Morphological changes of the intima have been observed in animal models of pulmonary hypertension, induced by administration of α -napthylthyiourea (Rounds et al., observed in animal models of pulmonary hypertension,
induced by administration of α -napthylthyiourea
(Rounds et al., 1985), monocrotaline (Rosenberg et al.,
1985; Kanai et al., 1993), endotoxin (Peach et al., 1989),
an observed in animal models of pulmonary hypertension,
induced by administration of α -napthylthyiourea
(Rounds et al., 1985), monocrotaline (Rosenberg et al., 1985; Kanai et al., 1993), endotoxin (Peach et al., 1989), t
 induced by administration of α -napthylthyiourea va
(Rounds et al., 1985), monocrotaline (Rosenberg et al., (N
1985; Kanai et al., 1993), endotoxin (Peach et al., 1989), the
and systemic-to-pulmonary arterial shunts (Es (Rounds et al., 1985), monocrotaline (Rosenberg et al., 1985; Kanai et al., 1993), endotoxin (Peach et al., 1989), and systemic-to-pulmonary arterial shunts (Esterly et al., 1968). Pulmonary endothelial structural changes 1985; Kanai et al., 1993), endotoxin (Peach et al., 1989),
and systemic-to-pulmonary arterial shunts (Esterly et 1
al., 1968). Pulmonary endothelial structural changes are t
also found in patients with primary (Meyrick et and systemic-to-pulmonary arterial shunts (Esterly et al., 1968). Pulmonary endothelial structural changes are
also found in patients with primary (Meyrick et al., 1974) and secondary pulmonary hypertension resulting 1
fro al., 1968). Pulmonary endothelial structural changes are
also found in patients with primary (Meyrick et al.,
1974) and secondary pulmonary hypertension resulting
from COPD (Magee et al., 1988; Wilkinson et al., 1988)
and also found in patients with primary (Meyrick et al., ma
1974) and secondary pulmonary hypertension resulting her
from COPD (Magee et al., 1988; Wilkinson et al., 1988) et
and congenital heart defects (Rabinovitch et al., 1 1974) and secondary pulmonary hypertension resul
from COPD (Magee et al., 1988; Wilkinson et al., 19
and congenital heart defects (Rabinovitch et al., 19
Pulmonary artery rings from patients with COPD
Eisenmenger's syndrom from COPD (Magee et al., 1988; Wilkinson et al., 1988)
and congenital heart defects (Rabinovitch et al., 1986).
Pulmonary artery rings from patients with COPD and
Eisenmenger's syndrome exhibit an impaired endotheli-
um-de and congenita
Pulmonary ar
Eisenmenger'_i
1990, 1991).
Impairment

Eisenmenger's syndrome exhibit an impaired endotheli-
um-dependent relaxant response (Dinh-Xuan et al.,
1990, 1991).
Impairment of the pulmonary vasodilatory response
to ACh has also observed in vivo in patients with pri-
 um-dependent relaxant response (Dinh-Xuan et al., 1990, 1991).

Impairment of the pulmonary vasodilatory response

to ACh has also observed in vivo in patients with pri-

mary (Conraads et al., 1993) and secondary pulmonar 1990, 1991).
Impairment of the pulmonary vasodilatory resporto ACh has also observed in vivo in patients with p
mary (Conraads et al., 1993) and secondary pulmona
hypertension (Celermajer et al., 1993). This is in contra-
 Impairment of the pulmonary vasodilatory response (Weitz
to ACh has also observed in vivo in patients with priverse α
mary (Conraads et al., 1993) and secondary pulmonary
hypertension (Celermajer et al., 1993). This is to ACh has also observed in vivo in patients with pri-
mary (Conraads et al., 1993) and secondary pulmonary
hypertension (Celermajer et al., 1993). This is in contra-
diction to most of the early reports that ACh and BK
r mary (Conraads et al., 1993) and secondary pulmona
hypertension (Celermajer et al., 1993). This is in contradiction to most of the early reports that ACh and I
reduce PPA and/or PVR in patients with various types
pulmonary hypertension (Celermajer et al., 1993). This is in contra-
diction to most of the early reports that ACh and BK
reduce PPA and/or PVR in patients with various types of
pulmonary hypertension (Peach et al., 1989). Differ-
e diction to most of the early reports that ACh and BK
reduce PPA and/or PVR in patients with various types of
pulmonary hypertension (Peach et al., 1989). Differ-
ences in the severity of disease may explain this dis-
crepa reduce PPA and/or PVR in patients with various types of pulmonary hypertension (Peach et al., 1989). Differences in the severity of disease may explain this discrepancy. The majority of these early studies did not compare pulmonary hypertension (Peach et al., 1989). Differences in the severity of disease may explain this discrepancy. The majority of these early studies did not compare ACh-mediated responses of hypertensive pulmonary vascula ences in the severity of disease may explain this discrepancy. The majority of these early studies did no
compare ACh-mediated responses of hypertensive pul
monary vascular beds with those of normal pulmonary
vascular beds

ND LIU
of endothelium-dependent responses is that pulmonary
vasodilator response to most of the endothelium-depen-ND LIU
of endothelium-dependent responses is that pul
vasodilator response to most of the endothelium
dent vasodilators are tone-dependent. A mode ND LIU
of endothelium-dependent responses is that pulmonary
vasodilator response to most of the endothelium-depen-
dent vasodilators are tone-dependent. A moderate re-
duction in endothelium-dependent relaxation could well of endothelium-dependent responses is that pulmonary
vasodilator response to most of the endothelium-depen-
dent vasodilators are tone-dependent. A moderate re-
duction in endothelium-dependent relaxation could well
be com of endothelium-dependent responses is that pulmonary
vasodilator response to most of the endothelium-dependent vasodilators are tone-dependent. A moderate reduction in endothelium-dependent relaxation could well
be compens vasodilator response to most of the endothelium-deptent vasodilators are tone-dependent. A moderate duction in endothelium-dependent relaxation could w
be compensated by an increase in tone. Collective
these results sugges dent vasodilators are tone-dependent. A moderate duction in endothelium-dependent relaxation could be compensated by an increase in tone. Collectiese results suggest that pulmonary vessels in pary hypertension have an impa duction in endothelium-dependent relaxation could well
be compensated by an increase in tone. Collectively,
these results suggest that pulmonary vessels in pulmo-
nary hypertension have an impaired endothelium-de-
pendent be compensated by an increase in tone. Collectivel
these results suggest that pulmonary vessels in pulm
nary hypertension have an impaired endothelium-de
pendent response. Whether this impairment is a caus
or a result of t these results suggest that pulmonary vessels in puln
nary hypertension have an impaired endothelium-
pendent response. Whether this impairment is a cau
or a result of the disease is unclear. Nevertheless, en
thelium-derive nary hypertension have an impaired endothelium-de-
pendent response. Whether this impairment is a cause
or a result of the disease is unclear. Nevertheless, endo-
thelium-derived NO is an important inhibitory mecha-
nism. pendent response. Whether this impairment is a cause
or a result of the disease is unclear. Nevertheless, endo-
thelium-derived NO is an important inhibitory mecha-
nism. Loss of this protective mechanism, reduction in
NO or a result of the disease is unclear. Nevertheless, end
thelium-derived NO is an important inhibitory mech
nism. Loss of this protective mechanism, reduction i
NO and/or PGI_2 production, not only predisposes a p
tie nism. Loss of this protective mechanism, reduction in NO and/or PGI_2 production, not only predisposes a patient to pulmonary vasoconstriction but may also facilitate the proliferation of pulmonary vascular smooth muscle NO and/or PGI₂ production, not only predisposes a pa-

I. Role of Endothelium in Pulmonary Vascular Disease
 I. Role of Endothelium in Pulmonary Vascular Disease
 I. Role of Endothelium in Pulmonary Vascular Disease
 I. Role of Endothelium in Pulmonary Vascular Disease important structures in the regulation of pulmonary proliferation action of interferon- γ on vascular smooth vascular cellular functions, there has muscle cells (Nunokawa and Tanaka, 1992). Loss of the NO-re!easing agents and cGMP inhibit vascular tient to pulmonary vasoconstriction but may also facilitate the proliferation of pulmonary vascular smooth
muscle cells.
NO-releasing agents and cGMP inhibit vascular
smooth muscle mitogenesis and proliferation (Garg and
H tate the proliferation of pulmonary vascular smoot
muscle cells.
NO-releasing agents and cGMP inhibit vascula
smooth muscle mitogenesis and proliferation (Garg an
Hassid, 1989). In cultured human umbilical vein end
thelial muscle cells.
NO-releasing agents and cGMP inhibit vascular
smooth muscle mitogenesis and proliferation (Garg and
Hassid, 1989). In cultured human umbilical vein endo-
thelial cells, endogenous NO inhibits hypoxia-induced NO-releasing agents and cGMP inhibit vascu
smooth muscle mitogenesis and proliferation (Garg a
Hassid, 1989). In cultured human umbilical vein en
thelial cells, endogenous NO inhibits hypoxia-induc
ET-1 and platelet-deriv sinooth muscle imtogenesis and promeration (carg and

Hassid, 1989). In cultured human umbilical vein endo-

thelial cells, endogenous NO inhibits hypoxia-induced

ET-1 and platelet-derived growth factor- β gene expresthelial cells, endogenous NO inhibits hypoxia-induce
ET-1 and platelet-derived growth factor- β gene expres
sion (Kourembanas et al., 1993). Moreover, endotheli
um-derived NO mediates heparin-induced inhibition on
ET-1 ET-1 and platelet-derived growth factor- β gene expression (Kourembanas et al., 1993). Moreover, endotheli-
um-derived NO mediates heparin-induced inhibition on
ET-1 production (Yokokawa et al., 1993) and the anti-
prol sion (Kourembanas et al., 1993). Moreover, endotheli-
um-derived NO mediates heparin-induced inhibition on
ET-1 production (Yokokawa et al., 1993) and the anti-
proliferation action of interferon- γ on vascular smooth
m um-derived NO mediates heparin-induced inhibition of ET-1 production (Yokokawa et al., 1993) and the antiproliferation action of interferon- γ on vascular smootimuscle cells (Nunokawa and Tanaka, 1992). Loss of the endo ET-1 production (Yokokawa et al., 1993) and the anti-
proliferation action of interferon- γ on vascular smooth
muscle cells (Nunokawa and Tanaka, 1992). Loss of the
endothelium-dependent inhibitory mechanism will facilpromeration action of interferon-y on vascular sim
muscle cells (Nunokawa and Tanaka, 1992). Loss of
endothelium-dependent inhibitory mechanism will fitate the process of pulmonary vascular remodelling
thus accelerate the sion. dothelium-dependent inhibitory mechanism will facil-
hte the process of pulmonary vascular remodelling and
us accelerate the development of pulmonary hyperten-
on.
Endogenous NO is also likely to be involved in septic
ock

Eisenmenger's syndrome exhibit an impaired endotheli-
un-dependent relaxant response (Dinh-Xuan et al., reported to attenuate pulmonary hypertension and im-
1990, 1991).
Impairment of the pulmonary vasodilatory response (W itate the process of pulmonary vascular remodelling and
thus accelerate the development of pulmonary hyperten-
sion.
Endogenous NO is also likely to be involved in septic
shock (Stoclet et al., 1993), although the NO media thus accelerate the development of pulmonary hypertension.
 \overrightarrow{B} is also likely to be involved in septic

shock (Stoclet et al., 1993), although the NO mediating

the hypotension is probably derived predominantly from sion.

Endogenous NO is also likely to be involved in septic

shock (Stoclet et al., 1993), although the NO mediating

the hypotension is probably derived predominantly from

vascular smooth muscle cells and inflammatory c Endogenous NO is also likely to be involved in sept
shock (Stoclet et al., 1993), although the NO mediatii
the hypotension is probably derived predominantly fro
vascular smooth muscle cells and inflammatory cel
(Nakayama e shock (Stoclet et al., 1993), although the NO mediating
the hypotension is probably derived predominantly from
vascular smooth muscle cells and inflammatory cells
(Nakayama et al., 1992; Liu et al., 1993, 1994b). Endo-
the the hypotension is probably derived predominantly from
vascular smooth muscle cells and inflammatory cells
(Nakayama et al., 1992; Liu et al., 1993, 1994b). Endo-
thelial cells may also express the iNOS (Moncada et al.,
19 vascular smooth muscle cells and inflammatory cells
(Nakayama et al., 1992; Liu et al., 1993, 1994b). Endo-
thelial cells may also express the iNOS (Moncada et al.,
1991; Stoclet et al., 1993) and therefore also contribute (Nakayama et al., 1992; Liu et al., 1993, 1994b). Endo-
thelial cells may also express the iNOS (Moncada et al.,
1991; Stoclet et al., 1993) and therefore also contribute
to the excess formation of NO. Down-regulation of e thelial cells may also express the iNOS (Moncada et al., 1991; Stoclet et al., 1993) and therefore also contribute
to the excess formation of NO. Down-regulation of eNOS
may also play an important role in the early pulmona 1991; Stoclet et al., 1993) and therefore also contribute
to the excess formation of NO. Down-regulation of eNOS
may also play an important role in the early pulmonary
hemodynamic changes during septic shock (Yoshizumi
et to the excess formation of NO. Down-regulation of eNOS
may also play an important role in the early pulmonary
hemodynamic changes during septic shock (Yoshizumi
et al., 1993). The protective role of endogenous NO
against n may also play an important role in the early pulmonary
hemodynamic changes during septic shock (Yoshizumi
et al., 1993). The protective role of endogenous NO
against neurogenic pulmonary edema (Liu et al., 1994a)
suggests et al., 1993). The protective role of endogenous NO
against neurogenic pulmonary edema (Liu et al., 1994a)
suggests that NO may be of potential therapeutic benefit
to patients with ARDS. Indeed, inhaled NO has been
reporte to patients with ARDS. Indeed, inhaled NO has been reported to attenuate pulmonary hypertension and imverse underlying diseases (Gerlach et al., 1993).
 VI. Second-messengers
 A. Cyclic Nucleotides
 Cyclic nucleotides are important in the regulation of

