Cardiovascular Responses in Ageing: A Review

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I. Introduction

AGEING is associated with a variety of alterations in cardiovascular function, at the level of the cardiovascular autacoid receptors, at postreceptor levels, in neuromuscular function, in circulating levels of autacoids, and in autonomic reflexes; yet, despite these changes, the cardiovascular system continues to function reasonably well at least at rest.

Ageing is also associated with an increased incidence of cardiovascular disorders including coronary artery disease, heart failure, hypertension, and postural hypotension, although it is difficult to separate purely age-related changes from underlying pathological changes in humans. Animal models of ageing may be useful in clarifying the effects of ageing per se on cardiovascular responsiveness and can be supplemented by investigations of human-isolated tissues and by studies of relatively disease-free elderly populations. This review seeks to examine the evidence for physiological, pharmacological, and biochemical alterations in the cardiovascular system with ageing. We will first examine how cardiovascular responsiveness is altered at the receptor level in isolated tissues, then look at changes occurring in neurotransmission, and finally examine how overall cardiovascular control is altered in ageing.

A. Maturation and Ageing

Before beginning, it is necessary to explain the convention of classifying changes as occurring in maturation or ageing. Maturation can be defined as changes occurring from birth to adulthood and ageing or senescence as changes occurring between adulthood and old age. In some studies, an immature population was compared with an aged population, but for convenience, any changes will be assumed to have occurred in ageing. Second, because the most commonly used animal model of ageing is the rat, it is worth considering the life span of the rat. Rats of approximately 1.5–2 mo or less can be regarded as immature, rats of 3–6 mo can be regarded as young adult, and rats of approximately 24 mo or more can be regarded as aged, although there are differences between strains in longevity. Several strains of rat have been used in ageing studies, including Fischer 344, Sprague-Dawley, Wistar, Long-Evans, and Ivanos rats, adding the further complication of possible differences between strains in the effects of ageing. In human studies, the elderly population is usually taken as those older than 60, 65, or 70 years, depending on the study.

B. Alterations in Receptor-Mediated Responses

Alterations in isolated tissue responsiveness can be examined in terms of individual receptor subtypes, but because alterations in responsiveness at a postreceptor level may alter the responses mediated by several receptor subtypes, it is first best to subgroup cardiovascular responses into vasoconstriction, vasodilation, and cardiac responses and examine patterns of change in these physiological responses in isolated tissues.

II. Isolated Tissues

A. Vasoconstriction

Two measures of the vasoconstrictor response to an agonist can be obtained: potency and maximum response. Potency is an absolute measure, being normally taken as the concentration producing 50% of maximum response to the agonist. However, potency is not the same as affinity, which is a measure of the interaction between the agonist and the receptor and can only be readily obtained in ligand-binding studies. Maximum response will be discussed later. However, potency and maximum response are not unrelated. In a system with many spare receptors (i.e., where the agonist can produce maximum contraction by activating only a proportion of receptors), a loss of receptors can result in decreased agonist potency. In contrast, in a system with few or no spare receptors, a loss of receptors should result in a decreased maximum contraction to the agonist. Potency can also be altered by change in agonist affinity for the receptor or altered coupling of the receptor, and maximum response can also be altered by postreceptor changes. Only in ligand-binding studies can we talk of changes in receptor number or affinity for the receptor. However, changes in functional response to an agonist are most meaningful in terms of physiological function of the cardiovascular system.

1. α-Adrenoceptors. Vascular α-adrenoceptors are not a homogeneous population but comprise both α_1- and α_2-adrenoceptors (Docherty, 1989). However, the majority of ageing studies have failed to distinguish subtypes or have examined tissues in which only α_1-adrenoceptors are present. Except when α_2-adrenoceptors are explicitly mentioned, α_1-adrenoceptors are probably being discussed.

In the majority of studies, no change in the vasoconstrictor potency of NA* was reported either during maturation or ageing (table 1). However, studies of the rat aorta, a tissue widely used in ageing research, have generally reported a reduced responsiveness during maturation and ageing (table 1) or a reduced receptor reserve in tissues from aged rats (Wanstall and O'Donnell, 1988, 1989). However, the rat aorta may not be the most suitable tissue for the study of age-related changes specifically in α-adrenoceptor function, because the response to a variety of vasoconstrictors including 5-HT (Docherty, 1988a; Wanstall and O'Donnell, 1989) and angiotensin II (fig. 1) are reduced by maturation or ageing in the rat aorta (see below).

In the human saphenous vein, where stimulation-evoked contractions are mediated predominantly by α_2-adrenoceptors, there was a significant negative correlation between the potency of yohimbine at inhibiting

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* Abbreviations: ANP, atrial natriuretic peptide; EDR, endothelium-dependant relaxations; EDRF, endothelium-dependent relaxant factor; NA, noradrenaline; 5-HT, 5-hydroxytryptamine.

TABLE 1

Effects of maturation and ageing on vascular contractions mediated by α-adrenoceptors in isolated tissues[*]

Species and tissue	Effects of maturation	Effects of ageing	Reference
Human blood vessels		↔	Scott & Reid, 1982
			Stevens et al., 1982
Dog			
Mesenteric artery	↓	↔	Toda & Shimizu, 1987
Cerebral arteries	↔		Toda et al., 1986
Rat			
Femoral and carotid artery, vein		↔	Duckles et al., 1985
Tail artery		↓	Fouda & Atkinson, 1986
Aorta	↓		Carrier et al., 1979
			McAdams & Waterfall, 1986
	↔	↔	Hynes & Duckles, 1987
		↓	Tuttle, 1966
			Simpkins et al., 1983
			Hyland et al., 1987
			Wanstall & O'Donnell, 1989
Perfused kidney	↔		Janssens & Van Neuten, 1986
Rabbit			
Ear artery	↔		Duckles, 1983
Aorta	↔		Hayashi & Toda, 1978
Skeletal artery	↓		Owen, 1986

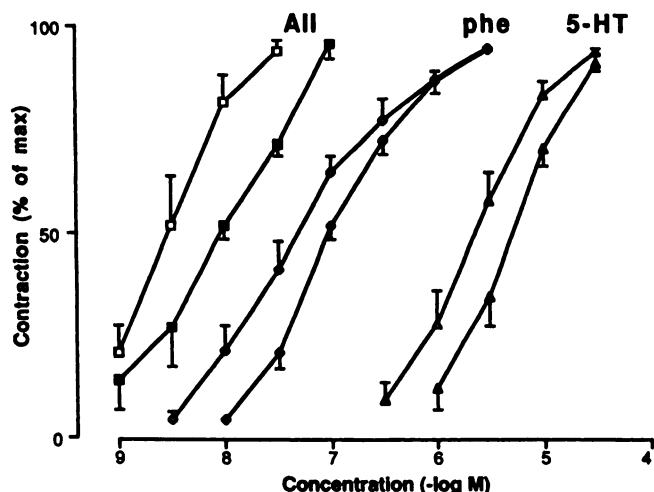[*] Symbols: ↔, unchanged; ↓, decreased potency in maturation or ageing.

FIG. 1. Contractions to angiotensin II (*AII*), the α_1-adrenoceptor agonist phenylephrine (*phe*), and *5-HT* in aortas from young adult (6 mo: □, ◇, △) and aged (24 mo: ■, ◆, ▲) rats. Responses to an agonist are expressed as percentages of maximum to that agonist, with *bars* representing standard errors of the mean from at least 4 experiments. Adapted and expanded from Docherty (1988).

stimulation-evoked contractions and age so that yohimbine was less potent in tissues from elderly patients (Hyland and Docherty, 1985a). Because the potency of NA was unchanged by ageing in the human saphenous vein (J. R. Docherty and L. Hyland, unpublished), it seems that the change in response to yohimbine does not involve alteration in affinity for α_2-adrenoceptors but rather the nerve-mediated response may become increasingly non-α_2-adrenergic in ageing. Further investigation is necessary to decide whether this finding has implications for the neural control of veins in the elderly, given that postural hypotension is more prevalent in the elderly (see later).

In the human platelet, where α_2-adrenoceptors mediate aggregation, ligand-binding studies report no change, a decrease, or even an increase in the maximum number of α_2-binding sites with age (table 2). Aggregation responses to α_2-agonists are reported to be unchanged or increased by increasing age (table 3).