VI. Second-messengers
A. Cyclic Nucleotides

VI. Second-messengers
Cyclic Nucleotides
Cyclic nucleotides are important in the regulation of
Imonary vascular tone. cGMP is the key second-mes-**1. Second-messengers**
 2. Cyclic Nucleotides
 2. Cyclic nucleotides are important in the regulation
 2. pulmonary vascular tone. cGMP is the key second-senger of NO-induced pulmonary vasodilation, where A. Cyclic Nucleotides
Cyclic nucleotides are important in the regulation of
pulmonary vascular tone. cGMP is the key second-mes-
senger of NO-induced pulmonary vasodilation, whereas
cAMP plays a central role in the pulmona A. Cyclic Nucleotides
Cyclic nucleotides are important in the regulation of
pulmonary vascular tone. cGMP is the key second-mes-
senger of NO-induced pulmonary vasodilation, whereas
cAMP plays a central role in the pulmona Cyclic nucleotides are important in the regulation of
pulmonary vascular tone. CGMP is the key second-mes-
senger of NO-induced pulmonary vasodilation, whereas
cAMP plays a central role in the pulmonary vasodilator
respon pulmonary vascular tone. cGMP is the key second-messenger of NO-induced pulmonary vasodilation, whereas cAMP plays a central role in the pulmonary vasodilator response to many directly acting vasodilators, including β -

aspet

REGULATION **OF PULMONARY** VASCULAR **TONE** ¹¹³ REGULATION OF PULMONARY VASCULAR TONE
nous cGMP and cAMP themselves are potent pulmonary phorylation of substrates involved in the contractile
vasodilators (Haynes et al., 1992; McMahon et al., 1992, process. Activation of REGULATION OF PULMO

nous cGMP and cAMP themselves are potent pulmonary

vasodilators (Haynes et al., 1992; McMahon et al., 1992,

1993a). The mechanism responsible for cGMP-induced

vasodilation is incompletely understood nous cGMP and cAMP themselves are potent pulmonary photon vasodilators (Haynes et al., 1992; McMahon et al., 1992, pro 1993a). The mechanism responsible for cGMP-induced hunderstood but is related to Savactivation of prote

vasodilators (Haynes et al., 1992; McMahon et al., 1992, pi
1993a). The mechanism responsible for cGMP-induced hvasodilation is incompletely understood but is related to Sactivation of protein kinase G, inhibition of IP_3 1993a). The mechanism responsible for cGMP-induced hyposodilation is incompletely understood but is related to Sactivation of protein kinase G, inhibition of IP₃, dephosphorylation of myosin light chain kinase, stimulat vasodilation is incompletely understood but is related
activation of protein kinase G, inhibition of IP₃, deph
phorylation of myosin light chain kinase, stimulation
Ca²⁺-ATPase, opening of K⁺ channels, and inhibitio activation of protein kinase G, inhibition of IP_3 , dephos-
phorylation of myosin light chain kinase, stimulation of
 Ca^{2+} -ATPase, opening of K⁺ channels, and inhibition of
 Ca^{2+} influx (Lincoln, 1989). Likewise, s phorylation of myosin light chain kinase, stimulation of Ca^{2+} -ATPase, opening of K^+ channels, and inhibition of Ca^{2+} influx (Lincoln, 1989). Likewise, several mechanisms may mediate the vasodilator response to cA Ca^{2+} influx (Lincoln, 1989). Likewise, several mechanisms may mediate the vasodilator response to cAMP, including activation of cAMP-dependent protein kinase, resulting in a decreased myosin light chain kinase activity Ca^{2+} influx (Lincoln, 1989). Likewise, several mecha-
nisms may mediate the vasodilator response to cAMP, et
including activation of cAMP-dependent protein kinase, presulting in a decreased myosin light chain kinase ac misms may mediate the vasodilator response to cAMP, et
including activation of cAMP-dependent protein kinase, presulting in a decreased myosin light chain kinase ac-
tivity and reduced myosin phosphorylation, inhibition o including activation of cAMP-dependent protein kinase,
resulting in a decreased myosin light chain kinase activity and reduced myosin phosphorylation, inhibition of
 Ca^{2+} influx, stimulation of Ca^{2+} efflux, and openi resulting in a decreased myosin light chain kinase ac-
tivity and reduced myosin phosphorylation, inhibition of PKC
Ca²⁺ influx, stimulation of Ca²⁺ efflux, and opening of eden
Ca²⁺-dependent K⁺ channels (Murray, Example 1 and reduced myoshi phosphoryiation, inhibition of Ca^{2+} influx, stimulation of Ca^{2+} efflux, and opening of Ca^{2+} -dependent K^+ channels (Murray, 1990). Inhibition Tay of cGMP degradation by a cGMP speci Ca²⁺-dependent K⁺ channels (Murray, 1990). Inhibition
of cGMP degradation by a cGMP specific (type V) PDE
inhibitor decreases pulmonary perfusion pressure in
constant perfused pulmonary vascular bed (McMahon et
al., 19 of cGMP degradation by a cGMP specific (type V) PDE
inhibitor decreases pulmonary perfusion pressure in
constant perfused pulmonary vascular bed (McMahon et
al., 1993a). In isolated endothelium-denuded pulmonary
artery ri inhibitor decreases pulmonary perfusion pressure in

constant perfused pulmonary vascular bed (McMahon et

al., 1993a). In isolated endothelium-denuded pulmonary

artery rings, there is a basal level of cGMP (Ignarro et
 al., 1993a). In isolated endothelium-denuded pulmonary
artery rings, there is a basal level of cGMP (Ignarro et
al., 1987c). Both cAMP and cGMP modulate HPV and
inhibit the development of hypoxic pulmonary hyperten-
sion. artery rings, there is a basal level of cGMP (Ignarro et are critical in smooth muscle contraction or relaxation
al., 1987c). Both cAMP and cGMP modulate HPV and and the initiation of other cellular responses. The regu-
i artery rings, there is a basal level of CGMP (Ignarro et al., 1987c). Both cAMP and cGMP modulate HPV and inhibit the development of hypoxic pulmonary hypertension. Stimulation of cAMP and cGMP formation inhibits pulmonary inhibit the development of hypoxic pulmonary hypertension. Stimulation of cAMP and cGMP formation inhibits Capulmonary endothelial permeability to albumin and reduces pulmonary edema formation (Harada et al., 1989; ultill sion. Stimulation of cAMP and coulmonary endothelial permeal
duces pulmonary edema format
Liu et al., 1994a), suggesting the
protective against lung injury.
P. Pheaphoinasitide Huduslavia *B. Phosphoinositide Hydrolysis*
B. Phosphoinositide Hydrolysis
B. Phosphoinositide Hydrolysis
Activation of phospholipase C

Liu et al., 1994a), suggesting that cAMP and cGMP are
protective against lung injury.
B. Phosphoinositide Hydrolysis
Activation of phospholipase C, resulting from stimu-
lation of G-protein coupled receptors, leads to the protective against lung injury.

B. Phosphoinositide Hydrolysis

Activation of phospholipase C, resulting from stim

lation of G-protein coupled receptors, leads to the hydr

lysis of phosphoinositol bisphosphate-₂ and c B. Phosphoinositide Hydrolysis
Activation of phospholipase C, resulting from stimu-
lation of G-protein coupled receptors, leads to the hydro-
lysis of phosphoinositol bisphosphate-₂ and consequent
generation of two sec B. Phosphomostical Hydrotysts

Activation of phospholipase C, resulting from stin

lation of G-protein coupled receptors, leads to the hyd

lysis of phosphoinositol bisphosphate-₂ and conseque

generation of two second-Activation of phospholipase C, resulting from stimulation of G-protein coupled receptors, leads to the hydrolysis of phosphoinositol bisphosphate-₂ and consequent generation of two second-messengers, IP₃ and 1,2-dia-c lation of G-protein coupled receptors, leads to the hydressis of phosphoinositol bisphosphate-₂ and conseque generation of two second-messengers, IP_3 and 1,2-dicylglycerol. IP_3 mobilizes Ca^{2+} from intracellular s lysis of phosphoinositol bisphosphate-₂ and consequent
generation of two second-messengers, IP_3 and 1,2-dia-
cylglycerol. IP_3 mobilizes Ca^{2+} from intracellular stores,
followed by the activation of $Ca^{2+}/calod}$ mod generation of two second-messengers, IP_3 and 1,2-diacylglycerol. IP_3 mobilizes Ca^{2+} from intracellular stores followed by the activation of Ca^{2+}/c almodulin-myosilight chain kinase, phosphorylation of myosin light followed by the activation of $Ca^{2+}/calmodulin-myosin$ light chain kinase, phosphorylation of myosin light chain, and vascular smooth muscle contraction (Ber-
ridge and Irvine, 1989), whereas 1,2-diacy!glycerol acti-
vates PKC (se followed by the activation of $Ca^{2+}/calodulin-myosin$ cle

light chain kinase, phosphorylation of myosin light inti-

chain, and vascular smooth muscle contraction (Ber-

ridge and Irvine, 1989), whereas 1,2-diacylglycerol acti-
 light chain kinase, phosphorylation of myosin li
chain, and vascular smooth muscle contraction (F
ridge and Irvine, 1989), whereas 1,2-diacylglycerol a
vates PKC (see VI.C.). Many humoral substances a
mediators affect pulm chain, and vascular smooth muscle contraction (Ber-
ridge and Irvine, 1989), whereas 1,2-diacylglycerol acti-
vates PKC (see VI.C.). Many humoral substances and
mediators affect pulmonary vascular tone via stimula-
tion o ridge and Irvine, 1989), whereas 1,2-diacylglycerol
vates PKC (see VI.C.). Many humoral substances
mediators affect pulmonary vascular tone via stin
tion of G-protein coupled receptors (Birnbaumer, 19
There is an increase vates PKC (see VI.C.). Many humoral substances and C mediators affect pulmonary vascular tone via stimula-
tion of G-protein coupled receptors (Birnbaumer, 1990). Pr
There is an increase in IP_3 generation with norepin mediators affect pulmonary vascular tone via sumulation of G-protein coupled receptors (Birnbaumer, 1990). pot
There is an increase in IP_3 generation with norepinephrine-
pulmonary artery, suggesting that IP_3 is not i There is an
rine- but n
pulmonary
hypoxic con
al., 1993). pulmonary artery, suggesting that IP₃ is not involved in
 c. Protein Kinases
 C. Protein Kinases

Protein kinases play an important regulatory role in

mypoxic contraction of large pulmonary arteries (of et and
al., 1993).
C. Protein Kinases
Protein kinases play an important regulatory role in rem
many physiological processes. As described above, al.,
cAMP-dependent prote C. Protein Kinases

Protein kinases play an important regulatory role in

many physiological processes. As described above,

cAMP-dependent protein kinase and cGMP-dependent

protein kinase are involved in pulmonary vascul Protein kinases play an important regulatory role in
many physiological processes. As described above,
cAMP-dependent protein kinase and cGMP-dependent
protein kinase are involved in pulmonary vascular re-
laxation. Anothe protein kinase are involved in pulmonary vascular
laxation. Another protein kinase family, PKC is a
vated by 1,2-diacylglycerol and is present in high
centration in vascular smooth muscle (Kariya
Takai, 1987). PKC particip laxation. Another protein kinase family, PKC is accorded by 1,2-diacylglycerol and is present in high contraction in vascular smooth muscle (Kariya a Takai, 1987). PKC participates in the signal transduction process involv Takai, 1987). PKC participates in the signal transduction process involved in excitation-contraction of pulmonary vascular smooth muscles, presumably via phos-

NARY VASCULAR TONE 113
phorylation of substrates involved in the contractile MARY VASCULAR TONE
phorylation of substrates involved in the contractile
process. Activation of PKC constricts isolated rat and
human pulmonary artery rings (Orton et al., 1990; 113

phorylation of substrates involved in the contractile

process. Activation of PKC constricts isolated rat and

human pulmonary artery rings (Orton et al., 1990;

Savineau et al., 1991), and increases pulmonary perfuphorylation of substrates involved in the contractiprocess. Activation of PKC constricts isolated rat and human pulmonary artery rings (Orton et al., 1993), and increases pulmonary perfusion pressure in perfused pulmonary phorylation of substrates involved in the contractile
process. Activation of PKC constricts isolated rat and
human pulmonary artery rings (Orton et al., 1990;
Savineau et al., 1991), and increases pulmonary perfu-
sion pre process. Activation of PKC constricts isolated rat and
human pulmonary artery rings (Orton et al., 1990)
Savineau et al., 1991), and increases pulmonary perfu-
sion pressure in perfused pulmonary vascular beds of
rats (Ort human pulmonary artery rings (Orton et al., 1990;
Savineau et al., 1991), and increases pulmonary perfu-
sion pressure in perfused pulmonary vascular beds of
rats (Orton et al., 1990; Michael et al., 1993). PKC acti-
vatio Bavilleau et al., 1991), and increases pullholary perfusion pressure in perfused pullmonary vascular beds of rats (Orton et al., 1990; Michael et al., 1993). PKC activation also increases albumin permeability in bovine pul rats (Orton et al., 1990; Michael et al., 1993). PKC activation also increases albumin permeability in bovine
pulmonary vascular endothelial cell monolayers (Lynch
et al., 1990) and inhibits isoproterenol-elicited cAMP
pro vation also increases albumin permeability in bovine
pulmonary vascular endothelial cell monolayers (Lynch
et al., 1990) and inhibits isoproterenol-elicited cAMP
production (Newman et al., 1989). All of these factors
promo pulmonary vascular endothelial cell monolayers (Lynch
et al., 1990) and inhibits isoproterenol-elicited cAMP
production (Newman et al., 1989). All of these factors
promote the formation of pulmonary edema. Indeed,
PKC acti et al., 1990) and inhibits isoproterenol-elicited cAMP
production (Newman et al., 1989). All of these factors
promote the formation of pulmonary edema. Indeed,
PKC activators have been reported to cause pulmonary
edema in production (Newman et al., 1989). All of these factors
promote the formation of pulmonary edema. Indeed,
PKC activators have been reported to cause pulmonary
edema in rats and guinea pigs (Johnson, 1988; Perry and
Tavlor, FRC activators have been
edema in rats and guine
Taylor, 1988).
D. Calcium Channels
Changes in intracelly

vylor, 1988).

Calcium Channels

Changes in intracellular Ca²⁺ concentration $[Ca^{2+}]$,

e critical in smooth muscle contraction or relaxation D. Calcium Channels

Changes in intracellular Ca^{2+} concentration $[Ca^{2+}]$ _i

are critical in smooth muscle contraction or relaxation

and the initiation of other cellular responses. The regu-D. Calcium Channels
Changes in intracellular Ca^{2+} concentration $[Ca^{2+}]$ _i
are critical in smooth muscle contraction or relaxation
and the initiation of other cellular responses. The regu-
lation of $[Ca^{2+}]$, involves D. Calcium Channels

Changes in intracellular Ca^{2+} concentration $[Ca^{2+}]$ _i

are critical in smooth muscle contraction or relaxation

and the initiation of other cellular responses. The regu-

lation of $[Ca^{2+}]$ _i in Changes in intracellular Ca^{2+} concentration $[Ca^{2+}]$;
are critical in smooth muscle contraction or relaxation
and the initiation of other cellular responses. The regu-
lation of $[Ca^{2+}]$; involves a complex interaction are critical in smooth muscle contraction or relaxatio
and the initiation of other cellular responses. The regulation of $[Ca^{2+}]$, involves a complex interaction betwee
 Ca^{2+} entry and extrusion across the plasmalemma a and the initiation of other cellular responses. The regulation of $[Ca^{2+}]$; involves a complex interaction between Ca^{2+} entry and extrusion across the plasmalemma and Ca^{2+} release and re-uptake from the sarcoplasmic lation of $[Ca^{2+}]$, involves a complex interaction between Ca^{2+} entry and extrusion across the plasmalemma and Ca^{2+} release and re-uptake from the sarcoplasmic reticulum. This Ca^{2+} movement is controlled mainly b Ca^{2+} entry and extrusion across the plasmalen Ca^{2+} release and re-uptake from the sarcoplasm
ulum. This Ca^{2+} movement is controlled mainly
channels. Two major classes of Ca^{2+} channels
pressed in vascular smoot Ca^{2+} release and re-uptake from the sarcoplasmic retic-
ulum. This Ca^{2+} movement is controlled mainly by Ca^{2+}
channels. Two major classes of Ca^{2+} channels are ex-
pressed in vascular smooth muscle cells—voltag ulum. This Ca²⁺ movement is controlled mainly by Ca²⁺
channels. Two major classes of Ca²⁺ channels are ex-
pressed in vascular smooth muscle cells—voltage-depen-
dent Ca²⁺ channels on the plasmalemma and intracelchannels. Two major classes of Ca^{2+} channels are expressed in vascular smooth muscle cells—voltage-dependent Ca^{2+} channels on the plasmalemma and intracel-
lular Ca^{2+} release channels on the endoplasmic reticulum pressed in vascular smooth muscle cells—voltage-dependent Ca^{2+} channels on the plasmalemma and intracel-
lular Ca^{2+} release channels on the endoplasmic
reticulum (Marks, 1992). There are several types of volt-
age-d dent Ca^{2+} channels on the plasmalemma and intracel-
lular Ca^{2+} release channels on the endoplasmic
reticulum (Marks, 1992). There are several types of volt-
age-dependent Ca^{2+} channels, including L-type, T-type,
 lular Ca^{2+} release channels on the endoplasmi
reticulum (Marks, 1992). There are several types of volt
age-dependent Ca^{2+} channels, including L-type, T-type
N-type and P-type, which differ in structure, function
and reticulum (Marks, 1992). There are several types of volt
age-dependent Ca²⁺ channels, including L-type, T-type
N-type and P-type, which differ in structure, function
and pharmacological properties (Tsien et al., 1991). age-dependent Ca²⁺ channels, including L-type, T-type,
N-type and P-type, which differ in structure, function,
and pharmacological properties (Tsien et al., 1991). Volt-
age-dependent Ca²⁺ channels on vascular smooth N-type and P-type, which differ in structure, function,
and pharmacological properties (Tsien et al., 1991). Volt-
age-dependent Ca²⁺ channels on vascular smooth mus-
cle cells are usually of the L-type, whereas the rel and pharmacological properties (Tsier age-dependent Ca^{2+} channels on vas
cle cells are usually of the L-type, whe
intracellular Ca^{2+} is controlled by IP
coplasmic reticulum (Marks, 1992).
There is little electrophys Exercise is also a variable on variable electrophysion in the release of tracellular Ca²⁺ is controlled by IP₃ receptors on sarplasmic reticulum (Marks, 1992). There is little electrophysiological data regarding the

cAMP-dependent protein kinase and cGMP-dependent causes Ca^{2+} influx into cultured pulmonary artery
protein kinase are involved in pulmonary vascular re-
mooth muscle cells of adult rats (Salvaterra and Gold-
laxation. cle cells are usually of the L-type, whereas the release of intracellular Ca^{2+} is controlled by IP_3 receptors on sar-
coplasmic reticulum (Marks, 1992).
There is little electrophysiological data regarding the
 Ca^{2+} intracellular Ca²⁺ is controlled by IP₃ receptors on sar-
coplasmic reticulum (Marks, 1992).
There is little electrophysiological data regarding the
Ca²⁺ channels or Ca²⁺-currents in pulmonary vascular
smooth musc coplasmic reticulum (Marks, 1992).

There is little electrophysiological data regarding t
 Ca^{2+} channels or Ca^{2+} -currents in pulmonary vascul

smooth muscle cells. Hypoxia reduces cell membra

potential, concomitant Ca^{2+} channels or Ca^{2+} -currents in pulmonary vascular
smooth muscle cells. Hypoxia reduces cell membrane
potential, concomitant with contraction in small pulmo-
nary artery rings of cats (Harder et al., 1985). It has smooth muscle cells. Hypoxia reduces cell membrane
potential, concomitant with contraction in small pulmo-
nary artery rings of cats (Harder et al., 1985). It has
been speculated that this is caused by a Ca^{2+} -dependent potential, concomitant with contraction in small pulmo-
nary artery rings of cats (Harder et al., 1985). It has
been speculated that this is caused by a Ca^{2+} -dependent
action potential (Harder et al., 1985). Evidence s hypoxia inhibits K^+ channel activity (both voltage-gated nary artery rings of cats (Harder et al., 1985). It has
been speculated that this is caused by a Ca^{2+} -dependent
action potential (Harder et al., 1985). Evidence support-
ing this suggestion are the recent demonstration been speculated that this is caused by a Ca^{2+} -dependention potential (Harder et al., 1985). Evidence suppling this suggestion are the recent demonstration hypoxia inhibits K^+ channel activity (both voltage-gand Ca^{2 action potential (Harder et al., 1985). Evidence supporting this suggestion are the recent demonstration that hypoxia inhibits K^+ channel activity (both voltage-gated and Ca^{2+} -activated K^+ channels), induces depo ing this suggestion are the recent demonstration that
hypoxia inhibits K^+ channel activity (both voltage-gated
and Ca^{2+} -activated K^+ channels), induces depolariza-
tion of pulmonary artery smooth muscle cells—but hypoxia inhibits K^+ channel activity (both voltage-gated
and Ca^{2+} -activated K^+ channels), induces depolariza-
tion of pulmonary artery smooth muscle cells—but not
renal or mesenteric artery smooth muscle cells (P and Ca^{2+} -activated K^+ channels), induces depolarization of pulmonary artery smooth muscle cells—but not renal or mesenteric artery smooth muscle cells (Post et al., 1992; Yuan et al., 1993b; Cornfield et al., 1994) tion of pulmonary artery smooth muscle cells—but no
renal or mesenteric artery smooth muscle cells (Post ϵ
al., 1992; Yuan et al., 1993b; Cornfield et al., 1994)—an
causes Ca^{2+} influx into cultured pulmonary arter
s renal or mesenteric artery smooth muscle cells (Post et al., 1992; Yuan et al., 1993b; Cornfield et al., 1994)—and causes Ca^{2+} influx into cultured pulmonary artery smooth muscle cells of adult rats (Salvaterra and Gol an, 1992; I uan et an, 19930; Cornnel et an, 1994)—and
causes Ca^{2+} influx into cultured pulmonary artery
smooth muscle cells of adult rats (Salvaterra and Gold-
man, 1993) and fetal lambs (Cornfield et al., 1994).
Thus smooth muscle cells of adult rats (Salvaterra and Goldman, 1993) and fetal lambs (Cornfield et al., 1994).
Thus, it is possible that hypoxia inhibits K^+ channels,
resulting in membrane depolarization of pulmonary
smoot man, 1993) and fetal lambs (Corniference and $(1, 1994)$)
Thus, it is possible that hypoxia inhibits K^+ channels
resulting in membrane depolarization of pulmonary
smooth muscle cells, leading to the opening of Ca^{2+}
 traction.

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PHARM
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PHARMACOLOGICAL REVIEWS

BARNES AND LIU
Functional studies also suggest that Ca^{2+} channels tenance of basal pulmonary vascular tone (Hasunuma et
are important in the regulation of pulmonary vascular al., 1991b). In human small pulmonary arteri 114

Functional studies also suggest that Ca^{2+} channels

are important in the regulation of pulmonary vascular

tone. Dihydropyridine Ca^{2+} antagonists inhibit HPV in 114

Functional studies also suggest that Ca^{2+} channels tens

are important in the regulation of pulmonary vascular al.,

tone. Dihydropyridine Ca^{2+} antagonists inhibit HPV in chan

animals in situ (McMurtry et al., Functional studies also suggest that Ca^{2+} channels
are important in the regulation of pulmonary vascular
tone. Dihydropyridine Ca^{2+} antagonists inhibit HPV in
animals in situ (McMurtry et al., 1976), in vivo (Tucker Functional studies also suggest that Ca^{2+} channels
are important in the regulation of pulmonary vascular
tone. Dihydropyridine Ca^{2+} antagonists inhibit HPV in
animals in situ (McMurtry et al., 1976), in vivo (Tucker are important in the regulation of pulmonary vascular
tone. Dihydropyridine Ca^{2+} antagonists inhibit HPV in
animals in situ (McMurtry et al., 1976), in vivo (Tucker
et al., 1976a; Young et al., 1983), and in human subj animals in situ (McMurtry et al., 1976), in vivo (Tucker
et al., 1976a; Young et al., 1983), and in human subjects
(Simonneau et al., 1981; Burghuber, 1987). BAY K 8644,
a dihydropyridine Ca^{2+} agonist, has no effect on animals in situ (McMurtry et al., 1976), in vivo (Tucker
et al., 1976a; Young et al., 1983), and in human subjects
(Simonneau et al., 1981; Burghuber, 1987). BAY K 8644,
a dihydropyridine Ca²⁺ agonist, has no effect on b et al., 1976a; Young et al., 1983), and in human subjects
(Simonneau et al., 1981; Burghuber, 1987). BAY K 8644,
a dihydropyridine Ca²⁺ agonist, has no effect on basal
pulmonary perfusion pressure but markedly enhances
h (Simonneau et al., 1981; Burghuber, 1987). BAY K 86
a dihydropyridine Ca²⁺ agonist, has no effect on ba
pulmonary perfusion pressure but markedly enhan
hypoxic pulmonary vasoconstriction (McMurtry, 198
Ca²⁺ antagonist a dihydropyridine Ca^{2+} agonist, has no effect on basal
pulmonary perfusion pressure but markedly enhances
hypoxic pulmonary vasoconstriction (McMurtry, 1985).
 Ca^{2+} antagonists also inhibit, and BAY K 8644 potenti-
a pulmonary perfusion pressure but markedly enhan
hypoxic pulmonary vasoconstriction (McMurtry, 193
Ca²⁺ antagonists also inhibit, and BAY K 8644 pote
ates, the constrictor response to A-II or PGF_{2*a*}. Howe
the effect o hypoxic pulmonary vasoconstriction (McMurtry, 1985)
Ca²⁺ antagonists also inhibit, and BAY K 8644 potent
ates, the constrictor response to A-II or PGF_{2a}. Howeve
the effect on HPV is much greater than on A-II contra
ti Ca^{2+} antagonists also inhibit, and BAY K 8644 potentiates, the constrictor response to A-II or $PGF_{2\alpha}$. However, the effect on HPV is much greater than on A-II contraction, suggesting that HPV is more dependent on ex *E. Potassium Channels* much greater than on A-II contraction, suggesting that HPV is more dependent on extracellular Ca²⁺ (McMurtry et al., 1976; McMurtry, 1985).
 E. Potassium Channels Membrane depolarization and hyp

cellular Ca²⁺ (McMurtry et al., 1976; McMurtry, 1985).
 E. Potassium Channels

Membrane depolarization and hyperpolarization,

through inhibition and activation of K^+ channels, re-

spectively, are important mechan through inhibition and activation of K^+ channels, re-E. Polassium Channels

Membrane depolarization and hyperpolarization

through inhibition and activation of K^+ channels,

spectively, are important mechanisms regulation

smooth muscle contraction and relaxation. The de Membrane depolarization and hyperpolarization,
through inhibition and activation of K^+ channels, re-
spectively, are important mechanisms regulating $\frac{1}{2}$
smooth muscle contraction and relaxation. The develop-
ment through inhibition and activation of K^+ channels, respectively, are important mechanisms regulating smooth muscle contraction and relaxation. The development of selective K^+ channel openers has facilitated investiga spectively, are important mechanisms regulating
smooth muscle contraction and relaxation. The develop-
ment of selective K^+ channel openers has facilitated
investigation into the role of K^+ channels in the control
o smooth muscle contraction and relaxation. The development of selective K^+ channel openers has facilitated
investigation into the role of K^+ channels in the control
of pulmonary vascular tone and in pulmonary vascula investigation into the role of K^+ channels in the control
of pulmonary vascular tone and in pulmonary vascular
physiology. Several types of K^+ channels have been
identified and cloned (Pongs, 1992; Quast, 1993). Mos of pulmonary vascular tone and in pulmonary vascular
physiology. Several types of K^+ channels have been
identified and cloned (Pongs, 1992; Quast, 1993). Most of
these channels are present in vascular smooth muscle
cel identified and cloned (Pongs, 1992; Quast, 1993). Most of these channels are present in vascular smooth muscle cells (Kajioka et al., 1991). K^+ channels described on pulmonary vascular smooth muscles include voltage-ga identified and cloned (Pongs, 1992; Quast, 1993). Mo
these channels are present in vascular smooth mu
cells (Kajioka et al., 1991). K⁺ channels described
pulmonary vascular smooth muscles include volt
gated K⁺ channel these channels are present in vascular smooth muscle
cells (Kajioka et al., 1991). K⁺ channels described on
pulmonary vascular smooth muscles include voltage-
gated K⁺ channels (Yuan et al., 1993a, b), Ca²⁺-acti-
va cells (Kajioka et al., 1991). K⁺ channels described on
pulmonary vascular smooth muscles include voltage-
gated K⁺ channels (Yuan et al., 1993a, b), Ca²⁺-acti-
vated K⁺ channels (Lee et al., 1991b; Robertson et al punnonary vascular smooth muscles include voltage-
gated K^+ channels (Yuan et al., 1993a, b), Ca²⁺-acti-
vated K^+ channels (Lee et al., 1991b; Robertson et al.,
1992), including large conductance Ca²⁺-activated vated K⁺ channels (Lee et al., 1991b; Robertson et 1992), including large conductance Ca^{2+} -activated channels (Kirber et al., 1992), delayed rectifier chan (Okabe et al., 1987; Smirmov et al., 1994) and *l* sensitive 92), including large conductance Ca^{2+} -activated K⁺
annels (Kirber et al., 1992), delayed rectifier channels
kabe et al., 1987; Smirmov et al., 1994) and ATP-
nsitive K⁺ channels (Clapp and Gurney, 1992).
Activation

channels (Kirber et al., 1992), delayed rectifier channels

(Okabe et al., 1987; Smirmov et al., 1994) and ATP-

sensitive K⁺ channels (Clapp and Gurney, 1992).

Activation of K_{ATP} channels relaxes precontracted

pulm (Okabe et al., 1987; Smirmov et al., 1994) and ATP-
sensitive K⁺ channels (Clapp and Gurney, 1992).
Activation of K_{ATP} channels relaxes precontracted 1
pulmonary vessel rings in vitro (Clapp et al., 1993;
Savineau and sensitive K⁺ channels (Clapp and Gurney, 1992).
Activation of K_{ATP} channels relaxes precontracted
pulmonary vessel rings in vitro (Clapp et al., 1993;
Savineau and Marthan, 1993), pulmonary vascular beds
in situ (Hoo Activation of K_{ATP} channels relaxes precontracted
pulmonary vessel rings in vitro (Clapp et al., 1993;
Savineau and Marthan, 1993), pulmonary vascular beds
in situ (Hood et al., 1991a, b), and pulmonary vascular
beds u pulmonary vessel rings in vitro (Clapp et al., 1993; Savineau and Marthan, 1993), pulmonary vascular beds in situ (Hood et al., 1991a, b), and pulmonary vascular beds under basal conditions in vivo (Minkes et al., 1991; Ch Savineau and Marthan, 1993), pulmonary vascular beds
in situ (Hood et al., 1991a, b), and pulmonary vascular
beds under basal conditions in vivo (Minkes et al., 1991;
Chang et al., 1992). K_{ATP} channel activation also r in situ (Hood et al., 1991a, b), and pulmonary vascular
beds under basal conditions in vivo (Minkes et al., 1991;
Chang et al., 1992). K_{ATP} channel activation also re-
verses HPV, causes pulmonary vascular hyporeactivity beds under basal conditions in vivo (Minkes et al., 1991;
Chang et al., 1992). K_{ATP} channel activation also re-
verses HPV, causes pulmonary vascular hyporeactivity
to other vasoconstrictors (Savineau and Marthan, 1993), Chang et al., 1992). K_{ATP} channel activation also reverses HPV, causes pulmonary vascular hyporeactivity to other vasoconstrictors (Savineau and Marthan, 1993), and mediates pulmonary vasodilatory response to severses HPV, causes pulmonary vascular hyporeactivi
to other vasoconstrictors (Savineau and Marthan, 1993
and mediates pulmonary vasodilatory response to s
vere hypoxia (Wiener et al., 1991). It is reported th
chronic hypox to other vasoconstrictors (Savineau and Marthan, 1993
and mediates pulmonary vasodilatory response to severe hypoxia (Wiener et al., 1991). It is reported the
chronic hypoxia for 72 h augments K_{ATP} channel med
ated rel and mediates pulmonary vasodilatory response to severe hypoxia (Wiener et al., 1991). It is reported that chronic hypoxia for 72 h augments K_{ATP} channel mediated relaxation in the rat pulmonary vascular bed (Rodman, 19 vere hypoxia (Wiener et al., 1991). It is reported that vascular beds of patients with PPH (Ihbar et al., 1993).