There are reports of an increased (Lai et al., 1983) or

TABLE 2

Age-related alterations in the number of α_2-adrenoceptor, β-adrenoceptor, and muscarinic cholinergic ligand-binding sites[*]

Species and tissue	Effects of ageing	Reference
Human		
Platelet no. of α_2-binding sites	↔	Elliott & Grahame-Smith, 1982
		Jones et al., 1983
		Motulsky et al., 1983
		Davis & Silski, 1987
		Buckley et al., 1986
	↑	Yokoyama et al., 1984
	↓	Brodde et al., 1982
Lymphocyte no. of β-binding sites	↔	Landmann et al., 1981
		Abrass & Scarpace, 1981
		Doyle et al., 1982
	↓	Schocken & Roth, 1977
	↑	Middeke et al., 1984
Lymphocyte β-receptor agonist affinity	↓	Feldman et al., 1984
		Montamat & Davies, 1989
Rat		
Heart no. of β-binding sites	↔	Guarnieri et al., 1980
		Narayanan & Derby, 1982
		Tumer et al., 1989
	↑	Kusiak & Pitha, 1983
	↓	Fan & Banerjee, 1985
Heart no. of muscarinic binding sites	↔	Elfellah et al., 1986
	↑	Narayanan & Derby, 1982

[*] Symbols: ↑, increased; ↔, unchanged; ↓, decreased response or number of binding sites in ageing.

TABLE 3
*Effects of ageing on the aggregatory response of human platelets**

Stimulus	Effects of ageing	Reference
α_2-Agonist	↔	Elliott & Grahame-Smith, 1982
		Davis & Silski, 1987
	↑	Johnson et al., 1975
		Yokoyama et al., 1984
Adenosine diphosphate	↑	Johnson et al., 1975
	↔	Davis & Silski, 1987
Collagen	↑	Johnson et al., 1975
Arachidonic acid	↑	Johnson et al., 1975

* Symbols: ↑, increased; ↔, unchanged response in ageing.

TABLE 4
*Effects of maturation and ageing on vascular contractions mediated by 5-HT receptors**

Species and tissue	Effects of maturation	Effects of ageing	Reference
Rabbit aorta	↓		Hayashi & Toda, 1978
Rat			
Aorta	↓		Cohen & Berkowitz, 1974
		↓	Docherty, 1988a
			Wanstall & O'Donnell, 1989
		↑	Emmick & Cohen, 1986
Mesenteric artery		↔	Emmick & Cohen, 1986
	↑		Tsujimoto et al., 1986
Carotid artery		↔	Emmick & Cohen, 1986
Perfused kidney	↑		Janssens & Van Neuten, 1986
Dog			
Cerebral artery	↓		Toda et al., 1986
Coronary artery		↔	Toda et al., 1987
Human			
Saphenous vein		↔	Docherty & Hyland, 1985
Forearm		↔	Blauw et al., 1988

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased potency in maturation or ageing.

decreased (Schaefer and Williams, 1986) number of α_1-binding sites in the rat heart and an unchanged (Lai et al., 1983) or increased number (Takayanagi et al., 1986) in the rat vas deferens in maturation but a reduction (Partilla et al., 1982; Miyamoto and Ohshika, 1989) or no change (Schaffer and Williams, 1986) with ageing in the rat ventricle and a reduction with ageing in the rabbit heart and spleen (Dalrymple et al., 1982).

Although it is difficult to correlate ligand-binding and functional data because altered ligand-binding site number need not necessarily be reflected in altered functional response, ligand binding seems especially useful in identifying receptor subtypes in terms of ligand affinity. Hence, because the majority of binding studies show no differences with maturation and ageing in affinity for the binding site, we might cautiously conclude that it is likely that changes in agonist potency seen in functional studies of α-adrenoceptors do not reflect altered affinity for the receptor but are probably due to loss of receptors or less efficient coupling with signal transduction mechanisms.

2. 5-Hydroxytryptamine. Vascular contractions to 5-HT are mediated predominantly by 5-HT$_2$ receptors in the majority of tissues, although contractions may be additionally mediated by 5-HT$_1$ receptors in some tissues (Bradley et al., 1986). During maturation, there is a decreased contractile response to 5-HT in rabbit (relative to KCl) and rat aortas and dog cerebral arteries and an increased potency in perfused rat kidney and rat mesenteric arteries (table 4). During ageing most studies report no change in the contractile potency of 5-HT (table 4) but a decreased or even increased potency has been reported in the rat aorta (table 4; fig. 1).

Because platelets are the main source of 5-HT in the cardiovascular system, it is of interest to examine how ageing affects platelet 5-HT function. In rat platelets, 5-HT content is reported to be unchanged in males and decreased in females by ageing, although the release of 5-HT in response to collagen is increased by ageing (Yonezawa et al., 1989). In human platelets, 5-HT content is also reported to be decreased with ageing (Shuttleworth and O'Brien, 1981), but the maximum velocity of 5-HT uptake is reported to increase in platelets from elderly subjects (Marazziti et al., 1989). There are reports of increased or unchanged aggregatory response of platelets to a variety of stimuli including adenosine diphosphate, collagen, adrenaline, and arachidonic acid during ageing (table 3). An increased aggregation response to stimuli may in part be due to a decline in the function of adenylate cyclase with age, leading to a decrease in cyclic adenosine monophosphate (which inhibits platelet aggregation) (see later). It remains to be established whether responses to 5-HT are increased in ageing and whether an increased responsiveness to 5-HT makes up for decreased content of 5-HT in platelets.

3. Histamine. In the rabbit aorta (Hayashi and Toda, 1978) and skeletal artery (Owen, 1986), there was no change in the vasoconstrictor response to histamine in maturation, but the potency of histamine is reported to decrease during maturation in the dog cerebral artery (Toda et al., 1986).

4. Angiotensin II. There are reports of no change during maturation in the response to angiotensin II in dog mesenteric and coronary arteries (Toda and Shimizu, 1987; Toda et al., 1987) but a decline in potency in the rat aorta (J. R. Docherty, unpublished; fig. 1). This decline in potency of angiotensin during maturation in the rat aorta is matched by a decline in potency of NA and 5-HT (fig. 1).

5. Maximum contraction to vasoconstrictors. The major problem in comparing maximum vascular contractile responses to agonists in isolated tissues from animals of different ages (and thus tissues of different dimensions) is which measurement to take: absolute tension, tension

per unit cross-sectional area, tension per unit tissue weight, or tension as a percentage of the maximum to a reference agent such as KCl. Similar problems are encountered in other situations such as in assessing the effects of experimental diabetes on the maximum contractile response to α-adrenoceptor agonists in the rat aorta, because diabetes reduces tissue weight (Mulhern and Docherty, 1989). In ageing studies, problems of interpretation are magnified by the need to compare results from different tissues using drugs acting at a variety of receptors. Hence, when the effects of ageing on the maximum response to agonists in a single tissue are assessed, it is best to compare responses on a variety of agents acting at different receptors.

In absolute terms, there was no change with ageing in the maximum response to NA or 5-HT in the rat renal artery, and during maturation and adulthood the maximum response to NA (Moritoki et al., 1986a; Duckles, 1987a) and 5-HT (Emmick and Cohen, 1986; Tsujimoto et al., 1986) increases in the rat mesenteric artery. In contrast, the pressor response to 5-HT increases during maturation in the perfused rat kidney without change in the response to NA (Janssens and Van Neuten, 1986).

In rat femoral and renal arteries and veins, the maximum response to KCl (Duckles et al., 1985) and NA (Duckles, 1987a) are unchanged by ageing, but in dog coronary (Toda et al., 1987) and cerebral (Toda et al., 1986) arteries, the rabbit aorta (Karaki et al., 1985), and the rat aorta (McAdams and Waterfall, 1986; Hyland et al., 1987), the maximum response to KCl increases in maturation. This increase in the maximum to KCl is matched by an increase in the maximum to NA in rabbit (Hayashi and Toda, 1978; Karaki et al., 1985) and rat (Hyland et al., 1987) aortas. However, when expressed relative to the KCl contraction, the maximum response to 5-HT increases with maturation in rat coronary arteries (Nyborg and Mikkelson, 1985) but is unchanged in dog cerebral (Toda et al., 1986) and mesenteric arteries (Toda and Shimizu, 1987) and decreases in the rabbit aorta (Hayashi and Toda, 1978) and increases with ageing in rat (Nyborg and Mikkelson, 1985) and dog (Toda et al., 1987) coronary arteries. Although the absolute maximum tension produced by KCl increases with maturation in dog cerebral arteries, the tension produced per unit cross-sectional area remains constant (Toda et al., 1986). In contrast, the maximum contraction to KCl per unit cross-sectional area increases during maturation but not ageing in the dog mesenteric artery (Toda and Shimizu, 1987). The problems of assessing responses relative to the contraction to KCl is illustrated by the results of Stevens et al. (1982). These authors found no difference with age in the maximum response of human arteries to NA in absolute terms, but an increased maximum response to NA relative to KCl was found in tissues from older men due to a decline with age in the maximum contraction to KCl.