chronic hypoxia for 72 h augments K_{ATP} channel medi-

ated relaxation in the rat pulmonary vascular bed a partial depolarization (Smirnov et al., 1994). Both ated relaxation in the rat pulmonary vascular bed (Rodman, 1992). Smooth muscle cells isolated from small lumonary arteries of rats exposed to chronic hypoxia zin show a reduced resting membrane potential, suggesting 1984 man, 1992). Smooth muscle cells isolated from small M
pulmonary arteries of rats exposed to chronic hypoxia zine
show a reduced resting membrane potential, suggesting 198
a partial depolarization (Smirnov et al., 1994). B pulmonary arteries of rats exposed to chromonour show a reduced resting membrane potential a partial depolarization (Smirnov et al., 1994).
delayed rectifier and K^+_{ATP} channels are this depolarization (Smirnov et al., show a reduced resting memorane potential, suggesting
a partial depolarization (Smirnov et al., 1994). Both
delayed rectifier and K^+_{ATP} channels are involved in
this depolarization (Smirnov et al., 1994).
Voltage-gate

delayed rectifier and K^{+} _{ATP} channels are involved in this depolarization (Smirnov et al., 1994).
Voltage-gated K^{+} channel activity on cultured pulmotary artery smooth muscle cells is inhibited by hypoxia⁷ and this depolarization (Smirnov et al., 1994). d
Voltage-gated K^+ channel activity on cultured pulmo-
nary artery smooth muscle cells is inhibited by hypoxia T
and has been implicated in hypoxic contraction (Yuan et dal., Voltage-gated K⁺ channel activity on cultured pulm
nary artery smooth muscle cells is inhibited by hypox
and has been implicated in hypoxic contraction (Yuan
al., 1993b) or HPV (Post et al., 1992). Voltage-gated Ca^{2+}

ND LIU
tenance of basal pulmonary vascular tone (Hasunuma et
al., 1991b). In human small pulmonary arteries, K_{ATP} ND LIU
tenance of basal pulmonary vascular tone (Hasunuma et
al., 1991b). In human small pulmonary arteries, K_{ATP}
channels mediate the dilator response to K⁺ channel ND LIU
tenance of basal pulmonary vascular tone (Hasunuma et
al., 1991b). In human small pulmonary arteries, K_{ATP}
channels mediate the dilator response to K⁺ channel
openers, such as levacromakalim, whereas the large c tenance of basal pulmonary vascular tone (Hasunuma et al., 1991b). In human small pulmonary arteries, K_{ATF}
channels mediate the dilator response to K^+ channel
openers, such as levacromakalim, whereas the large con-
 denance of basal pullifolially vascular tone (riasumula et al., 1991b). In human small pulmonary arteries, K_{ATP} channels mediate the dilator response to K^+ channel openers, such as levacromakalim, whereas the large and the relaxation response to K^+ channels mediate the dilator response to K^+ channel openers, such as levacromakalim, whereas the large conductance Ca^{2+} -activated K^+ channel that is blocked by charybdotoxin i ductance Ca^{2+} -activated K⁺ channel that is blocked by charybdotoxin is involved in the relaxation response to nitroprusside (Crawley et al., 1992b). Vascular endothelial cells also contain various K⁺ channels (Reve ductance Ca^{2+} -activated K⁺ channel that is blocked by
charybdotoxin is involved in the relaxation response to
nitroprusside (Crawley et al., 1992b). Vascular endothe-
lial cells also contain various K⁺ channels (Re charybdotoxin is involved in the relaxation response to
nitroprusside (Crawley et al., 1992b). Vascular endothe-
lial cells also contain various K^+ channels (Revest and
Abbott, 1992). Ca²⁺-activated K^+ channels ar mitroprusside (Crawley et al., 1992b). Vascular endothe-
lial cells also contain various K^+ channels (Revest and
Abbott, 1992). Ca^{2+} -activated K^+ channels are involved
in the shear stress-induced release of NO in has not been demonstrated K^+ channels (Revest Abbott, 1992). Ca^{2+} -activated K^+ channels are invision the shear stress-induced release of NO in system arteries (Cooke et al., 1991), although this mecha has not bee arteries (Cooke et al., 1991), although this mechanism
has not been demonstrated in pulmonary vessels.
VII. Pulmonary Vasodilators as Therapy has not been demonstrated in pulmonary vessels.

 $E. Potassium Channels$

Membrane depolarization and hyperpolarization, The rationale for treating pulmonary hypertension

through inhibition and activation of K^+ channels, re-

spectively, are important mechanisms regulating plicati VII. Pulmonary Vasodilators as Therapy
General Principles
The rationale for treating pulmonary hypertension
th vasodilators was stimulated by the successful ap-VII. Pulmonary Vasodilators as Therapy
A. General Principles
The rationale for treating pulmonary hypertension
with vasodilators was stimulated by the successful ap-
plication of vasodilator therapy to systemic hypertension, and virtually every vasodilator agent has been Fractionally and virtually every vasodilator agent has been investigated. There has been a search for drugs that investigated. There has been a search for drugs that The rationale for treating pulmonary hypertension
with vasodilators was stimulated by the successful ap-
plication of vasodilator therapy to systemic hyperten-
sion, and virtually every vasodilator agent has been
investiga with vasodilators was stimulated by the successful application of vasodilator therapy to systemic hypertension, and virtually every vasodilator agent has been investigated. There has been a search for drugs that vasodilate plication of vasodilator therapy to systemic hypertension, and virtually every vasodilator agent has been investigated. There has been a search for drugs that vasodilate the pulmonary circulation without lowering the syste sion, and virtually every vasodilator agent has been
investigated. There has been a search for drugs that
vasodilate the pulmonary circulation without lowering
the systemic blood pressure and cardiac output to an
extent th vasodilate the pulmonary circulation without lowering
the systemic blood pressure and cardiac output to an
extent that causes side effects. Unfortunately, most pul-
monary vasodilators have been unsuccessful, either be-
ca vasodilate the pulmonary circulation without lowering
the systemic blood pressure and cardiac output to an
extent that causes side effects. Unfortunately, most pul-
monary vasodilators have been unsuccessful, either be-
c the systemic blood pressure and cardiac output to a
extent that causes side effects. Unfortunately, most pu
monary vasodilators have been unsuccessful, either b
cause of therapeutic failure or intolerable side effects.
few extent that causes side effects. Unfortunately, most pulmonary vasodilators have been unsuccessful, either because of therapeutic failure or intolerable side effects. A few drugs, such as hydralazine, PGI_2 , and Ca^{2+} monary vasodilators have been unsuccessful, either be-
cause of therapeutic failure or intolerable side effects. A
few drugs, such as hydralazine, PGI_2 , and Ca^{2+} -channel
blockers, have been the most promising vasodil cause of therapeutic failure or intolerable side effects.
few drugs, such as hydralazine, PGI_2 , and Ca^{2+} -channe
blockers, have been the most promising vasodilated
drugs, with effective reduction of PPA with relative blockers, have been the most promising vasodilator drugs, with effective reduction of PPA with relatively little reduction in systemic arterial pressure or resistance and an increase in cardiac output in some patients (Ric blockers, have been the most promising vasodilator
drugs, with effective reduction of PPA with relatively
little reduction in systemic arterial pressure or resis-
tance and an increase in cardiac output in some patients
(R drugs, with effective reduction of PPA with relatively
little reduction in systemic arterial pressure or resis-
tance and an increase in cardiac output in some patients
(Rich et al., 1983a). Additionally, vasodilator thera little reduction in systemic arterial pressure or resistance and an increase in cardiac output in some patients (Rich et al., 1983a). Additionally, vasodilator therapy with these agents may improve survival over 5 years an tance and an increase in cardiac output in some patients (Rich et al., 1983a). Additionally, vasodilator therapy with these agents may improve survival over 5 years and improve the quality of life (Beltran Gamez et al., 19 (Rich et al., 1983a). Additionally, vasodilator therapy
with these agents may improve survival over 5 years
and improve the quality of life (Beltran Gamez et al.,
1988; Rich et al., 1992). However, these drugs are not
sele with these agents may improve survival over 5 years
and improve the quality of life (Beltran Gamez et al.,
1988; Rich et al., 1992). However, these drugs are not
selective for the pulmonary circulation. At present, the
onl and improve the quality of life (Beltran Gamez et a 1988; Rich et al., 1992). However, these drugs are a selective for the pulmonary circulation. At present, to only available selective pulmonary vasodilator is of gen. Re 1988; Rich et al., 1992). However, these drugs are not selective for the pulmonary circulation. At present, the only available selective pulmonary vasodilator is oxygen. Recently, acute infusion of adenosine and inhalation A. *General Principles*
The rationale for treating pulmonary hypertension with vasodilators was stimulated by the successful ap-
plication of vasodilator therapy to systemic hypertension, and virtually every vasodilator a only available selective pulmonary vasodilator is oxy-
gen. Recently, acute infusion of adenosine and inhala-
tion of NO gas have been shown to reduce pulmonary
vascular resistance, without obvious effects on SVR and
cardi gen. Recently, acute infusion of adenosine and inhalation of NO gas have been shown to reduce pulmonary vascular resistance, without obvious effects on SVR and cardiac output (Morgan et al., 1991b; Pepke-Zaba et al., 1991) tion of NO gas have been shown to reduce pulmonary
vascular resistance, without obvious effects on SVR and
cardiac output (Morgan et al., 1991b; Pepke-Zaba et al.,
1991). Additionally, adenosine has been shown to be
addit vascular resistance, without obvious effects on SVR and
cardiac output (Morgan et al., 1991b; Pepke-Zaba et al.,
1991). Additionally, adenosine has been shown to be
additive to Ca^{2+} -channel blockers in dilating pulmona additive to Ca²⁺-channel blockers in dilating pulmonary

Most clinical studies on the effectiveness of hydradazine
Most clinical studies on the effectiveness of hydra
ne in pulmonary hypertension were conducted in vascular beds of patients with FFH (Inbar et al., 1993).

B. Hydralazine

Most clinical studies on the effectiveness of hydrala-

zine in pulmonary hypertension were conducted in the

1980s with small numbers of subjects a 1980s B. Hydralazine

1980s clinical studies on the effectiveness of hydrala-

1980s with small numbers of subjects and provided con-

1980s with small numbers of subjects and provided con-

flicting results. Rubin and Pet Fluit Most clinical studies on the effectiveness of hydrala-
zine in pulmonary hypertension were conducted in the
1980s with small numbers of subjects and provided con-
flicting results. Rubin and Peter (1980) reported tha Most clinical studies on the effectiveness of hydralazine in pulmonary hypertension were conducted in the 1980s with small numbers of subjects and provided conflicting results. Rubin and Peter (1980) reported that oral hyd zine in pulmonary hypertension were conducted in t
1980s with small numbers of subjects and provided co
flicting results. Rubin and Peter (1980) reported th
oral hydralazine effectively reduced PVR at rest as
during exerci 1980s with small numbers of subjects and provided conflicting results. Rubin and Peter (1980) reported that oral hydralazine effectively reduced PVR at rest and during exercise in four patients with PPH. The reduction in P flicting results. Rubin and Peter (1980) reported that
oral hydralazine effectively reduced PVR at rest and
during exercise in four patients with PPH. The reduc-
tion in PRV was sustained with chronic oral therapy.
They al oral hydralazine effectively reduced PVR at rest and
uring exercise in four patients with PPH. The reduction in PRV was sustained with chronic oral therapy
They also showed a reduction in right ventricular end
diastolic pr during exercise in four patients with PPH. The reduction in PRV was sustained with chronic oral therapy.
They also showed a reduction in right ventricular end-
diastolic pressure and improved right ventricular func-
tion (tion in PRV was sustained with chronic oral therapy.
They also showed a reduction in right ventricular end-
diastolic pressure and improved right ventricular func-
tion (Rubin et al., 1982a). However, others failed to
conf

REGULATION OF PULMON

al., 1983b; Fisher et al., 1984). The reason for this in-

consistency may relate to the severity of the disease or REGULATION OF PULMONA
showed deleterious effects (Packer et al., 1982; Rich et
al., 1983b; Fisher et al., 1984). The reason for this in-
consistency may relate to the severity of the disease or W
differences in individual showed deleterious effects (Packer et al., 1982; Rich et wo
al., 1983b; Fisher et al., 1984). The reason for this in-
consistency may relate to the severity of the disease or Wit
differences in individual responsiveness. i

al., 1983b; Fisher et al., 1984). The reason for this is
consistency may relate to the severity of the disease
differences in individual responsiveness.
Lupi-Herrera et al. found that their 12 patients wi
PPH could be divi consistency may relate to the severity of the disease or Wiidfferences in individual responsiveness. The Lupi-Herrera et al. found that their 12 patients with bot PPH could be divided into responders and nonresponders (6 p differences in individual responsiveness.

Lupi-Herrera et al. found that their 12 patients wi

PPH could be divided into responders and nonre-

sponders (6 patients in each group). Responders h

lower pulmonary pressure a Lupi-Herrera et al. found that their 12 patients with
PPH could be divided into responders and nonre-
sponders (6 patients in each group). Responders had
lower pulmonary pressure and PVR, whereas nonre-
sponders had higher PPH could be divided into responders and nonre-
sponders (6 patients in each group). Responders had
lower pulmonary pressure and PVR, whereas nonre-
sponders had higher PPA and a higher PVR. Responders
showed a beneficial sponders (6 patients in each group). Responders hilower pulmonary pressure and PVR, whereas nonresponders had higher PPA and a higher PVR. Respondes both acutely and chronically, up to 8 months (Lup Herrera et al., 1982). lower pulmonary pres
sponders had higher Pr
showed a beneficial pul
both acutely and chro
Herrera et al., 1982).
Hydralazine was als sponders had inglief FFA and a higher FVK. Responders
showed a beneficial pulmonary hemodynamic responses,
both acutely and chronically, up to 8 months (Lupi-
Herrera et al., 1982).
Hydralazine was also used in patients wi

both acutely and chronically, up to 8 months (Lupi-
Herrera et al., 1982).
Hydralazine was also used in patients with hypoxic
pulmonary hypertension, with similarly controversial
results. Some reported that hydralazine was ab. Herrera et al., 1982). as

Hydralazine was also used in patients with hypoxic applinonary hypertension, with similarly controversial results. Some reported that hydralazine was beneficial, with reduction in PPA, improv Hydralazine was also used in patients with hypoxic
pulmonary hypertension, with similarly controversial
results. Some reported that hydralazine was beneficial,
with reduction in PPA, improved cardiac index, oxygen
transpor pulmonary hypertension, with similarly controversial results. Some reported that hydralazine was beneficial, with reduction in PPA, improved cardiac index, oxygen transport, alveolar ventilation, and exercise tolerance lef results. Some reported that hydralazine was beneficial,
with reduction in PPA, improved cardiac index, oxygen
transport, alveolar ventilation, and exercise tolerance
(Keller et al., 1984; Lupi-Herrera et al., 1985; Corrive with reduction in PPA, improved cardiac index, oxygen
transport, alveolar ventilation, and exercise tolerance
(Keller et al., 1984; Lupi-Herrera et al., 1985; Corriveau
et al., 1987). Other investigators found that hydrala (Keller et al., 1984; Lupi-Herrera et al., 1985; Corriveau
et al., 1987). Other investigators found that hydralazine
had no beneficial effects on these patients (Tuxen et al.,
1984; Cerda et al., 1985; Dal Nogare and Rubin et al., 1987). Other investigators found that hydralazine et al., 1987). Other investigators found that hydralazine with the obeneficial effects on these patients (Tuxen et al., et al., 1984; Cerda et al., 1985; Dal Nogare and Rubin, 1986). con Beltran Gamez et al. (1988) analyze had no beneficial effects on these patients (Tuxen et al., et 1984; Cerda et al., 1985; Dal Nogare and Rubin, 1986). Consider the Rubin Camez et al. (1988) analyzed the long-term ef-time fects of vasodilator therapy in 40 1984; Cerda et al., 1985; Dal Nogare and Rubin, 1986). c
Beltran Gamez et al. (1988) analyzed the long-term ef-
fects of vasodilator therapy in 40 patients with PPH who
received hydralazine or nifedipine and had been fol-Beltran Gamez et al. (1988) analyzed the long-term ef-
fects of vasodilator therapy in 40 patients with PPH who
received hydralazine or nifedipine and had been fol-
had lowed for an average of 50 ± 8 months. Twenty were fects of vasodilator therapy in 40 patients with PPH who
received hydralazine or nifedipine and had been fol-
lowed for an average of 50 ± 8 months. Twenty were
classified as responders and 20 as nonresponders. The
5-ye received hydralazine or nifedipine and had been fol-
lowed for an average of 50 ± 8 months. Twenty were (lassified as responders and 20 as nonresponders. The
5-year probability of survival was 86% and 45% for re-
sponde lowed for an average of 50 ± 8 months. Twenty were (R
classified as responders and 20 as nonresponders. The
5-year probability of survival was 86% and 45% for re-
sponders and nonresponders, respectively, although ca
th 5-year probability of survival was 86% and 45% for responders and nonresponders, respectively, although these two figures are not comparable, inasmuch as the two groups had different basal hemodynamic profiles. Howe these two figures are not comparable, inasmuch as the two groups had different basal hemodynamic profiles.
However, most of the responders (13 with nifedipine, 7 with hydralazine) showed a significant improvement in their these two figures are not comparable, inasmuch as the
two groups had different basal hemodynamic profiles.
However, most of the responders (13 with nifedipine, 7
with hydralazine) showed a significant improvement in
their two groups had different basal hemodynamic profiles. response to the responders (13 with nifedipine, 7 during hydralazine) showed a significant improvement in 1 their quality of life and maintained a good hemodynamic spres However, mos
with hydralaz
their quality of
response during
et al., 1988). *C. Calcium-Channel Blockers* sponse during the period of follow-up (Beltran Gamez t
al., 1988).
Calcium-Channel Blockers
Ca²⁺-channel blockers are the most widely used pul-
onary vasodilators. In a review of reports published c

et al., 1966).
C. Calcium-Channel Blockers
Ca²⁺-channel blockers are the most widely used pul-
monary vasodilators. In a review of reports published
between 1978 and 1985 of vasodilator therapy in the C. Calcium-Channel Blockers