B. Vasodilation

1. Rat aorta. It is well established that the relaxation to the β-adrenoceptor agonist isoprenaline is reduced or lost during maturation and senescence in the rat aorta (table 5; fig. 2). This loss of vasodilator response to isoprenaline in the rat aorta has been reported at 3–6 mo (Fleisch, 1971; Hyland et al., 1987; Sawyer and Docherty, 1987), 7 mo (Cohen and Berkowitz, 1974), 10 mo (Fleisch and Hooker, 1976), 16 mo (O'Donnell and Wanstall, 1984,1986) and 22 mo (Parker et al., 1978) without reduction of the maximum relaxation to sodium nitrite (Fleisch, 1971; O'Donnell and Wanstall, 1986) or nitroglycerine (Cohen and Berkowitz, 1974; Fleisch and Hooker, 1976; Parker et al., 1978), although Fleisch and Hooker (1976) reported a reduced potency of nitroglycerine and Moritoki et al. (1988) and Sawyer and Docherty (1987) reported a reduced maximum response to sodium nitroprusside in tissues from older animals (table 6). In all of these studies, relaxations to nitroglycerine, sodium nitrite, or nitroprusside were of a mag-

TABLE 5

*Effects of maturation and ageing on vascular relaxation to
β-adrenoceptor agonists in isolated tissues**

Species and tissue	Effects of maturation	Effects of ageing	Reference
Rat			
Aorta	↓		Fleisch, 1971; Cohen & Berkowitz, 1974; Fleisch & Hooker, 1976; Simpkins et al., 1983; Hyland et al., 1987; Sawyer & Docherty, 1987; Duckles & Hurlbert, 1986
		↓	Parker et al., 1978; Simpkins et al., 1983; O'Donnell & Wanstall, 1986
Pulmonary artery	↓		Fleisch & Hooker, 1976; Duckles & Hurlbert, 1986
		↓	O'Donnell & Wanstall, 1986
Jugular vein		↔	Duckles & Hurlbert, 1986
Portal vein		↔	Emmick & Cohen, 1986
Mesenteric artery	↓		Tsujimoto et al., 1986
Rabbit			
Aorta	↓	↓	Fleisch & Hooker, 1976
Pulmonary artery	↓	↓	Fleisch & Hooker, 1976
Portal vein	↔	↔	Fleisch & Hooker, 1976
Dog			
Mesenteric artery		↓	Shimizu & Toda, 1986
Cerebral arteries	↑		Toda et al., 1986
Human			
Saphenous vein		↓	Ikezono et al., 1987
Hand vein		↓	Pan et al., 1986; Hiremath et al., 1989

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased response in maturation or ageing.
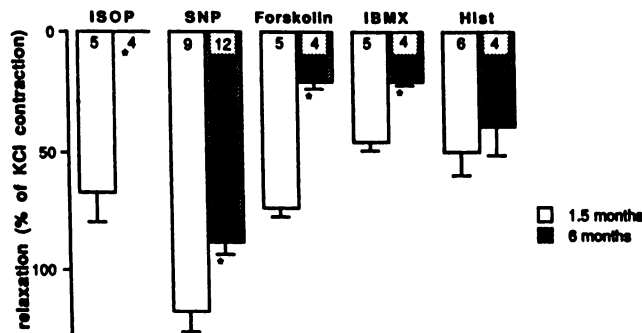
FIG. 2. Maximum relaxation to isoprenaline (*ISOP*), sodium nitroprusside (*SNP*), *forskolin*, the phosphodiesterase inhibitor isobutyl methylxanthine (*IBMX*), and histamine (*Hist*) in aortas contracted with 40 mM KCl from immature (1.5 mo: *hatched columns*) and young adult (6 mo: *open columns*) rats. Values indicate numbers of experiments and *bars* indicate standard errors of the mean. Adapted and expanded from Hyland et al. (1987), Sawyer and Docherty (1987), Carvajal et al. (1989).

TABLE 6

*Effects of maturation and ageing on vascular relaxations to nitrovasodilators**

Species and tissue	Effects of maturation	Effects of ageing	Reference
Rat			
Aorta	↔		Fleisch, 1971
			Cohen & Berkowitz, 1974
	↓		Fleisch & Hooker, 1976
			Sawyer & Docherty, 1987
	↓	↓	Moritoki et al., 1988
		↔	O'Donnell & Wanstall, 1986
			Parker et al., 1978
Mesenteric artery		↔	Tsujimoto et al., 1986
Portal vein	↔		Fleisch & Hooker, 1976
Rabbit			
Aorta	↓	↓	Fleisch & Hooker, 1976
		↓	Karaki et al., 1985
Portal vein	↔	↔	Fleisch & Hooker, 1976

* Symbols: ↔, unchanged; ↓, decreased response in maturation or ageing.

nitude to abolish the KCl contraction, whereas the relaxation to isoprenaline was usually much smaller even in young animals. Hence, it is important to compare like with like: it may be difficult to demonstrate a loss of relaxation if the maximum relaxation in aortas from young animals is of a magnitude to abolish the KCl contraction and can be considered maximal for the tissue. The degree of relaxation to an agonist depends on the degree of contraction induced by the contractile agent. Hence, a reduction in the maximum relaxation to sodium nitroprusside can be demonstrated during maturation in the rat aorta if tissues are contracted with 40 mM KCl but not if tissues are contracted with 20 mM KCl (Sawyer and Docherty, 1987).

2. Endothelium-dependent relaxations. Whereas isoprenaline or the nitrovasodilators cause vasodilation by acting directly on the vascular smooth muscle, some vasodilators act by releasing EDRF from the endothelial cells, and this EDRF acts to cause vasodilation (Furchgott, 1984; Vanhoutte et al. 1986; Moncada et al. 1988).

Hence, alterations in response to agents such as histamine could be due to several factors: loss of response of endothelial cells to histamine, loss of endothelial cells, loss of vascular response to EDRF. Additionally, endothelium-derived contractile factors may be released by endothelial cells (Vanhoutte et al., 1986). Endothelin is a newly discovered contractile agent from the endothelium (Yanagisawa et al., 1988). EDR to histamine are unchanged (Carvajal et al., 1989) and relaxations to atriopeptin are reported to decline during maturation (Emmick and Cohen, 1986; Mulvany, 1987; Carvajal et al., 1989) but not during ageing (Duckles, 1987a) in the rat aorta, and for both agents the maximum relaxation was <100% of the KCl contraction (table 7). Relaxations to histamine are reported to decline during maturation and ageing in the rat mesenteric artery (Moritoki et al., 1986a). However, there is insufficient evidence to suggest that EDR are selectively affected by ageing, especially as the potency of acetylcholine at producing EDR is increased by ageing in the rat aorta (table 7) without change in the maximum relaxation (fig. 3). Note also that, because EDRF is thought to cause vascular relaxation in the same way as the nitrovasodilators (through stimulation of cyclic guanosine monophosphate production) and because the response to sodium nitroprusside is unchanged by ageing in the rat aorta, it is possible that neither the release nor effect of EDRF is decreased by ageing in the rat aorta.

3. Other tissues. A decreased maximum relaxation to isoprenaline has also been reported during maturation in the rabbit aorta, rat pulmonary artery, and rat mesenteric artery and during ageing in the human saphenous vein, human dorsal hand vein, rat pulmonary artery, and dog mesenteric artery (table 6). An increased response to isoprenaline has been reported during maturation in dog cerebral arteries but no change in potency or maximum relaxation with ageing in rat jugular vein and rat and rabbit portal veins (table 6).

The relaxation to sodium nitrite or nitroprusside is decreased by ageing in the rabbit aorta (Karaki et al., 1985) but not in rat mesenteric arteries (Tsujimoto et al., 1986), and the potency of nitroglycerine is reduced by maturation and ageing in rat and rabbit aortas (Fleisch and Hooker, 1976).

Relaxations to acetylcholine or other muscarinic agonists involve EDRF and are decreased, unchanged, or even increased by ageing in rat and dog blood vessels (table 7). In vivo, there are reports of a reduced vasodilation to acetylcholine in older patients but no change in the rat (table 8).