Ca²⁺-channel blockers are the most widely used pul-

monary vasodilators. In a review of reports published di

between 1978 and 1985 of vasodilator therapy in the ou

treatment of PPH, 45 of monary vasodilators. In a review of reports published
between 1978 and 1985 of vasodilator therapy in the
treatment of PPH, 45 of the 117 reported patients were
treated with Ca^{2+} -channel blockers (Reeves et al., 1986). monary vasodilators. In a review of reports published detween 1978 and 1985 of vasodilator therapy in the observation of PPH, 45 of the 117 reported patients were titreated with Ca^{2+} -channel blockers (Reeves et al., 19 between 1976 and 1980 of vasourator dietapy in the otter
treatment of PPH, 45 of the 117 reported patients were tide
treated with Ca²⁺-channel blockers, including verapamil, dil-
stiazem, felodipine, nisoldipine, and bep treated with Ca^{2+} -channel blockers (Reeves et al., 1986).
Several Ca^{2+} -channel blockers, including verapamil, diltiazem, felodipine, nisoldipine, and bepridil have been
tested, although nifedipine was the most exten tiazem, felodipine, nisoldipine, and bepridil have been tested, although nifedipine was the most extensively evaluated. Nifedipine has been used in PPH (Rubin, 1985; Reeves et al., 1986), pulmonary hypertension secondary t tiazem, felodipine, nisoldipine, and bepridil have been
tested, although nifedipine was the most extensively
evaluated. Nifedipine has been used in PPH (Rubin,
1985; Reeves et al., 1986), pulmonary hypertension sec-
ondary tested, although nifedipine was the most extensively
evaluated. Nifedipine has been used in PPH (Rubin,
1985; Reeves et al., 1986), pulmonary hypertension sec-
ondary to COPD (Michael et al., 1985; Rubin et al.,
1986), sys evaluated. Nifedipine has been used in PPH (R
1985; Reeves et al., 1986), pulmonary hypertension
ondary to COPD (Michael et al., 1985; Rubin e
1986), systemic sclerosis (Ohar et al., 1985), inters
lung disease (Ohar et al. 1985; Reeves et al., 1986), pulmonary hypertension secondary to COPD (Michael et al., 1985; Rubin et al., 1986), systemic sclerosis (Ohar et al., 1985), interstitial lung disease (Ohar et al. 1985), chronic thromboembolism ondary to COPD (Michael et al., 1985; Rubin et a
1986), systemic sclerosis (Ohar et al., 1985), interstit
lung disease (Ohar et al. 1985), chronic thromboeml
lism (Galie et al., 1985), obliterative pulmonary vascu
disease lung disease (Ohar et al. 1985), chronic thromboembo-
lism (Galie et al., 1985), obliterative pulmonary vascular
disease (Packer et al., 1984), bronchopulmonary dyspla-
ment group after a follow-up period of 12 to 18 month The discusse (Onar et al. 1989), chronic thromodemotism (Galie et al., 1985), obliterative pulmonary vascular disease (Packer et al., 1984), bronchopulmonary dysplasia (Brownlee et al., 1988), and congenital heart disease nsm (Gane et al., 1980), obliterative pulmonary vascular
disease (Packer et al., 1984), bronchopulmonary dyspla-
sia (Brownlee et al., 1988), and congenital heart disease
(Wimmer at al., 1988). The majority of these report sia (Brownlee et al., 1988), and congenital heart disease (Ve
(Wimmer at al., 1988). The majority of these reports ies
obtained favorable results, with the exceptions of pa-
tients with chronic thromboembolic pulmonary hyp

showed deleterious effects (Packer et al., 1982; Rich et worsening or an equivocal pulmonary hemodynamic re-
al., 1983b; Fisher et al., 1984). The reason for this in- sponse was observed after nifedipine (Galie et al., 198 sponse was observed after nifedipine (Galie et al., 1985; vary vascular tone
worsening or an equivocal pulmonary hemodynamic re-
sponse was observed after nifedipine (Galie et al., 1985;
Wimmer et al., 1988). Acute administration of nifedip-VARY VASCULAR TONE

worsening or an equivocal pulmonary hemodynamic

sponse was observed after nifedipine (Galie et al., 19

Wimmer et al., 1988). Acute administration of nifed

ine, either orally or sublingually, (a) lowe worsening or an equivocal pulmonary hemodynamic response was observed after nifedipine (Galie et al., 1985; Wimmer et al., 1988). Acute administration of nifedipine, either orally or sublingually, *(a)* lowers PPA, PVR, or worsening or an equivocal pulmonary hemodynamic response was observed after nifedipine (Galie et al., 1985; Wimmer et al., 1988). Acute administration of nifedipine, either orally or sublingually, *(a)* lowers PPA, PVR, or sponse was observed after nifedipine (Galie et al., 1985;
Wimmer et al., 1988). Acute administration of nifedip-
ine, either orally or sublingually, (a) lowers PPA, PVR, or
both, (b) increases cardiac output, (c) improves Wimmer et al., 1988). Acute administration of nifedip-
ine, either orally or sublingually, (a) lowers PPA, PVR, or
both, (b) increases cardiac output, (c) improves right
ventricular function, and (d) improves exercise ine, either orally or sublingually, (α) lowers PPA, PVR, or
both, (b) increases cardiac output, (c) improves right
ventricular function, and (d) improves exercise tolerance
(Rubin, 1985; Michael et al., 1985; Ree both, (*b*) increases cardiac output, (*c*) improves right
ventricular function, and (*d*) improves exercise tolerance
(Rubin, 1985; Michael et al., 1985; Reeves et al., 1986).
Although nifedipine results in some deterior ventricular function, and (d) improves exercise tolerance
(Rubin, 1985; Michael et al., 1985; Reeves et al., 1986).
Although nifedipine results in some deterioration of V/Q
matching, PaO₂ is unchanged or slightly incre Although nifedipine results in some deterioration of V/Q matching, $PaO₂$ is unchanged or slightly increased or decreased. $O₂$ delivery is increased. Nifedipine also reduces systemic blood pressure, SVR, or b matching, $PaO₂$ is unchanged or slightly increased or matching, PaO₂ is unchanged or slightly increased or decreased. O₂ delivery is increased. Nifedipine also reduces systemic blood pressure, SVR, or both to a tolerable extent in the majority of patients. Nifedipine the duces systemic blood pressure, SVR, or both to a toler-
duces systemic blood pressure, SVR, or both to a toler-
apy is also effective in PPH. Rubin et al. (1983) first
reported favorable effects in 6 patients with PPH trea able extent in the majority of patients. Nifedipine therapy is also effective in PPH. Rubin et al. (1983) first reported favorable effects in 6 patients with PPH treated with oral nifedipine for 4 to 14 months. In two unco apy is also effective in PPH. Rubin et al. (1983) first
reported favorable effects in 6 patients with PPH treated
with oral nifedipine for 4 to 14 months. In two uncon-
trolled trials, a total of 21 patients with PPH were reported favorable effects in 6 patients with PPH treated
with oral nifedipine for 4 to 14 months. In two uncon-
trolled trials, a total of 21 patients with PPH were fol-
lowed for more than 1 year; there was a general imwith oral nifedipine for 4 to 14 months. In two uncontrolled trials, a total of 21 patients with PPH were followed for more than 1 year; there was a general improvement in pulmonary hemodynamics and symptoms without any in trolled trials, a total of 21 patients with PPH were followed for more than 1 year; there was a general im provement in pulmonary hemodynamics and symptom without any intolerable side effects in 14 patients (Richet al., 19 provement in pulmonary hemodynamics and symptoms
without any intolerable side effects in 14 patients (Rich
et al., 1985; Khossein et al., 1988). A recent large-scale,
controlled clinical trial showed that a sustained reduc whilout any molerable side effects in 14 patients (Kich
et al., 1985; Khossein et al., 1988). A recent large-scale,
controlled clinical trial showed that a sustained reduc-
tion in PPA and PVR and improvement of survival o controlled clinical tron in PPA and PVR
period of 5 years can
have a favorable in
(Rich et al., 1992).
There are concer. on in PPA and PVR and improvement of survival over a
riod of 5 years can be achieved in PPH patients who
we a favorable initial response to acute nifedipine
ich et al., 1992).
There are concerns about the side effects of

sponders and nonresponders, respectively, although case of severe pulmonary edema in a patient with PPH
these two figures are not comparable, inasmuch as the given nifedipine was reported (Batra et al., 1985), and
two gro with oral nifedipine for 4 to 14 months. In two uncon-
trolled trials, a total of 21 patients with PPH were fol-
lowed for more than 1 year; there was a general im-
provement in pulmonary hemodynamics and symptoms
without period of 5 years can be achieved in PPH patients who
have a favorable initial response to acute nifedipine
(Rich et al., 1992).
There are concerns about the side effects of Ca^{2+} -
channel blockers in the treatment of P have a favorable initial response to acute nifedipine

(Rich et al., 1992).

There are concerns about the side effects of Ca^{2+} -

channel blockers in the treatment of PPH. In 1985, a

case of severe pulmonary edema in a (Rich et al., 1992).
There are concerns about the side effects of Ca^{2+} -
channel blockers in the treatment of PPH. In 1985, a
case of severe pulmonary edema in a patient with PPH
given nifedipine was reported (Batra et channel blockers in the treatment of PPH. In 1985, a given nifedipine was reported (Batra et al., 1985), and sponse test should be carried out before starting longgiven nifedipine was reported (Batra et al., 1985), and recently, nifedipine was reported to contribute to the death of a 17-year-old patient with PPH (Partanen et al. 1993). Thus, appropriate assessment and an acute resp recently, nifedipine was reported to contribute to the death of a 17-year-old patient with PPH (Partanen et al., 1993). Thus, appropriate assessment and an acute response test should be carried out before starting long-te death of a 17-year-old patient with PPH (Partanen et al., 1993). Thus, appropriate assessment and an acute response test should be carried out before starting long-
term, high-dose Ca^{2+} -blocker therapy. Because Ca^{2+} 1993). Thus, appropriate assessment and an acute response test should be carried out before starting long-
term, high-dose Ca^{2+} -blocker therapy. Because Ca^{2+} -
channel blockers inhibit HPV very effectively in both
an sponse test should be carried out before starting long-
term, high-dose Ca^{2+} -blocker therapy. Because Ca^{2+} -
channel blockers inhibit HPV very effectively in both
animals and human subjects (Kennedy et al., 1984;
Mic term, high-dose Ca^{2+} -blocker therapy. Because Ca^{2+} channel blockers inhibit HPV very effectively in both animals and human subjects (Kennedy et al., 1984). Michael et al., 1984), nifedipine is also widely used in the channel blockers inhibit HPV very effectively in both
animals and human subjects (Kennedy et al., 1984;
Michael et al., 1984), nifedipine is also widely used in
the treatment of hypoxic pulmonary hypertension. Nife-
dipine animals and human subjects (Kennedy et al., 1984;
Michael et al., 1984), nifedipine is also widely used in
the treatment of hypoxic pulmonary hypertension. Nife-
dipine (a) lowers PPA, PVR, or both, (b) increases cardiac
o Michael et al., 1984), nifedipine is also widely used in
the treatment of hypoxic pulmonary hypertension. Nife-
dipine (a) lowers PPA, PVR, or both, (b) increases cardiac
output, and (c) improves exercise tolerance in the treatment of hypoxic pulmonary hypertension. Nife-
dipine (a) lowers PPA, PVR, or both, (b) increases cardiac
output, and (c) improves exercise tolerance in these pa-
tients (Gassener et al., 1986; Morley et al. dipine (a) lowers PPA, PVR, or both, (b) increases cardiac output, and (c) improves exercise tolerance in these patients (Gassener et al., 1986; Morley et al., 1987;
Gassener et al., 1990). Nifedipine lowers PVR to a grea butput, and (c) improves exercise tolerance in these pa-
tients (Gassener et al., 1986; Morley et al., 1987;
Gassener et al., 1990). Nifedipine lowers PVR to a
greater extent than SVR and increased O_2 delivery in
patie Gassener et al., 1990). Nifedipine lowers PVR to a greater extent than SVR and increased O_2 delivery in patients with COPD (Gassener et al., 1986; Saadjian et al., 1987). Pa O_2 is reduced (Saadjian et al., 1987) or u patients with COPD (Gassener et al., 1986; Saadjian et al., 1987). Pa O_2 is reduced (Saadjian et al., 1987) or unchanged (Morley et al., 1987; Mookherjee et al., 1988) by nifedipine. However, in contrast to its acute be patients with COPD (Gassener et al., 1986; Saadjian et al., 1987) or
al., 1987). PaO₂ is reduced (Saadjian et al., 1987) or
unchanged (Morley et al., 1987; Mookherjee et al., 1988)
by nifedipine. However, in contrast to al., 1987). PaO₂ is reduced (Saadjian et al., 1987) or
unchanged (Morley et al., 1987; Mookherjee et al., 1988)
by nifedipine. However, in contrast to its acute benefi-
cial effects, nifedipine does not have long-term be unchanged (Morley et al., 1987; Mookherjee et al., 1988)
by nifedipine. However, in contrast to its acute benef
cial effects in these patients. Two large-scale, controlled tr
als showed no difference in either pulmonary he cial effects, nifedipine does not have long-term beneficial
effects in these patients. Two large-scale, controlled tri-
als showed no difference in either pulmonary hemody-
namics or survival rate in the long-term nifedipi effects in these patients. Two large-scale, controlled trials showed no difference in either pulmonary hemody
namics or survival rate in the long-term nifedipine treat
ment group after a follow-up period of 12 to 18 month
 als showed no difference in either pulmonary hemod
namics or survival rate in the long-term nifedipine tree
ment group after a follow-up period of 12 to 18 mont
(Vestri et al., 1988; Saadjian et al., 1988). Several stu
ies namics or survival rate in the long-term nifedipine treat-
ment group after a follow-up period of 12 to 18 months
(Vestri et al., 1988; Saadjian et al., 1988). Several stud-
ies have demonstrated that nifedipine causes a s ment group after a follow-up period of 12 to 18 months
(Vestri et al., 1988; Saadjian et al., 1988). Several stud-
ies have demonstrated that nifedipine causes a signifi-
cant reduction in both PPA and PRV when given acute cant reduction in both PPA and PRV when given acutely
but has no effect on pulmonary hemodynamics in the
same groups of patients when given as long-term treat-

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ment (Morley et al., 1987; Mookherjee et al., 1988; poor prognos

Gassner et al., 1990). Interestingly, a Chinese herbal indicated the BARNES

ment (Morley et al., 1987; Mookherjee et al., 1988;

Gassner et al., 1990). Interestingly, a Chinese herbal

remedy, ligustrazine, used to treat cardiovascular dis-BARNES
ment (Morley et al., 1987; Mookherjee et al., 1988;
Gassner et al., 1990). Interestingly, a Chinese herbal
remedy, ligustrazine, used to treat cardiovascular dis-
eases, relaxes human pulmonary vessels in vitro, pro ment (Morley et al., 1987; Mookherjee et al., 1988
Gassner et al., 1990). Interestingly, a Chinese herbe
remedy, ligustrazine, used to treat cardiovascular dis
eases, relaxes human pulmonary vessels in vitro, prob
ably by ment (Morley et al., 1987; Mookherjee et al., 1988;
Gassner et al., 1990). Interestingly, a Chinese herbal
remedy, ligustrazine, used to treat cardiovascular dis-
eases, relaxes human pulmonary vessels in vitro, prob-
ably remedy, ligustrazine, used to treat cardiovascular dis-

eases, relaxes human pulmonary vessels in vitro, prob-

ably by acting as a Ca^{2+} antagonist (Liu et al., 1990).
 D. Prostacyclin

PGI₂ is not only a potent v

ses, relaxes human pulmonary vessels in vitro, prob-
ly by acting as a Ca^{2+} antagonist (Liu et al., 1990). logi
Par
Prostacyclin 198
PGI₂ is not only a potent vasodilator but also an 203
tiplatelet aggregatory agent. ably by acting as a Ca^{2+} antagonist (Liu et al., 1990).