C. Cardiac Responses

1. β-Adrenoceptors. Cardiac responses to β-adrenoceptor agonists in vivo, which can be influenced by changes in baroreflex function, are discussed later. Some studies of cardiac β-adrenoceptor function have avoided the baroreflex problem by using pithed rats or by examining

TABLE 7

Effects of maturation and ageing on vascular relaxations to other vasodilators*

Species and tissue	Agent	Effects of maturation	Effects of ageing	Reference
Rat				
Aorta	Atriopeptin	↓		Emmick & Cohen, 1986
				Mulvany, 1987
			↔	Carvajal et al., 1989
				Duckles, 1987a
	Histamine	↔		Carvajal et al., 1989
	Acetylcholine		↑	Hynes & Duckles, 1987
				Carvajal et al., 1989
Carotid, renal, mesenteric arteries	Atriopeptin		↔	Duckles, 1987a
Mesenteric artery	Acetylcholine		↔	Hynes & Duckles, 1987
	Histamine	↓	↓	Moritoki et al., 1986a
Dog				
Coronary artery	Acetylcholine		↓	Toda et al., 1987
Mesenteric artery	Acetylcholine		↓	Toda & Shimizu, 1987

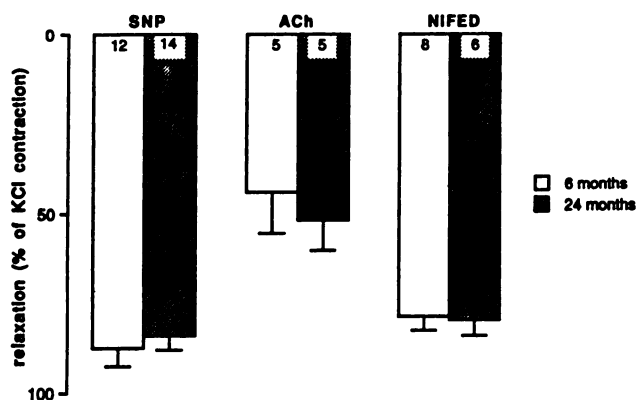* Symbols: ↑, increased; ↔, unchanged; ↓, decreased response in maturation or ageing.

FIG. 3. Maximum relaxation to sodium nitroprusside(*SNP*), acetylcholine (*ACh*), and nifedipine (*NIFED*) in aortas contracted with KCl from young adult (6 mo: *open columns*) and aged (24 mo: *hatched columns*) rats. Values indicate numbers of experiments and *bars* indicate standard errors of the mean. Adapted and expanded from Sawyer and Docherty (1987) and Carvajal et al.(1989).

responses in isolated cardiac tissues. In the pithed rat, a preparation in which central and reflex control of heart rate is abolished, there is an age-related decrease in the tachycardia to isoprenaline (Docherty, 1988b) (fig. 4). There is no change with age in the resting performance of isolated cardiac muscle, but there is a decreased maximum inotropic response to isoprenaline without change in potency and a decreased maximum response to dibutyryl cyclic adenosine monophosphate (Lakatta et al., 1975; Guarnieri et al., 1980) in cardiac muscle from aged rats suggesting a postreceptor change with ageing. In addition, there is an age-related decline in the maximum cardiac work in the perfused rat heart (Friberg et al., 1985). In maturation, the positive inotropic responses to isoprenaline, to the α_1-agonist phenylephrine, to 5-HT, and to calcium are reported to increase in the rat atria (Hashimoto et al., 1983).

Because most reports find no change with age in the number of β_1- or β_2-adrenoceptor-binding sites of the human lymphocyte and rat heart (table 2) and because

cyclic adenosine monophosphate production in response to forskolin, sodium fluoride, dibutyryl cyclic adenosine monophosphate, and glucagon (Kusiak and Pitha, 1983; Guarnieri et al., 1980; Robberecht et al., 1986) are also reduced by ageing in the rat myocardium and human lymphocyte (Krall et al., 1981), it seems likely that the alteration is not at the receptor level but in the coupling to the enzyme adenylate cyclase via G proteins. There are reports of a decreased affinity of β-adrenoceptor-binding sites of human lymphocytes for isoprenaline with ageing (table 2), due to a decrease in coupling of β-receptors to adenylate cyclase (Fan and Banerjee, 1985; Montamat and Davies, 1989).

2. Muscarinic receptors. The bradycardia to muscarinic agonists is reported to be unchanged (Elfellah et al., 1986), reduced (Kelliher and Conahan, 1980), or even increased (Kennedy and Seifen, 1990) and the negative inotropic response is reported to be reduced (Elfellah et al., 1986) by ageing in the rat atria. The increased potency of acetylcholine but not carbachol in aged rats reported by Kennedy and Seifen (1990) seems to be due to age-related reductions in acetylcholinesterase activity because differences are abolished by cholinesterase inhibitors (Kennedy and Seifen, 1990). Any diminished muscarinic responsiveness does not appear to be due to loss of receptors, because the density of sites is unchanged or even increased in atria from old rats (table 2).

3. Other cardiac responses. In rats, the positive inotropic response to ouabain is variously reported to decrease (Gerstenblith et al., 1979) or to increase (Katano et al., 1985) with ageing, and the toxic effects of ouabain on the myocardium (arrhythmogenic actions) are reported to occur at lower concentrations in old than in young rats (Katano et al., 1985). In contrast, the negative inotropic response to nifedipine is reported to be unchanged by ageing (Elfellah et al., 1986). In dogs, there was no difference between the neonate and adult in the ventricular response to ouabain (Lathrop et al., 1989).

TABLE 8
*Effects of ageing on the depressor response to vasodilators in vivo**

Vasodilator	Species	Effects of maturation	Effects of ageing	Reference
α-Adrenoceptor antagonists				
Prazosin	Man		↔	Elliot et al., 1982; McNeil et al., 1987
	Rat		↔	Docherty (unpublished)
	Rabbit		↔	Dalrymple et al., 1982
Phentolamine	Man		↔	Buhler et al., 1980
5-HT₂-receptor antagonists				
Ketanserin	Man		↑	De Cree et al., 1985; Rosendorff & Murray, 1986
Ritanserin	Man		↔	Blauw et al., 1988
β-Adrenoceptor agonists				
	Man		↔	Kendall et al., 1982
	Rat	↑	↔	Docherty, 1988b; Docherty et al., 1986
Acetylcholine				
	Man		↓	Hollenberg et al., 1974
	Rat	↔	↔	Kelliher & Conahan, 1980
Nitrovasodilators				
	Man		↔	McGarry et al., 1983; Irvine & Shepherd, 1984
	Rat		↔	Docherty, 1990; Docherty et al., 1986

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased response in maturation or ageing.

An age-related decline in Ca^{++} transport rather than an altered interaction between Ca^{++} and the contractile apparatus may be involved in decreased contractile ability in ageing (Froehlich et al., 1978; Guarnieri et al., 1980; Frolkis et al., 1988; Heyliger et al., 1988), because the response of the myofilament to Ca^{++} is unchanged by ageing in skinned fibres (Bhatnagar et al., 1984). For reviews of the effects of ageing on the physiology of the myocardium, see references by Lakatta (1987) and Walsh (1987).

III. Neurotransmission

A. Plasma Catecholamine Levels

In humans, plasma levels of NA have been widely reported to be increased by ageing both at rest (Pedersen and Christensen, 1975; Ziegler et al., 1976; Prinz et al., 1979; Bertel et al., 1980; MacGilchrist et al., 1989; Brodde et al., 1982; Krall et al., 1981; Wilkie et al., 1985; Vargas et al., 1986) and in response to physiological stress (Palmer et al., 1978; Saar and Gordon, 1979; Young et al., 1980; Sowers et al., 1983; Fleg et al., 1985; Vargas et al., 1986) (table 9). In contrast, plasma levels of adrenaline have not been consistently shown to increase with age in humans, with reports of no change (Prinz et al., 1979; Barnes et al., 1982; Vargas et al., 1986) or increased levels (Fleg et al., 1985). Urinary excretion of NA but not adrenaline is reported to increase with age in humans (Lehmann and Keul, 1986). In the rat, plasma levels of both NA and adrenaline have been reported to increase with age (Hoffman et al., 1985).

Increased plasma levels of NA (and adrenaline) can be due to an increased rate of appearance in the plasma or to a decreased plasma clearance, or both. Plasma clearance of NA has been variously reported to be unchanged (Young et al., 1980; Rubin et al., 1982) or decreased (Esler et al., 1981) by ageing in humans, and clearance of adrenaline has even been reported to increase in ageing (Wilkie et al., 1985) (table 10). The rate of appearance of NA in the plasma has been reported to increase with ageing in humans (Rubin et al., 1982; Veith et al., 1986; Hoeldtke and Cilmi, 1985; MacGilchrist et al., 1989) (table 10), and age and percentage of body fat are independent determinants of rate of appearance of NA (Schwartz et al., 1987). Because an altered plasma clearance might be expected to affect plasma NA and adrenaline equally, it seems that the important age-related alteration may be an increased rate of appearance of NA in the plasma, due either to increased neurotransmission or to a decreased function of the NA reuptake process (fig. 5). An increased neurotransmission with age seems unlikely because, at least in the rat, catecholamine content of tissues is generally reported to decrease with ageing (see below).

B. Catecholamine Content

The catecholamine content of the heart (Martinez et al., 1981: male but not female Fischer 344 rat; Rappaport et al., 1981: Fischer 344 rat) and some arteries (Fouda and Atkinson, 1986: Ivanos rat; Handa and Duckles, 1987a: Fischer 344 rat) is reported to decrease with age in the rat (table 11), and there is histological evidence for a loss of nerve terminals at least in some tissues (McLean et al., 1983: Fischer 344 rat; Amenta and Mione 1988: Wistar rat; Dhall et al., 1986: guinea pig). Admittedly, catecholamine content is reported to be unchanged by ageing in rat veins (Handa and Duckles, 1987a) and nerve density is increased by age in some rat blood vessels

TABLE 9
*Effects of ageing on plasma levels of NA and adrenaline**

Species	Agent	Effects of ageing	Reference
Human	NA	↑	Pedersen & Christensen 1975; Ziegler et al., 1976; Palmer et al., 1978; Prinz et al., 1979; Saar & Gordon, 1979; Young et al., 1980; Bertel et al., 1980; Krall et al., 1981; Brodde et al., 1982; Wilkie et al., 1985; Vargas et al., 1985; MacGilchrist et al., 1989
Human	Adrenaline	↑	Fleg et al., 1985
		↔	Prinz et al., 1979; Barnes et al., 1982; Vargas et al., 1986
Rat	NA	↑	Hoffman et al., 1985
	Adrenaline	↑	Hoffman et al., 1985

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased levels in ageing.

TABLE 10
*Effects of ageing on rates of appearance and clearance of NA and adrenaline in man**

Agent		Effect of ageing	Reference
NA	Appearance	↑	Rubin et al., 1982; Hoeldte & Cilmi, 1985; Veith et al., 1986; Schwartz et al., 1987; MacGilchrist et al., 1989
NA	Clearance	↔	Young et al., 1980; Rubin et al., 1982
		↓	Esler et al., 1981
Adrenaline	Clearance	↑	Wilkie et al., 1985

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased response in ageing.

TABLE 11
*Effects of ageing on catecholamine content of tissues in rats**

Strain and tissue	Effects of ageing	Reference
F344		
Heart (male)	↓	Martinez et al., 1981; Rappaport et al., 1981
Heart (female)	↔	Martinez et al., 1981
Tail artery	↑	Handa & Duckles, 1987a
Arteries and veins	↔ or ↓	Duckles et al., 1985; Handa & Duckles, 1987a
Ivanos tail artery	↓	Fouda & Atkinson, 1986

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased content with ageing.
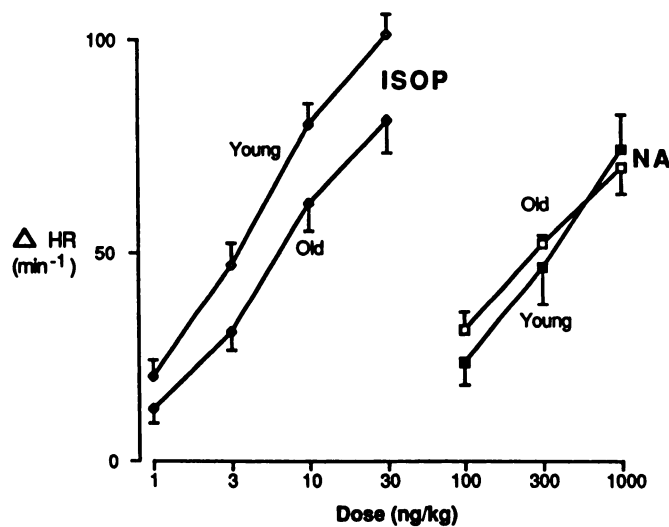

FIG. 4. Tachycardia to isoprenaline (*ISOP*) and *NA* in young adult (◇, □) and aged (◆, ■) pithed rats. *Bars* represent standard errors of the mean. *HR*, heart rate. Adapted and expanded from Borton and Docherty (1989).

(Mione et al., 1988). Conflicting results have been reported for the rat tail artery: an increased (Handa and Duckles, 1987a: Fischer 344 rat) or decreased (Fouda and Atkinson, 1986: Ivanos rat) catecholamine content in tissues from aged rats. Similarly, in terms of the ability to accumulate [^{3}H]NA, there is no evidence for age-related changes in adrenergic nerve density of Fischer 344 rat blood vessels (Duckles et al., 1985). However, there are some reports of increased synthesis of catecholamines in tissues from aged rats with an increased activity of tyrosine hydroxylase in the superior cervical ganglion (Partanen et al., 1985) and an increased activity of dopamine β-hydroxylase in the adrenal gland (Banerji et al., 1984). In the cholinergic system, the activity of choline acetyltransferase is also increased by ageing in the superior cervical ganglion (Partanen et al., 1985), although the activity of acetylcholinesterase is reported to be reduced by ageing in rat atria (Kennedy and Seifen, 1990).

Overall, the consensus seems to be that adrenergic nerve density may decline with ageing, at least in some tissues, and this could explain reports of reduced stimulation-evoked release of NA as a percentage of tissue tritium in rat atria (Borton and Docherty, 1989) and heart (Daly et al., 1988).

C. Neuronal Uptake

Because the evidence does not seem to favour an increased neurotransmission in ageing, is there evidence that transmitter disposition mechanisms are reduced? Perhaps the most important transmitter disposition mechanism at the neuromuscular junction is the neuronal NA reuptake process which functions to limit spillover into the circulation (fig. 5). The effectiveness of the neuronal NA reuptake process can be assessed using the neuronal uptake blocker cocaine: a decreased ability of cocaine to potentiate responses should indicate a decreased effectiveness of the uptake process. In rat blood vessels the effectiveness of cocaine is reduced by ageing in the tail artery but not renal or femoral arteries (Duckles, 1987b), and in the rat isolated heart or atria the effectiveness of cocaine is variously reported to increase (Kreider et al., 1984) or decrease (Borton and Docherty, 1989) with age. There are reports of no change in the uptake process during maturation in the rabbit aorta (Shibata et al., 1971) but a decrease in the rabbit ear artery (Duckles, 1983). In the vasculature of the anaesethetised (Docherty and Hyland, 1986) and pithed rat (Borton and Docherty, 1989), potency of cocaine decreases with age, whereas in the rat hindlimb potency of cocaine is reported to increase with age (Handa and Duckles, 1987b) (table 12). In studies looking directly at stimulation-evoked release of radiolabeled NA, the effectiveness of cocaine is variously reported to increase with age in the rat isolated heart (Kreider et al., 1984) but to decrease with age in rat atria (Borton and Docherty, 1989) (table 12). Accumulation of NA declines with age in the rat hypothalamus (McIntosh and Westfall, 1987).