D. Prostacyclin

PGI₂ is not only a potent vasodilator but also an 2

antiplatelet aggregatory agent. PGI₂ has no selectivity 7

for pulmonary vessels. Early *F*. Prostacyclin

PGI₂ is not only a potent vasodilator but also an 20

antiplatelet aggregatory agent. PGI₂ has no selectivity T.

for pulmonary vessels. Early studies showed that acute W

infusion of PGI₂ into pu PGI_2 is not only a potent vasodilator but also an 203
antiplatelet aggregatory agent. PGI_2 has no selectivity The
for pulmonary vessels. Early studies showed that acute Wo
infusion of PGI_2 into pulmonary circulation antiplatelet aggregatory agent. PGI₂ has no selectivity
for pulmonary vessels. Early studies showed that acute
infusion of PGI₂ into pulmonary circulation through a
pulmonary artery catheter reduced PVR and SVR to a
s for pulmonary vessels. Early studies showed that acute
infusion of PGI_2 into pulmonary circulation through a
pulmonary artery catheter reduced PVR and SVR to a
similar extent, with a marked increase in cardiac output
(R pulmonary artery catheter reduced PVR and SVR to a
similar extent, with a marked increase in cardiac output
(Rubin et al., 1982b; Groves et al., 1985; Bush et al., 1
1985). The advantage of PGI_2 over other vasodilators similar extent, with a marked increase in cardiac output pectric (Rubin et al., 1982b; Groves et al., 1985; Bush et al., the 1985). The advantage of PGI_2 over other vasodilators is How its half-life of minutes, providin (Rubin et al., 1982b; Groves et al., 1985; Bush et al., th
1985). The advantage of PGI_2 over other vasodilators is Hits half-life of minutes, providing greater control over Tr
systemic effects. Clinical studies indicate 1985). The advantage of PGI_2 over other vasodilators is Ho
its half-life of minutes, providing greater control over Tri
systemic effects. Clinical studies indicate that it can
effectively reduce PVR with tolerable side systemic effects. Clinical studies indicate that it can
effectively reduce PVR with tolerable side effects (Rubin
et al., 1982b; Grove et al., 1985; Jones et al., 1987) and
that it is very effective in relieving pulmonary systemic effects. Clinical studies indicate that it can
effectively reduce PVR with tolerable side effects (Rubin
et al., 1982b; Grove et al., 1985; Jones et al., 1987) and
that it is very effective in relieving pulmonary effectively reduce PVR with tolerable side effects (Rubin
et al., 1982b; Grove et al., 1985; Jones et al., 1987) and
that it is very effective in relieving pulmonary hyperten-
sive crises in PPH (Scott et al., 1991). PGI₂ et al., 1982b; Grove et al., 1985; Jones et al., 1987) and
that it is very effective in relieving pulmonary hyperten-
sive crises in PPH (Scott et al., 1991). PGI₂ also im-
proves O_2 delivery in these patients (Jones that it is very effective in relieving pulmonary hypertensive crises in PPH (Scott et al., 1991). PGI₂ also improves O_2 delivery in these patients (Jones et al., 1987). PGI₂ has been reported be equally effective t sive crises in PPH (Scott et al., 1991). P
proves O_2 delivery in these patients (Jones
PGI₂ has been reported be equally effective
(Barst, 1986) but has a better pulmonary
action than tolazoline (Bush et al., 1988).
 oves O_2 delivery in these patients (Jones et al., 1987). highly also been reported be equally effective to nifedipine to the arst, 1986) but has a better pulmonary vasodilator revion than tolazoline (Bush et al., 1988)

pulmonary hypertension secondary to congenital heart

(Barst, 1986) but has a better pulmonary vasodilator reaction than tolazoline (Bush et al., 1988). be

PGI₂ is additive with oxygen therapy in patients with sp

pulm action than tolazoline (Bush et al., 1988). bet
 PGI_2 is additive with oxygen therapy in patients with

pulmonary hypertension secondary to congenital heart

disease (Bush et al., 1986). There is a report that PGI_2 is PGI_2 is additive with oxygen therapy in patients with
pulmonary hypertension secondary to congenital heart
disease (Bush et al., 1986). There is a report that PGI_2 is
ineffective in PPH (Guadagni et al., 1981), but th pulmonary hypertension secondary to congenital heart
disease (Bush et al., 1986). There is a report that PGI_2 is
ineffective in PPH (Guadagni et al., 1981), but this may
reflect a difference in individual responses to t disease (Bush et al., 1986). There is a report that PGI_2 is
ineffective in PPH (Guadagni et al., 1981), but this may
reflect a difference in individual responses to this drug.
In a study of nine patients aged 9 months t ineffective in PPH (Guadagni et al., 1981), but this may der
reflect a difference in individual responses to this drug. PPI
In a study of nine patients aged 9 months to 23 years ass
with pulmonary hypertension secondary to reflect a difference in individual responses to this drug.
In a study of nine patients aged 9 months to 23 years
with pulmonary hypertension secondary to congenital
heart disease, Barst (1986) found five responders and
fou In a study of nine patients aged 9 months to 23 years as
with pulmonary hypertension secondary to congenital ve
heart disease, Barst (1986) found five responders and ze
four nonresponders, using a 20% fall in PPA, an incre with pulmonary hypertension secondary to congenital vers
heart disease, Barst (1986) found five responders and zen
four nonresponders, using a 20% fall in PPA, an increase O
in cardiac index, and no change in PVR: SVR rati heart disease, Barst (1986) found five responders and z
four nonresponders, using a 20% fall in PPA, an increase
in cardiac index, and no change in PVR: SVR ratio as
criteria. All the nonresponders also failed to respo four nonresponders, using a 20% fall in PPA, an increase
in cardiac index, and no change in PVR: SVR ratio as
criteria. All the nonresponders also failed to respond to
mifedipine. This feature and its short half-life prov in cardiac mdex, and no change in $\mathbf{F} \mathbf{v} \mathbf{K}$: $\mathbf{S} \mathbf{v} \mathbf{K}$ ratio as
criteria. All the nonresponders also failed to respond to
infedipine. This feature and its short half-life provide
the basis for the us mifedipine. This feature and its short half-life provide
the basis for the use of PGI_2 as a predictor in assessing
pulmonary vascular reactivity to long-term vasodilator
treatment and for heart-lung transplantation (Roz e basis for the use of $PGI₂$ as a predictor in assessing
ilmonary vascular reactivity to long-term vasodilato
eatment and for heart-lung transplantation (Rozkove
al., 1988; Jones et al., 1989; Palevsky et al., 1990) pulmonary vascular reactivity to long-term vasodilator
treatment and for heart-lung transplantation (Rozkovec
et al., 1988; Jones et al., 1989; Palevsky et al., 1990).
 PGL_2 is very effective in the acute treatment of

determination (Rozkovec nearching transplantation (Rozkovec nearchines)
et al., 1988; Jones et al., 1989; Palevsky et al., 1990). dys
PGI₂ is very effective in the acute treatment of post-
operative pulmonary hypertensio PGI_2 is very effective in the acute treatment of post-
operative pulmonary hypertension associated with pul-
monary edema (Pascual et al., 1990; Schranz et al., F
1992) and allograft failure (Esmore et al., 1990), and b operative pulmonary hypertension associated with pu
monary edema (Pascual et al., 1990; Schranz et al.
1992) and allograft failure (Esmore et al., 1990), an
pulmonary hypertension complicating various types
ARDS (Radermac monary edema (Pascual et al., 1990; Schranz et a
1992) and allograft failure (Esmore et al., 1990), a
pulmonary hypertension complicating various types
ARDS (Radermacher et al., 1990; Clarke, 1990). Lor
term infusion of PG 1992) and allograft failure (Esmore et al., 1990), and
pulmonary hypertension complicating various types of
ARDS (Radermacher et al., 1990; Clarke, 1990). Long-
term infusion of $PGI₂$ is also used to treat PPH (Hig pulmonary hypertension complicating various types of 194
ARDS (Radermacher et al., 1990; Clarke, 1990). Long-
term infusion of PGI₂ is also used to treat PPH (Higen-
bottam et al., 1984). A randomized clinical trial in ARDS (Radermacher et al., 1990; Clarke, 1990). Long-
term infusion of PGI_2 is also used to treat PPH (Higen-
bottam et al., 1984). A randomized clinical trial in pa-
tients with PPH shows that chronic infusion of PGI_2 term infusion of PGI₂ is also used to treat PPH (Hige bottam et al., 1984). A randomized clinical trial in ptients with PPH shows that chronic infusion of PC produces a substantial and sustained reduction in PV (Rubin e bottam et al., 1984). A randomized clinical trial in patients with PPH shows that chronic infusion of PGI_2 produces a substantial and sustained reduction in PVR (Rubin et al., 1990). However, chronic infusion is expensi produces a substantial and sustained reduction in PVR ubin et al., 1990). However, chronic infusion is expen-
 $\begin{array}{c}\nOxygen \\
Nypoxemia is always seen in patients with pulmonary\n\end{array}$

Hypoxemia is always seen in patients with pulmonary

pertension secondary to COPD and contributes to the

sive, and there is a risk of infection. 40

E. Oxygen

hypoxemia is always seen in patients with pulmonary

hypertension secondary to COPD and contributes to the mi

pulmonary artery catheter reduced PVR and SVR to a indicate that long-term oxygen therapy prolongs life ex-
similar extent, with a marked increase in cardiac output pectancy and the quality of life in these patients. Nei-ND LIU
poor prognosis of these patients. Numerous studies have
indicated that correction of this hypoxemia using long-ND LIU
poor prognosis of these patients. Numerous studies have indicated that correction of this hypoxemia using long-
term oxygen therapy reduces PPA, decreases erythrocy ND LIU
poor prognosis of these patients. Numerous studies h
indicated that correction of this hypoxemia using le
term oxygen therapy reduces PPA, decreases erythr
tosis, and improves exercise tolerance and neuropsy poor prognosis of these patients. Numerous studies have
indicated that correction of this hypoxemia using long-
term oxygen therapy reduces PPA, decreases erythrocy-
tosis, and improves exercise tolerance and neuropsycho-
 indicated that correction of this hypoxemia using long-
term oxygen therapy reduces PPA, decreases erythrocy-
tosis, and improves exercise tolerance and neuropsycho-
logical function (Medical Research Council Working
Party term oxygen therapy reduces PPA, decreases erythrocytosis, and improves exercise tolerance and neuropsychological function (Medical Research Council Working Party, 1981; Nocturnal Oxygen Therapy Trial Group, 1980). Two lar tosis, and improves exercise tolerance and neuropsychological function (Medical Research Council Working
Party, 1981; Nocturnal Oxygen Therapy Trial Group,
1980). Two large-scale, controlled clinical trials involved
203 an logical function (Medical Research Council Working
Party, 1981; Nocturnal Oxygen Therapy Trial Group,
1980). Two large-scale, controlled clinical trials involved
203 and 87 patients with COPD (Nocturnal Oxygen
Therapy Tria Party, 1981; Nocturnal Oxygen Therapy Trial Group,
1980). Two large-scale, controlled clinical trials involved
203 and 87 patients with COPD (Nocturnal Oxygen
Therapy Trial Group, 1980; Medical Research Council
Working Par 1980). Two large-scale, controlled clinical trials involved
203 and 87 patients with COPD (Nocturnal Oxygen
Therapy Trial Group, 1980; Medical Research Council
Working Party, 1981), and one retrospective analysis
involving 203 and 87 patients with COPD (Nocturnal Oxygen
Therapy Trial Group, 1980; Medical Research Council
Working Party, 1981), and one retrospective analysis
involving 127 COPD patients (Miyamoto et al., 1992); all
indicate tha Working Party, 1981), and one retrospective analysis
involving 127 COPD patients (Miyamoto et al., 1992); all Working Party, 1981), and one retrospective analysis
involving 127 COPD patients (Miyamoto et al., 1992); all
indicate that long-term oxygen therapy prolongs life ex-
pectancy and the quality of life in these patients. Nei indicate that long-term oxygen therapy prolongs life ex-
pectancy and the quality of life in these patients. Nei-
ther of the two earlier trials showed a reduction in PPA.
However, a later trial by the Nocturnal Oxygen Th pectancy and the quality of life in these patients. Neither of the two earlier trials showed a reduction in PPA.
However, a later trial by the Nocturnal Oxygen Therapy
Trial Group showed that hemodynamic responses to
longther of the two earlier trials showed a reduction in PPA.
However, a later trial by the Nocturnal Oxygen Therapy
Trial Group showed that hemodynamic responses to
long-term oxygen therapy over a period of 3 to 6 months
rela However, a later trial by the Nocturnal Oxygen Therapy
Trial Group showed that hemodynamic responses to
long-term oxygen therapy over a period of 3 to 6 months
related to survival, suggesting that the pulmonary vas-
cular Trial Group showed that hemodynamic responses to
long-term oxygen therapy over a period of 3 to 6 months
related to survival, suggesting that the pulmonary vas-
cular response is an important factor (Timms et al.,
1985). long-term oxygen therapy over a period of 3 to 6 months
related to survival, suggesting that the pulmonary vas-
cular response is an important factor (Timms et al.,
1985). Hypoxic patients with a reduction in PPA in re-
s related to survival, suggesting that the pulmonary vacular response is an important factor (Timms et a 1985). Hypoxic patients with a reduction in PPA in a sponse to breathing O_2 (responder) showed a mushigher rate of cular response is an important factor (Timms et al., 1985). Hypoxic patients with a reduction in PPA in response to breathing O_2 (responder) showed a much higher rate of survival than did nonresponders (Ashutosh and Du 1985). Hypoxic patients with a reduction in PPA in response to breathing O_2 (responder) showed a much higher rate of survival than did nonresponders (Ashutosh and Dunsky, 1987). A postmortem investigation revealed no d sponse to breathing O_2 (responder) showed a mu
higher rate of survival than did nonresponders (Ash
tosh and Dunsky, 1987). A postmortem investigati
revealed no difference in pulmonary vascular structure
between respond higher rate of survival than did nonresponders (Ashutosh and Dunsky, 1987). A postmortem investigation revealed no difference in pulmonary vascular structures between responders and age- and PPA-matched nonresponders (Wrig tosh and Dunsky, 1987). A postmortem investigation
revealed no difference in pulmonary vascular structures
between responders and age- and PPA-matched nonre-
sponders (Wright et al., 1992). These results indicate
that HPV revealed no difference in pulmonary vascular structures
between responders and age- and PPA-matched nonre-
sponders (Wright et al., 1992). These results indicate
that HPV is likely to be an important component of
hypoxic p between responders and age- and PPA-matched nonre-
sponders (Wright et al., 1992). These results indicate
that HPV is likely to be an important component of
hypoxic pulmonary hypertension. Accumulating evi-
dence indicates sponders (Wright et al., 1992). These results indicate
that HPV is likely to be an important component of
hypoxic pulmonary hypertension. Accumulating evi-
dence indicates that long-term oxygen therapy reduces
PPA, prevent hypoxic pulmonary hypertension. Accumulating evi-
dence indicates that long-term oxygen therapy reduces
PPA, prevents nocturnal arterial desaturation and its
associated PPA elevation (Geraads et al., 1984), and re-
verses hypoxic pulmonary hypertension. Accumulating evented dence indicates that long-term oxygen therapy reduce PPA, prevents nocturnal arterial desaturation and in associated PPA elevation (Geraads et al., 1984), and inverses t dence indicates that long-term oxygen therapy re
PPA, prevents nocturnal arterial desaturation as
associated PPA elevation (Geraads et al., 1984), a
verses the progression of pulmonary hypertension (
zenblum et al., 1985; However, a later trial by the Nocturnal Oxygen Therapy

Trial Group showed that hemodynamic responses to

Iong-term oxygen therapy over a period of 3 to 6 months

related to survival, suggesting that the pulmonary vas-

r

associated PPA elevation (Geraads et al., 1984), and reverses the progression of pulmonary hypertension (Weit zenblum et al., 1985; Weitzenblum et al., 1989).