Although the evidence is equivocal, there is some reason to suggest that neuronal reuptake may decline with age at least in some tissues and that, at least in the rat, the overall cardiovascular response to NA is unaffected by ageing (Sprague-Dawley rat: Docherty and Hyland, 1986; Borton and Docherty, 1989) (fig. 4), and plasma levels of NA are increased by ageing in the Sprague-Dawley rat (Hoffman et al., 1985). In both anaesthetised and pithed rabbits, blockers of neuronal reuptake have been shown to elevate plasma NA levels by reducing the plasma clearance of NA (Majewski et al., 1983a,b). In these experiments, uptake blockers did not increase the release of NA, and the authors suggested that after uptake blockade the prejunctional α_2-inhibitory system (see below) becomes increasingly activated to reduce transmitter release as demonstrated by the fact that α_2-adrenoceptor antagonists enhanced NA release more in the presence than absence of uptake blockade (Majewski, 1983a). Because the prejunctional α_2-inhibitory system may be impaired in ageing (see below), a diminished reuptake might affect both release and clearance of NA in the elderly. In humans, a diminished reuptake of NA results in both an increased rate of spillover and a decreased rate of clearance from the plasma (Esler et al., 1988). Hence, a reduced neuronal reuptake of NA in ageing is a feasible explanation for the increased plasma levels of NA in the elderly and can be explained in terms of a general run down of systems in ageing. A decreased density of adrenergic nerve terminals due to either a loss of nerve terminals (see above) or an increase in distance between the nerve terminals and the cardiovascular adrenoceptors (Guimaraes and Paiva, 1981) due perhaps to morphological changes could produce decreased neuronal NA uptake. Hence, an altered reuptake of NA can be explained without need to speculate on alterations in the uptake system at the molecular level, although changes may also occur at the level of the uptake process. An increased activity of synthetic enzymes in adrenergic nerves (Banerji et al., 1984; Partanen et al., 1985) could occur as a result of failure to conserve NA due to diminished reuptake. If these age-related changes found in animal studies also occur in humans, then the increased plasma levels of NA found in the elderly can be explained in terms of a diminished reuptake of NA into nerves.

D. Prejunctional Receptors

Prejunctional α_2-adrenoceptors mediate a feedback inhibition whereby NA modulates its own release (Langer, 1977; Starke, 1977; Westfall, 1977) (fig. 5). An altered sensitivity of these prejunctional α_2-receptors could result in an altered release of NA so that a decreased sensitivity should result in an increased release of NA. During maturation, responsiveness of prejunctional α_2-adrenoceptors is reported to decrease in the rat vas deferens (McAdams and Waterfall, 1986) and increase in the pithed rat heart (De Jonge et al., 1983) (table 13). A decreased responsiveness with ageing of prejunctional α_2-adrenoceptors has been reported in the pithed rat heart (Docherty and Hyland, 1986), rat isolated heart (Daly et al., 1989), rat vas deferens (Hyland and Docherty, 1985b), rat cerebral cortex (Qi and Nomura, 1988), but not human saphenous vein (Hyland and Docherty 1985b) (table 13). In the rat vas deferens, a decreased function of prejunctional inhibitory 5-HT$_1$ receptors has

PREJUNCTIONAL Adrenergic nerve varicosty

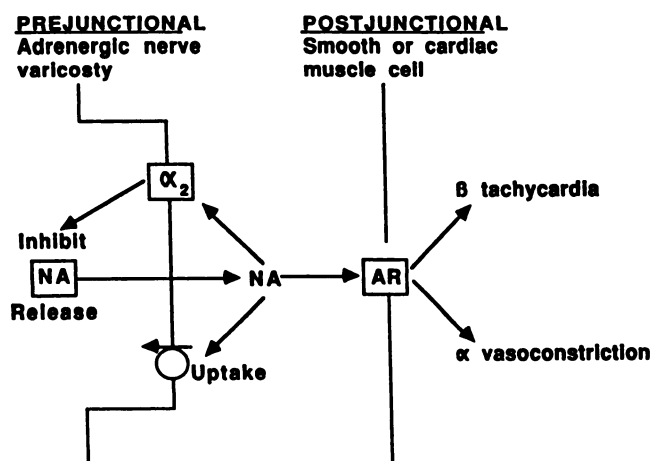**POSTJUNCTIONAL** Smooth or cardiac muscle cell

FIG. 5. Sites of drug action at adrenergic neuroeffector junctions in the cardiovascular system. AR, adrenoceptor.

TABLE 12

Effects of maturation or ageing on neuronal uptake of NA in rat and rabbit*

Species, strain, and tissue	Effects of maturation	Effects of ageing	Reference
Rat			
F344 heart		↑	Kreider et al., 1984; Daly et al., 1988
Sprague-Dawley heart		↓	Borton & Docherty, 1989
Wistar heart		↓	Docherty (unpublished)
Pithed Sprague-Dawley systemic		↓	Borton & Docherty, 1989
Anaesthetised Sprague-Dawley systemic		↓	Docherty & Hyland, 1986
F344 hindlimb		↑	Handa & Duckles, 1987b
F344 renal & femoral arteries		↔	Duckles, 1987b
F344 tail artery		↓	Duckles, 1987b
Rabbit			
Aorta	↔		Shibata et al., 1971
Ear artery	↓		Duckles, 1983

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased neuronal uptake in maturation or ageing.

TABLE 13

Effects of maturation or ageing on the responsiveness of prejunctional α_2-adrenoceptors*

Species and tissue	Effects of maturation	Effects of ageing	Reference
Rat			
Pithed heart		↓	Docherty & Hyland, 1986
	↑		De Jonge et al., 1983
Heart		↓	Daly et al., 1989
Vas deferens		↓	Hyland & Docherty, 1985b
	↓		McAdams & Waterfall, 1986
Human saphenous vein		↔	Hyland & Docherty, 1985a

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased responsiveness in maturation or ageing.

been reported (Moritoki et al., 1986b; Borton and Docherty, 1989), which has two components: the first, an age-related reduction in 5-HT₁-like receptor-mediated inhibition during maturation and ageing similar to the reduction in α_2-adrenoceptor-mediated reponsiveness; the second component, a loss of a 5-HT₁B-mediated response during maturation, presumably due to loss during maturation of 5-HT₁B receptors (Borton and Docherty, 1989). Hence, the age-related reduction of α_2-adrenoceptor-mediated responses in the rat vas deferens is not specific to α_2-adrenoceptors but also occurs for 5-HT₁-like receptors, suggesting a postreceptor site for this aged-related alteration. Therefore, it seems unlikely that the down-regulation of α_2-adrenoceptors is a result of overstimulation of the receptor by increased transmitter (NA) levels because down-regulation occurred both for autoreceptors (α_2) and heteroceptors (5-HT₁).

Although a decreased responsiveness of prejunctional α_2-adrenoceptors and the resultant increase in release of transmitter might be used to explain increased plasma NA levels in ageing, it should be remembered that, in the majority of studies, the stimulation-evoked release of transmitter is unchanged or declines with age (see above). Hence, decreased sensitivity of prejunctional α_2-adrenoceptors may at least partially restore transmission in the face of declining transmitter content.

IV. Cardiovascular Control

A. Control of Blood Pressure

1. Resting blood pressure. In humans blood pressure increases with age at least in Western societies, although this may not be a purely age-related phenomenon because blood pressure does not increase with age in some, usually small, isolated, "primitive" communities (Kotchen et al., 1982; Marmot, 1984; Ikeme, 1989). However, in most large scale studies, systolic pressure tends to increase with age throughout life, whereas diastolic pressure increases only to about the age of 60 years (Kannel, 1987; Kotchen et al., 1982; Robertson, 1989). Hence, the prevalence of isolated systolic hypertension increases with age (Probstfield et al., 1989). In rat models of ageing there are reports of no change (McCarty 1985; Docherty et al., 1986; Hoffman et al., 1985; Wei et al., 1987; Tuma et al., 1985) or an increase in blood pressure in aged conscious rats (Lee et al., 1972; Yu et al., 1985), and in rabbits (Owen, 1986) and dogs (Cox et al., 1981) blood pressure did not alter between adult and aged animals. Even in studies in which blood pressure was similar in conscious young and old rats, halothane anaesthesia caused a significantly greater decrease (Hoffman et al., 1985) and pentobarbitone anaesthesia caused a smaller increase (Docherty et al., 1986; Tuma et al., 1985) in blood pressure of aged as compared to young rats, resulting in a lower blood pressure in aged anaesthetised rats. Even in pithed rats, in which all central control of blood pressure is lost, resting diastolic blood pressure is significantly reduced in aged rats (Docherty et al., 1986) and this difference between young and old rats is abolished by the angiotensin-converting enzyme inhibitor captopril (Docherty, 1988a), suggesting that angiotensin maintains diastolic blood pressure in young but not old pithed rats.

Resting blood pressure is influenced by neuronal, hormonal, and reflex control and by structural and pathological changes in the cardiovascular system. Some of these factors such as the sympathetic nervous system and the baroreflex are involved mainly in short-term control of blood pressure, whereas other factors such as aldosterone and vasopressin are involved mainly in long-term control of blood volume, influenced by pathological changes. Because levels of circulating hormones can affect blood pressure in the short term, both by direct vascular actions and by indirectly influencing responses to other circulating agents, and in the long term by altering blood volume, it is worth considering how ageing affects blood levels of hormones. Although plasma levels of NA are increased by ageing (see above), it is not certain that these increased levels have any cardiovascular significance. Let us now consider several other hormones, the vasoconstrictor agents angiotensin and vasopressin (arginine vasopressin, antidiuretic hormone) and the vasodilator agent ANP, involved in the long-term control of blood pressure. Because the majority of control systems, both long and short term, act to increase blood pressure, it would appear that these systems have evolved mainly to maintain flow to vital organs in hypotensive situations and this may explain the tendency for blood pressure to increase with age.

2. Angiotensin. Angiotensin is involved both in the short-term control of blood pressure and, together with aldosterone, in the long-term control of blood volume. In the short-term control of blood pressure, angiotensin acts both as a direct vasoconstrictor and to facilitate vascular contractions particularly involving α_2-adrenoceptors (Palluk et al., 1985) and to facilitate adrenergic vasoconstriction by a prejunctional action (Gothert and Kollecker, 1986). Some of this angiotensin may be synthesised locally in the vascular wall (Gothert and Kollecker, 1986), although the physiological role of locally produced angiotensin has not been fully elucidated (Dzau, 1989). Although the vasoconstrictor response to angiotensin II is reported to be unchanged by ageing in the human vasculature (table 14), the activity of the renin-angiotensin-aldosterone system is reported to be reduced in the elderly in terms of morning plasma levels of renin and aldosterone activity (Crane and Harris, 1976; Tuck et al., 1973; Korkushko et al., 1984; James et al., 1986) and in terms of 24-h tonic and phasic levels (Cugini et al., 1987), and as a result it has been suggested that the ability of angiotensin-converting enzyme inhibitors to decrease blood pressure is diminished in elderly hypertensives due to lower plasma renin levels (Buhler et al., 1980), although other studies find angiotensin-converting enzyme inhibitors equally effective in elderly hypertensives (Jenkins et al., 1985; Baker, 1988; Cummings et al., 1989) perhaps because elderly hypertensives have increased plasma renin levels making them comparable to young hypertensives (Chebotarev et al., 1985;

TABLE 14
Effects of ageing on the pressor response to vasoconstrictors in vivo

Species and tissue	Effects of ageing	Reference
α-Adrenoceptor agonists		
Human systemic (α_1-agonist)	↓	Elliot et al., 1982;
(NA)	↔	Rosendorff et al., 1988
Human hand vein	↔	Martin et al., 1986; Pan et al., 1986
Anaesthetised rat (α_1-agonist)	↔	Docherty & Hyland, 1986
Pithed rat (α_1-agonist)	↔	Docherty & Hyland, 1986
Pithed rat (α_2-agonist)	↓	Docherty, 1988a
Pithed rat (captopril, α_2-agonist)	↔	Docherty, 1988a
Anaesthetised rabbit	↔	Dalrymple et al., 1982
Angiotensin II: human vasculature	↔	Hollenberg et al., 1974; Rosendorff et al., 1988

* Symbols: ↔, unchanged; ↓, decreased potency in ageing.

Cummings et al., 1989). Interestingly, it has been reported that tissue renin levels (Garst et al., 1979) increase during maturation (in spontaneously hypertensive rats) and angiotensinogen levels (Eggena et al., 1988) increase with age in cultured rat aortic smooth muscle cells in contrast to the situation in the plasma. The number of binding sites for angiotensin II in human platelets is reported to increase with age (Duggan et al., 1988), perhaps in response to diminished plasma levels of angiotensin II.

Diminished angiotensin II levels can influence the response to other vasoconstrictors. The pressor potency of the α_2-adrenoceptor agonist xylazine is reduced by ageing in the pithed rat but this age-related difference is abolished by captopril (Docherty, 1988a) (table 14), suggesting that angiotensin potentiates responses to α_2-adrenoceptor agonists (but not α_1-adrenoceptor agonists) and the diminished angiotensin levels in aged animals is reflected in a decreased α_2-adrenoceptor-mediated vasoconstriction. In humans, the pressor response to NA, which acts as an agonist both at α_1- and α_2-adrenoceptors, is reported to be slightly but not significantly reduced by ageing (Rosendorff et al., 1988). Pressor responses to α_1-adrenoceptor agonists are less influenced by captopril (Docherty, 1988a) and are generally unchanged by ageing (table 14), although there is a report of a reduced pressor potency of the α_1-selective agonist phenylephrine with ageing in humans (Elliott et al., 1982) (table 14).

3. Vasopressin. Although vasopressin (arginine vasopressin) has vasoconstrictor actions, its primary role is in blood pressure homeostasis by control of blood volume, and hence it is also known as antidiuretic hormone. The secretory capacity of vasopressin is reported to be unchanged or even increased during normal ageing in hu-

mans (Helderman et al., 1978; Kirkland et al., 1984) and experimental animals (Fliers and Swaab, 1983; Frolkis et al., 1982; Miller, 1987; Davies et al., 1990), and basal circulatory levels of vasopressin are increased in the elderly (Kirkland et al., 1984; Rondeau et al., 1982; Vargas et al., 1986; Davis and Davis, 1987). However, increased vasopressin in the elderly is offset by a decreased response of collecting tubules to vasopressin both in humans (Davis and Davis, 1987) and the rat (Miller, 1987; Phelps et al., 1989).

4. Atrial natriuretic peptide. Although they also produce vasodilation, the major role of the ANPs (atriopeptins) from the mammalian atria is in the hormonal control of blood volume by causing sodium and water excretion. Infusion of physiological concentrations of ANP causes increased sodium excretion without affecting blood pressure in humans (Anderson et al., 1987), but higher pharmacological concentrations decrease blood pressure (Ferrari et al., 1990). ANP is thought to be released mainly in response to atrial stretch, and hence levels are reported to be increased in congestive heart failure (Katoh et al., 1986; Schiffrin, 1988). In humans, the plasma levels of ANP are reported to increase with age (Haller et al., 1987; Montorsi et al., 1987; Singer et al., 1987; Duggan et al., 1988). Despite increased resting plasma levels of ANP, the elderly have reduced ability to concentrate urine and excrete a saline load (Davis and Davis, 1987), at least partly due to the 50% decrease in renal blood flow and glomerular filtration rate which occurs during ageing (Schmucker, 1985). However, although the elderly respond to a saline infusion with a larger absolute increase in plasma ANP, the increase is smaller than that occurring in a younger group when expressed as a percentage increase over basal levels (Haller et al., 1987). The higher plasma levels of ANP found in the elderly may be due to decreased renal responsiveness to ANP or to decreased plasma clearance or to the increased atrial pressure reported in the elderly, particularly during exercise (Ehrsam et al., 1983) ANP is also reported to blunt the aldosterone response to angiotensin II in humans (Anderson et al., 1986), but there is no information concerning the effects of ageing on this interaction, given that the activity of the renin-angiotensin-aldosterone system declines with age.

In conscious rats the depressor response to exogenous atriopeptin III is prolonged in aged animals without change in potency (Grimaldi et al., 1987), although this may simply reflect differences in baroreflex compensation (see later) rather than differences in metabolism between young and old because the depressor response to ANP in young adult dogs is minimised by the baroreflex (Koyama et al., 1986).

5. Pathological changes in the vascular wall. An increase in passive resistance of resistance vessels to distension occurs with ageing in rats (Folkow and Karlstrom, 1984) and dogs (Cox and Detweiler, 1988), probably due to the

age-related increase in intimal thickening with increased elastin levels (Yin, 1980). During human ageing, an increased incidence of atherosclerosis augments these purely age-related changes. Many elderly hypertensives have a disproportionately increased systolic blood pressure (O'Malley and O'Brien, 1980), mainly due to decreased elasticity of the major arteries (Gozna et al., 1974; Cox and Detweiler, 1988; Walsh, 1987; Lakatta, 1987; Kelly et al., 1989). Isolated systolic hypertension, usually defined as a systolic blood pressure >160 mm Hg and a diastolic blood pressure <90–95 mm Hg occurs in 10–30% of those >70 years of age (Davidson, 1989), and systolic blood pressure is a more important predictor of coronary heart disease than diastolic blood pressure (Fisher, 1985).