Oxygen is also an effective pulmonary vasodilator in other for verses the progression of pulmonary hypertension (Weitzenblum et al., 1985; Weitzenblum et al., 1989).

Oxygen is also an effective pulmonary vasodilator in

other forms of pulmonary hypertension. There are scattered repor zenblum et al., 1985; Weitzenblum et al., 1989).
Oxygen is also an effective pulmonary vasodilator
other forms of pulmonary hypertension. There are sc
tered reports that oxygen inhalation reduced PPA, PV
or both in PPH (Na Oxygen is also an effective pulmonary vasodilator
other forms of pulmonary hypertension. There are s
tered reports that oxygen inhalation reduced PPA, P
or both in PPH (Nagasaka et al., 1978) and that pulm
nary hypertensio other forms of pulmonary hypertension. There are scattered reports that oxygen inhalation reduced PPA, PVR, or both in PPH (Nagasaka et al., 1978) and that pulmonary hypertension was caused by pulmonary thromboembolic dise tered reports that oxygen inhalation reduced PPA, PVR,
or both in PPH (Nagasaka et al., 1978) and that pulmo-
nary hypertension was caused by pulmonary thrombo-
embolic disease (Dantzker and Bower, 1981), congenital
heart or both in PPH (Nagasaka et al., 1978) and that pulmonary hypertension was caused by pulmonary thrombo-
embolic disease (Dantzker and Bower, 1981), congenital
heart disease (Bush et al., 1985), bronchopulmonary
dysplasia (nary hypertension was caused by pulmonary thrombo-
embolic disease (Dantzker and Bower, 1981), congenital
heart disease (Bush et al., 1985), bronchopulmonary
dysplasia (Palmisano et al., 1990), systemic sclerosis
(Morgan e embolic disease (Dantzker and Bower, 1981), congenital
heart disease (Bush et al., 1985), bronchopulmonary
dysplasia (Palmisano et al., 1990), systemic sclerosis
(Morgan et al., 1991a), and pulmonary hypertension
associate heart disease (Bush et al., 1985), bronchopulmonary
dysplasia (Palmisano et al., 1990), systemic sclerosis
(Morgan et al., 1991a), and pulmonary hypertension
associated with liver cirrhosis (Tabuchi et al., 1990).
Failure dysplasia (Palmisano et al., 1990), systemic sclerosis (Morgan et al., 1991a), and pulmonary hypertension associated with liver cirrhosis (Tabuchi et al., 1990). Failure to reduce PPA or PVR by using oxygen has also been r 1991a). Failure to reduce PPA or PVR by using oxygen has also been reported in patients with PPH (Morgan et al., 1991a).
F. Nitric Oxide

NO is a potent pulmonary vasodilator and has a short 1991a).
F. Nitric Oxide
NO is a potent pulmonary vasodilator and has a short
half-life, making it an attractive treatment option for
pulmonary hypertension as an inhaled therapy (Pearl, F. Nitric Oxide

NO is a potent pulmonary vasodilator and has a short

half-life, making it an attractive treatment option for

pulmonary hypertension as an inhaled therapy (Pearl,

1993). In awake lambs, spontaneous breat NO is a potent pulmonary vasodilator and has a s
half-life, making it an attractive treatment option
pulmonary hypertension as an inhaled therapy (Pe
1993). In awake lambs, spontaneous breathing of N
40 to 80 parts per mil half-life, making it an attractive treatment option
pulmonary hypertension as an inhaled therapy (Pez
1993). In awake lambs, spontaneous breathing of NO
40 to 80 parts per million reversed pulmonary hypert
sion induced by pulmonary hypertension as an inhaled therapy (Pearl, 1993). In awake lambs, spontaneous breathing of NO at 40 to 80 parts per million reversed pulmonary hypertension induced by either hypoxia or infusion of a throm-boxane 1993). In awake lambs, spontaneous breathing of NO at 40 to 80 parts per million reversed pulmonary hypertension induced by either hypoxia or infusion of a throm-
boxane mimetic, without affecting systemic hemodynamics (Fr 40 to 80 parts per million reversed pulmonary hypertension induced by either hypoxia or infusion of a throm-
boxane mimetic, without affecting systemic hemodynamics (Frostell et al., 1991). Inhalation of 40 parts per milli

PHARMACOLOGICAL REVIEW!

 $PGI₂$ reduced both PVR and SVR (Pepke-Zaba et al., REGULATION OF PULMOM

reduce PVR, without effects on SVR in patients with

secondary pulmonary hypertension, whereas infusion of

PGI₂ reduced both PVR and SVR (Pepke-Zaba et al.,

1991). These results suggest that inhal reduce PVR, without effects on SVR in patients with secondary pulmonary hypertension, whereas infusion PGI₂ reduced both PVR and SVR (Pepke-Zaba et al 1991). These results suggest that inhaled NO is a sele tive pulmonary reduce PVR, without effection
secondary pulmonary hyperpositive pulmonary vasodilator.
1991). These results suggestive pulmonary vasodilator.
Inhaled NO therapy was condary pulmonary hypertension, whereas infusion of SI_2 reduced both PVR and SVR (Pepke-Zaba et al., resp.)
91). These results suggest that inhaled NO is a selection
we pulmonary vasodilator. al.
Inhaled NO therapy was

PGI₂ reduced both PVR and SVR (Pepke-Zaba et al., 1991). These results suggest that inhaled NO is a selective pulmonary vasodilator.

Inhaled NO therapy was subsequently applied to the treatment of ARDS (Weizberg et al., 1991). These results suggest that inhaled NO is a selective pulmonary vasodilator.

Inhaled NO therapy was subsequently applied to the

treatment of ARDS (Weizberg et al., 1993; Rossiant et

al., 1993; Gerlach et al., 1993 Inhaled NO therapy was subsequently applied to the treatment of ARDS (Weizberg et al., 1993; Rossiant et al., 1993; Gerlach et al., 1993), pulmonary hypertension secondary to congenital heart disease (Roberts et al., 1993b treatment of ARDS (Weizberg et al., 1993; Rossiant al., 1993; Gerlach et al., 1993), pulmonary hypertensise
condary to congenital heart disease (Roberts et al., 1993b; Berner et al., 1993) and acquired heart disea
(Girard al., 1993; Gerlach et al., 1993), pulmonary hypertension
secondary to congenital heart disease (Roberts et al.,
1993b; Berner et al., 1993) and acquired heart disease
(Girard et al., 1992), infant persistent pulmonary hype secondary to congenital heart disease (Roberts et a
1993b; Berner et al., 1993) and acquired heart diseas
(Girard et al., 1992), infant persistent pulmonary hype
tension (Roberts et al., 1992; Kinsella et al., 1992
COPD (A 1993b; Berner et al., 1993) and acquired heart disease t (Girard et al., 1992), infant persistent pulmonary hypertension (Roberts et al., 1992; Kinsella et al., 1992), in COPD (Adnot et al., 1993; Adatia et al., 1993b), p (Girard et al., 1992), infant persistent pulmonary hyper-
tension (Roberts et al., 1992; Kinsella et al., 1992),
COPD (Adnot et al., 1993; Adatia et al., 1993b), pneu-
monia (Blomqvist et al., 1993) and used during cardiac tension (Roberts et al., 1992; Kinsella et al., 1992), inh
COPD (Adnot et al., 1993; Adatia et al., 1993b), pneu-
monia (Blomqvist et al., 1993) and used during cardiac
surgery (Rich et al., 1993). These studies show that
 COPD (Adnot et al., 1993; Adatia et al., 1993b), pneumonia (Blomqvist et al., 1993) and used during cardiac surgery (Rich et al., 1993). These studies show that inhaled NO is a selective pulmonary vasodilator and improves monia (Blomqvist et al., 1993) and used during cardiac
surgery (Rich et al., 1993). These studies show that
inhaled NO is a selective pulmonary vasodilator and
improves gas exchange, particularly in patients with
ARDS. The surgery (Rich et al., 1993). These studies show that
inhaled NO is a selective pulmonary vasodilator and
improves gas exchange, particularly in patients with
ARDS. The explanation for the paradoxical reversal of
HPV and im inhaled NO is a selective pulmonary vasodilator
improves gas exchange, particularly in patients v
ARDS. The explanation for the paradoxical reverss
HPV and improvement of pulmonary capillary gas
change is that inhaled NO r improves gas exchange, particularly in patients with ARDS. The explanation for the paradoxical reversal of HPV and improvement of pulmonary capillary gas exchange is that inhaled NO reaches only the well-ventilated lung re ARDS. The explanation for the paradoxical reversal of
HPV and improvement of pulmonary capillary gas ex-
change is that inhaled NO reaches only the well-venti-
lated lung regions and thereby improves the ventilation/
perfu HPV and improvement of pulmonary capillary gas exchange is that inhaled NO reaches only the well-vent lated lung regions and thereby improves the ventilation perfusion matching, thus facilitating gas exchang (Quinn and Val change is that inhaled NO reaches only the well-ventilated lung regions and thereby improves the ventilation/
perfusion matching, thus facilitating gas exchange
(Quinn and Vallance, 1993). Inhaled NO is also a bron-
chodil lated lung regions and thereby improves the ventilation/ tilat perfusion matching, thus facilitating gas exchange evident (Quinn and Vallance, 1993). Inhaled NO is also a bron- role chodilator in animals (Dupuy et al., 199 perfusion matching, thus facilitating gas exchange ev.
(Quinn and Vallance, 1993). Inhaled NO is also a bron-
chodilator in animals (Dupuy et al., 1992) and humans fur
(Högman et al., 1993), and this may also contribute to chodilator in animals (Dupuy et al., 1992) and humans (Högman et al., 1993), and this may also contribute to the improved gas exchange in some patients. The main advantages of inhaled NO therapy are its efficacy, cheapness chodilator in animals (Dupuy et al., 1992) and human (Högman et al., 1993), and this may also contribute the improved gas exchange in some patients. The main advantages of inhaled NO therapy are its efficacy cheapness, and (Högman et al., 1993), and this may also contribute t
the improved gas exchange in some patients. The main
advantages of inhaled NO therapy are its efficacy
cheapness, and selectivity for the pulmonary circulatior
However, the improved gas exchange in some patients. The main advantages of inhaled NO therapy are its efficacy, cheapness, and selectivity for the pulmonary circulation.
However, there are some concerns about toxicity, inasmuch as advantages of inhaled NO therapy are its efficated cheapness, and selectivity for the pulmonary circulation However, there are some concerns about toxicity, insemuch as high concentrations of NO are toxic (Beackmist al., 1 cheapness, and selectivity for the pulmonary circula
However, there are some concerns about toxicity, in
uch as high concentrations of NO are toxic (Beack
et al., 1990; Wink et al., 1991) and interact with h
globin to form However, there are some concerns about toxicity, inas-
much as high concentrations of NO are toxic (Beackman su
et al., 1990; Wink et al., 1991) and interact with hemo-
globin to form methemoglobin, resulting in methemoglo much as high concentrations of NO are toxic (Beackm et al., 1990; Wink et al., 1991) and interact with her globin to form methemoglobin, resulting in methemoglobinemia. Additional studies are needed to establish therapeuti et al., 1990; Wink et al., 1991) and interact with hemoglobin to form methemoglobin, resulting in methemoglobinemia. Additional studies are needed to establish the therapeutic range, particularly when repeated inhalations globin to form methemoglobin, resulting in methemoglo-
binemia. Additional studies are needed to establish the
therapeutic range, particularly when repeated inhala-
tions are used (Gerlach et al., 1993; Rich et al., 1993). binemia. Additional studies are needed to establish the therapeutic range, particularly when repeated inhalations are used (Gerlach et al., 1993; Rich et al., 1993). Moreover, NO has different redox forms under different c therapeutic range, particularly when repeated inhala-
tions are used (Gerlach et al., 1993; Rich et al., 1993).
Moreover, NO has different redox forms under different the
conditions and exerts its toxic actions through dif tions are used (Gerlach et al., 1993; Rich et al., 199
Moreover, NO has different redox forms under differed conditions and exerts its toxic actions through differed
mechanisms (Stamler et al., 1992), emphasizing 1
need to Moreover, NO has different redox forms under differe
conditions and exerts its toxic actions through differe
mechanisms (Stamler et al., 1992), emphasizing t
need to obtain more detailed time course and dose-
sponse relati conditions and exerts its toxic actions through different
mechanisms (Stamler et al., 1992), emphasizing the
need to obtain more detailed time course and dose-re-
sponse relationships under various pathophysiological
condi mechanisms (Stamler et al., 1992), emphasizing the on the need to obtain more detailed time course and dose-re-
sponse relationships under various pathophysiological that
conditions. Additionally, randomized controlled tri need to obtain more detailed time course and dose-re-
sponse relationships under various pathophysiological
conditions. Additionally, randomized controlled trials
are now required to study the effect of inhaled NO on
longconditions. Additionally, randomized controlled trials

vasodilators, has raised the question of whether selecing other vasodilators via the inhaled route. This may be For *Future Therapies* may be the inhaled NO, compared with other systems vasodilators, has raised the question of whether selectivity of pulmonary vasodilation can be achieved by giv-
ing other vasodilators via the inhal The selectivity of inhaled NO, compared with other
vasodilators, has raised the question of whether selec-
tivity of pulmonary vasodilation can be achieved by giv-
ing other vasodilators via the inhaled route. This may be vasodilators, has raised the question of whether selec-
tivity of pulmonary vasodilation can be achieved by giv-
ing other vasodilators via the inhaled route. This may be
ce
applied to PGI_2 , Ca^{2+} antagonists, K^+ -c tivity of pulmonary vasodilation can be achieved by giving other vasodilators via the inhaled route. This may be applied to PGI_2 , Ca^{2+} antagonists, K^+ -channel openers, and adenosine. The rationale for using vasodi ing other vasodilators via the inhaled route. This may be cells
applied to PGI_2 , Ca^{2+} antagonists, K^+ -channel openers, prov
and adenosine. The rationale for using vasodilators is cells
the reversal of an increase applied to PGI_2 , Ca^{2+} antagonists, K^+ -channel openers, pand adenosine. The rationale for using vasodilators is che reversal of an increase in pulmonary vascular of smooth muscle contraction, but these drugs have n and adenosine. The rationale for using vasodilators is cells, and studies of vascular smooth muscle cells from
the reversal of an increase in pulmonary vascular other vessels may be misleading. Similarly, it is difficult
s the reversal of an increase in pulmonary vascular
smooth muscle contraction, but these drugs have no
direct effect on pulmonary vascular remodelling (al-
though lowering PVR may slow down or reverse the
remodelling). This smooth muscle contraction, but these drugs have no
direct effect on pulmonary vascular remodelling (al-
though lowering PVR may slow down or reverse the
remodelling). This has suggested that new treatments
should target th

REGULATION OF PULMONARY VASCULAR TONE
reduce PVR, without effects on SVR in patients with changes caused by fibrosis and hyperplasia of vascular
secondary pulmonary hypertension, whereas infusion of smooth muscle. The mark NARY VASCULAR TONE 117
changes caused by fibrosis and hyperplasia of vascular
smooth muscle. The marked increase in ET-1 immuno-117

smooth muscle. The marked increase in ET-1 immuno-

reactivity in the pulmonary vessels of patients with pri-

mary and secondary pulmonary hypertension (Giaid et changes caused by fibrosis and hyperplasia of vascular
smooth muscle. The marked increase in ET-1 immuno-
reactivity in the pulmonary vessels of patients with pri-
mary and secondary pulmonary hypertension (Giaid et
al., 1 enanges caused by horosis and hyperplasia or vascular
smooth muscle. The marked increase in ET-1 immuno-
reactivity in the pulmonary vessels of patients with pri-
mary and secondary pulmonary hypertension (Giaid et
al., 19 mary and secondary pulmonary hypertension (Giaid et al., 1993) suggests that ET-antagonists may be useful as therapy in the future (Barnes, 1994). Recently, nonpeptide orally active ET-antagonists have become available and mary and secondary pulmonary hypertension (Giaid et al., 1993) suggests that ET-antagonists may be useful as therapy in the future (Barnes, 1994). Recently, nonpeptide orally active ET-antagonists have become available and al., 1993) suggests that ET-antagonists may be useful
therapy in the future (Barnes, 1994). Recently, nonpe
tide orally active ET-antagonists have become availal
and might be indicated in the treatment of pulmona
hypertens the apy in the future (barnes, 1994). Recently, hold
tide orally active ET-antagonists have become avail
and might be indicated in the treatment of pulmo-
hypertension (Clozel et al., 1993), inasmuch as ET
tagonists inhibi since of any active E1-antagonists have become available
and might be indicated in the treatment of pulmonary
hypertension (Clozel et al., 1993), inasmuch as ET-an-
tagonists inhibit the progress of pulmonary hyperten-
sio tagonists inhibit the progress of pulmonary hypertension in experimental animals (Miyauchi et al., 1993) and inhibit the proliferation of pulmonary vascular smooth muscle in vitro (Zamora et al., 1993b).
VIII. Conclusions inhibit the proliferation of pulmonary vascular smooth
muscle in vitro (Zamora et al., 1993b).
VIII. Conclusions and Future Perspectives
The pulmonary circulation is regulated by a complex

hibit the proliferation of pulmonary vascular smooth
uscle in vitro (Zamora et al., 1993b).
VIII. Conclusions and Future Perspectives
The pulmonary circulation is regulated by a complex
twork of neural and humoral factors muscle in vitro (Zamora et al., 1993b).
 VIII. Conclusions and Future Perspectives

The pulmonary circulation is regulated by a complex

network of neural and humoral factors that interact

with the passive forces impose VIII. Conclusions and Future Perspectives
The pulmonary circulation is regulated by a complex
network of neural and humoral factors that interact
with the passive forces imposed on this low-pressure
system from the systemi The pulmonary circulation is regulated by a complex
network of neural and humoral factors that interact
with the passive forces imposed on this low-pressure
system from the systemic circulation. These factors re-
sult in o Ine pullionary circulation is regulated by a complex
network of neural and humoral factors that interact
with the passive forces imposed on this low-pressure
system from the systemic circulation. These factors re-
sult in with the passive forces imposed on this low-pressure
system from the systemic circulation. These factors re-
sult in optimal matching of pulmonary perfusion to ven-
tilation in order to maintain normoxia. There is much
evi system from the systemic circulation. These factors result in optimal matching of pulmonary perfusion to ventilation in order to maintain normoxia. There is much evidence indicating that the endothelium plays a critical ro sult in optimal matching of pulmonary perfusion to ventilation in order to maintain normoxia. There is much evidence indicating that the endothelium plays a critical role in regulating pulmonary vascular tone, and dysfunct tilation in order to maintain normoxia. There is much
evidence indicating that the endothelium plays a critical
role in regulating pulmonary vascular tone, and dys-
function of pulmonary endothelial cells may play an
impor evidence indicating that the endothelium plays a critic role in regulating pulmonary vascular tone, and dy function of pulmonary endothelial cells may play important role in pulmonary vascular disease (Liu a Barnes, 1994). role in regulating pulmonary vascular tone, and dys-
function of pulmonary endothelial cells may play are
important role in pulmonary vascular disease (Liu and
Barnes, 1994). There is increasing interest in the molec-
ular function of pulmonary endothelial cells may play at important role in pulmonary vascular disease (Liu and Barnes, 1994). There is increasing interest in the molecular mechanisms involved in the secretion of endothelia medi important role in pulmonary vascular disease (Liu and
Barnes, 1994). There is increasing interest in the molec-
ular mechanisms involved in the secretion of endothelial
mediators, and the pathways involved seem to be com-
 Barnes, 1994). There is increasing interest in the molecular mechanisms involved in the secretion of endothelia mediators, and the pathways involved seem to be con plex. Several factors may influence the expression of surf mediators, and the pathways involved seem to be complex. Several factors may influence the expression of surface receptors, intracellular signalling pathways, and gene expression in these cells and thus may influence pulmo mediators, and the pathways involved seem to be com-
plex. Several factors may influence the expression of
surface receptors, intracellular signalling pathways,
and gene expression in these cells and thus may influ-
ence p plex. Several lactors may imitance the expression of
surface receptors, intracellular signalling pathways,
and gene expression in these cells and thus may influ-
ence pulmonary vascular tone. Pulmonary vascular
smooth musc surface receptors, intracement signalling pathward and gene expression in these cells and thus may in ence pulmonary vascular tone. Pulmonary vascus smooth muscle is also subject to many influences, and is now becoming app and gene expression in these cells and thus may influence pulmonary vascular tone. Pulmonary vascular smooth muscle is also subject to many influences, and it is now becoming apparent that these cells are metabolically act ence pulmonary vascular tone. Pulmonary vascular
smooth muscle is also subject to many influences, and it
is now becoming apparent that these cells are metabol-
ically active and may release mediators and cytokines
that in smooth muscle is also subject to many immences, and it
is now becoming apparent that these cells are metabol-
ically active and may release mediators and cytokines
that influence their tone. Both endothelial cells and
smoo ically active and may release mediators and cytokines
that influence their tone. Both endothelial cells and
smooth muscle cells release mediators that have effects
on the extracellular matrix of the vessel. The extracel-
l that influence their tone. Both endothelial cells a
smooth muscle cells release mediators that have effecon
the extracellular matrix of the vessel. The extrac
lular matrix is actively maintained, and the remodelli
that occ smooth muscle cells release mediators that have effects
on the extracellular matrix of the vessel. The extracel-
lular matrix is actively maintained, and the remodelling
that occurs in chronic pulmonary disease is an impor lular matrix is actively maintained, and the remodelling
that occurs in chronic pulmonary disease is an impor-
tant component of vascular resistance that may be diflar matrix is actively maintained, and the remodelling
at occurs in chronic pulmonary disease is an impo
nt component of vascular resistance that may be d
ult to reverse.
Despite intense investigation, HPV remains som
ing

are now required to study the effect of inhaled NO on ficult to reverse.

long-term survival and morbidity. Despite intense investigation, HPV remains some-

thing of a mystery. It is still unclear why small pulmo-

mary a that occurs in chronic pulmonary disease is an imp
tant component of vascular resistance that may be c
ficult to reverse.
Despite intense investigation, HPV remains son
thing of a mystery. It is still unclear why small pul tant component of vascular resistance that may be dif-
ficult to reverse.
Despite intense investigation, HPV remains some-
thing of a mystery. It is still unclear why small pulmo-
nary arteries have the opposite response f Systemic versels.

Despite intense investigation, HPV remains something of a mystery. It is still unclear why small pulmo-

nary arteries have the opposite response from that of

systemic vessels. While endothelial cells c thing of a mystery. It is still unclear why small pulmonary arteries have the opposite response from that of systemic vessels. While endothelial cells clearly have the capacity to modulate HPV and may play a modulatory rol nary arteries have the opposite response from that of systemic vessels. While endothelial cells clearly have the capacity to modulate HPV and may play a modulatory role, it is likely that pulmonary vascular smooth muscle c systemic vessels. While endothelial cells clearly have the capacity to modulate HPV and may play a modulatory role, it is likely that pulmonary vascular smooth muscle cells themselves hold the key to the mechanism. It has capacity to modulate HPV and may play a modulatory
role, it is likely that pulmonary vascular smooth muscle
cells themselves hold the key to the mechanism. It has
proved difficult to isolate and study these smooth muscle
c role, it is likely that pulmonary vascular smooth muscle
cells themselves hold the key to the mechanism. It has
proved difficult to isolate and study these smooth muscle
cells, and studies of vascular smooth muscle cells f cells themselves hold the key to the mechanism. It has proved difficult to isolate and study these smooth muscle cells, and studies of vascular smooth muscle cells from other vessels may be misleading. Similarly, it is dif sels. lls, and studies of vascular smooth muscle cells from
her vessels may be misleading. Similarly, it is difficult
isolate and culture endothelial cells from these ves-
ls.
Chronic influences on pulmonary vessels have been
or other vessels may be misleading. Similarly, it is difficult to isolate and culture endothelial cells from these vessels.
Chronic influences on pulmonary vessels have been more difficult to study at a cellular level, but th

to isolate and culture endothelial cells from these vessels.

Chronic influences on pulmonary vessels have been

more difficult to study at a cellular level, but the appli-

cation of molecular probes and the use of antise

aspet

118
gonucleotides in vivo may help to elucidate the molecure
lar pathways involved in chronic pulmonary vascu larm and the modern state of the chronic pulmonary of the molecular pathways involved in chronic pulmonary vascular diseases in the future. 118
gonucleotides in vivo n
lar pathways involved
diseases in the future.
The long-term thera nucleotides in vivo may help to elucidate the molecu-

r pathways involved in chronic pulmonary vascular and

seases in the future.

The long-term therapy of pulmonary hypertension is and

ill unsatisfactory because of th

gonucleotides in vivo may help to elucidate the molecular pathways involved in chronic pulmonary vascular adiseases in the future.
The long-term therapy of pulmonary hypertension is a still unsatisfactory because of the d lar pathways involved in chronic pulmonary vascul
diseases in the future.
The long-term therapy of pulmonary hypertension
still unsatisfactory because of the difficulty in selective
reducing pulmonary vascular resistance w diseases in the future.
The long-term therapy of pulmonary hypertension is
still unsatisfactory because of the difficulty in selectively
reducing pulmonary vascular resistance without affect-
ing the systemic circulation. The long-term therapy of pulmonary hypertension is
still unsatisfactory because of the difficulty in selectively
reducing pulmonary vascular resistance without affect-
ing the systemic circulation. The recent demonstration still unsatisfactory because of the difficulty in selectively
reducing pulmonary vascular resistance without affect-
ing the systemic circulation. The recent demonstration
that inhaled NO effectively lowers pulmonary vascu reducing pulmonary vascular resistance without affect-

ing the systemic circulation. The recent demonstration

that inhaled NO effectively lowers pulmonary vascular

pressures is of great interest, as this shows the vali ing the systemic circulation. The recent demonstration
that inhaled NO effectively lowers pulmonary vascular
pressures is of great interest, as this shows the validity
of an approach where a drug selectively targets the
p that inhaled NO effectively lowers pulmonary vascular pressures is of great interest, as this shows the validity of an approach where a drug selectively targets the pulmonary circulation. In the case of NO, this is becaus pressures is of great interest, as this shows the validity
of an approach where a drug selectively targets the
pulmonary circulation. In the case of NO, this is because
it is not able to reach the systemic circulation beca of an approach where a drug selectively targets the
pulmonary circulation. In the case of NO, this is because
it is not able to reach the systemic circulation because of
its rapid combination with hemoglobin, and this is t pulmonary circulation. In the case of NO, this is because it is not able to reach the systemic circulation because
its rapid combination with hemoglobin, and this is the
fore a special case (Pearl, 1993). Intravenous adeno it is not able to reach the systemic circulation because of
its rapid combination with hemoglobin, and this is there-
fore a special case (Pearl, 1993). Intravenous adenosine
also shows some selectivity for the pulmonary its rapid combination with hemoglobin, and this is there-
fore a special case (Pearl, 1993). Intravenous adenosine
also shows some selectivity for the pulmonary circula-
tion, again because it is so rapidly metabolized in fore a special case (Pearl, 1993). Intravenous adenosine
also shows some selectivity for the pulmonary circula-
tion, again because it is so rapidly metabolized in the
systemic circulation (Morgan et al., 1991b). However, also shows some selectivity for the pulmonary circula-
tion, again because it is so rapidly metabolized in the
systemic circulation (Morgan et al., 1991b). However,
while these treatments are useful in the acute reduction tion, again because it is so rapidly metabolized in the
systemic circulation (Morgan et al., 1991b). However,
while these treatments are useful in the acute reduction
of pulmonary vascular pressures, they are not suited t systemic circulation (Morgan et al., 1991b). However,
while these treatments are useful in the acute reduction
of pulmonary vascular pressures, they are not suited to
long-term use in ambulant patients. Oxygen should also while these treatments are useful in the acute reduct
of pulmonary vascular pressures, they are not suited
long-term use in ambulant patients. Oxygen should a
be considered as a selective pulmonary vasodilator, a
reverses of pulmonary vascular pressures, they are not suited to long-term use in ambulant patients. Oxygen should also
be considered as a selective pulmonary vasodilator, as it
reverses HPV and has no effect on the systemic circul long-term use in ambulant patients. Oxygen should also
be considered as a selective pulmonary vasodilator, as it
reverses HPV and has no effect on the systemic circula-
tion. Long-term oxygen therapy is indicated for patie be considered as a selective pulmonary vasodilator, as it

reverses HPV and has no effect on the systemic circula-

tion. Long-term oxygen therapy is indicated for patients

who have pulmonary hypertension secondary to CO reverses HPV and has no effect on the systemic circ
tion. Long-term oxygen therapy is indicated for patie
who have pulmonary hypertension secondary to CO
but it must be taken for more than 12 h each day an
not indicated fo tion. Long-term oxygen therapy is indicated for patients
who have pulmonary hypertension secondary to COPD,
but it must be taken for more than 12 h each day and is
not indicated for other forms of pulmonary hyperten-
sion who have pulmonary hypertension secondary to COPD,
but it must be taken for more than 12 h each day and is
not indicated for other forms of pulmonary hyperten-
sion. It is possible that delivery of drugs via the inhaled but it must be taken for more than 12 h each day and is
not indicated for other forms of pulmonary hyperten-
sion. It is possible that delivery of drugs via the inhaled
route may achieve some selectivity, and this approach not indicated for other forms of pulmonary hypertension. It is possible that delivery of drugs via the inhaled ANDE
route may achieve some selectivity, and this approach still
should be exploited using optimal lung delive The may achieve some selectivity, and this approach circ. Res. 21: 747-756, 1967.

Should be exploited using optimal lung delivery systems.

It is hoped that, in the future, it will be possible to

develop more selective p route may achieve some selectivity, and this approshould be exploited using optimal lung delivery system It is hoped that, in the future, it will be possible develop more selective pulmonary vasodilators, such drugs may em should be exploited using optimal lung delive
It is hoped that, in the future, it will be
develop more selective pulmonary vasodi
such drugs may emerge from more detailed
logical studies of the pulmonary circulation
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