B. Control of Heart Rate

1. Resting heart rate. In humans, resting supine heart rate is reported to be unchanged (Conway et al., 1971; Kostis et al., 1982; Yin et al., 1978a; Bertel et al., 1980; Rodeheffer et al., 1984; Goldstraw and Warren, 1985; Vargas et al., 1986; Simpson and Wicks, 1988; McGarry et al., 1983; Smith et al., 1987; Wilkie et al., 1985; Rubin et al., 1982) or to decrease (Cinelli et al., 1987) with age (table 15). This latter study looked at mean heart rate

TABLE 15
Resting heart rate (beats/min) in adult and aged humans

	Adult	Aged	Reference
Supine	75.6	74.9	McGarry et al., 1983
Supine	66.5	65.4	Simpson & Wicks, 1988
Supine	73	69	Conway et al., 1971
Semisupine	69.5	66.0	Yin et al., 1978a
Supine	57.1	59.7	Smith et al., 1987
Supine	69	64	Goldstraw & Warren, 1985
Supine	60	62	Rubin et al., 1982
Daily mean	78.8	62.3*	Cinelli et al., 1987

* Heart rate in aged significantly different from heart rate in adult.

throughout 24 h (Cinelli et al., 1987) and therefore differed from all of the other studies which looked at heart rate over a short period of time. However, another 24-h study of heart rate in elderly subjects also showed a decreased rate in those >70 as compared with those 58–70 years of age (Ribera et al., 1989). When resting heart rates obtained for young and old groups are plotted in a graph, there is a tendency for a smaller between-study variation in heart rate for the elderly than young group;
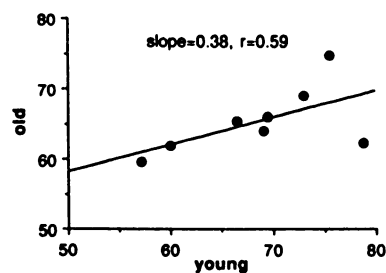

FIG. 6. Plot of resting heart rates in young and old humans. Data taken from table 15.

i.e., resting heart rate varies less between studies for the elderly (fig. 6) (see later).

There are reports of no change with age in resting heart rate in the unanaesthetised rat (Wei et al., 1987; Docherty et al., 1986; Rothbaum et al., 1974; Hoffman et al., 1985; Tuma et al., 1985), rabbit (Owen, 1986), and dog (Yin et al., 1978b) and reports of a decrease during maturation and ageing (Goldberg et al., 1988; Minami et al., 1989) or even an increase with age (McCarty, 1985) in resting heart rate in the rat (table 16) and a decrease with age in the resting heart rate of the anaesthetised dog and cat (Frolkis et al., 1988). In anaesthetised rats resting heart rate is reported to decrease during maturation (Kelliher and Conahan, 1980; Tanabe and Bunag, 1989) and to decrease (Docherty and Hyland, 1986; Docherty et al., 1986; Docherty, 1990) or to be unchanged (Kelliher and Conahan, 1980; Hoffman et al., 1985; Fouda and Atkinson, 1986; Tuma et al., 1985; Frolkis et al., 1988) by ageing (table 16). When resting heart rates obtained for young and old rats are plotted in a graph, differences emerge between data for conscious and anaesthetised animals. For conscious animals, there is a smaller between-study variation in heart rate for the old than young animals, but this did not occur in anaesthetised animals (fig. 7) (see later).

In the rat isolated heart basal heart rate is also reduced by ageing (Elfellah et al., 1986; Goldberg et al., 1988) even after chemical sympathectomy (Goldberg et al., 1988), but in pithed rats resting heart rate is not reduced by ageing (Docherty and Hyland, 1986).

2. Tachycardia. In humans there are many reports of a reduced positive chronotropic response to the β-adrenoceptor agonist isoprenaline (Vestal et al., 1979; Buhler et al., 1980; Kendall et al., 1982; Klein et al., 1986;
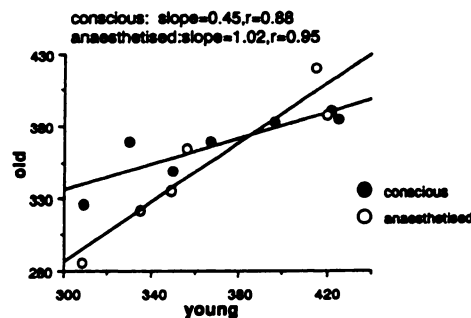

FIG. 7. Plot of resting heart rates in young and old conscious and anaesthetised rats. Data taken from table 16.

Montamat and Davies, 1989) (table 17). For instance, a 4.6-fold shift occurred in isoprenaline potency between those <35 years and those >60 years of age (Vestal et al., 1979). However, in the pithed rat preparation, used to avoid any reflex response to the vasodilator actions of isoprenaline, there is only a small 2-fold difference between young and old rats in the potency of isoprenaline at producing tachycardia (Docherty, 1988b) (fig. 4).

TABLE 17
*Effects of ageing on the tachycardia or positive inotropic response to isoprenaline or NA**

Species and tissue	Agonist	Effects of ageing	Reference
Rat			
Anaesthetised	Isoprenaline	↓	Simpkins et al., 1983
Pithed	Isoprenaline	↓	Borton & Docherty, 1989
	NA	↔	Borton & Docherty, 1989
Dog	Isoprenaline	↓	Yin et al., 1978b
Man	Isoprenaline	↓	Vestal et al., 1979; Buhler et al., 1980; Kendall et al., 1982; Klein et al., 1986; Montamat & Davies, 1989

* Symbols: ↔, unchanged; ↓, decreased response in ageing.

Hence a component of this diminished tachycardia to isoprenaline with age in intact humans or rats may be a diminished baroreflex tachycardia to the depressor response to isoprenaline. No change was found in the potency or maximum relaxation to β-adrenoceptor agonists during ageing in the human (Kendall et al., 1982) and rat vasculature (Docherty, 1988b; Docherty et al., 1986), although the potency of isoprenaline has been reported to increase during maturation in the rat (Docherty, 1988b) (table 15). In one human study, there were similar decreases of diastolic blood pressure in young (18–25 years) and old (68–83 years) to the β-agonist terbutaline but a significantly greater tachycardia in young than in old (Kendall et al., 1982). In another study, significant decreases in diastolic blood pressure and significant tachycardia to the β-agonist occurred in young humans, but no significant changes in diastolic blood pressure or heart rate occurred in old humans (Ebstein et al., 1985). Clearly, the direct cardiac stimu-

TABLE 16
Resting heart rate in conscious and anaesthetised rats

Strain	Immature	Adult	Aged	Reference
Conscious				
Wistar		309	326	Rothbaum et al., 1974
Lyon	412	357*		Su et al., 1986
F344	440	425	385*	Goldberg et al., 1988
F344		396.6	383	Wei et al., 1987
WKY	467	365*		Minami et al., 1989
F344		330	369*	McCarty, 1985
Sprague-Dawley		350	349	Hoffman et al., 1985
F344		422	391	Tuma et al., 1985
Sprague-Dawley		367	369	Docherty et al., 1986
Anaesthetised				
F344	440	415*	420*	Kelliher & Conahan, 1980
Sprague-Dawley	335	297*		Tanabe & Bunag, 1989
Ivanos		356	364	Fouda & Atkinson, 1986
Sprague-Dawley		308	286	Hoffman et al., 1985
F344		335	322	Tuma et al., 1985
Sprague-Dawley		420	388*	Docherty et al., 1986
		349	335	Frolkis et al., 1988

* Significantly different from immature or adult animals.

lant actions of the β-adrenoceptor agonist cannot be separated from baroreflex actions in these studies. Indeed, in pithed rats, the tachycardia to the physiological agonist NA is unchanged by ageing due to a diminished reuptake of NA with age (Borton and Docherty, 1989) (fig. 4), so that the use of isoprenaline or other exogenous agonists not substrates for uptake may overestimate the true alteration in cardiac responsiveness with age in terms of physiological function. The evidence for decreased cardiac β-adrenoceptor responsiveness with ageing is not as clear as it first appears.

3. Bradycardia. In the rat, bilateral vagotomy produced a significant tachycardia in young but not aged animals (Kelliher and Conahan, 1980), and the ability of the muscarinic antagonist atropine to produce tachycardia is reported to be unchanged in the rat (Rothbaum et al., 1974) or reduced with age both in the rat (Kelliher and Conahan, 1980) and in humans (Dauchot and Gravenstein, 1971), and the bradycardia to muscarinic agonists is reported to be reduced in the rat (Kelliher and Conahan, 1980). However, in these cardiovascular studies in vivo, alterations seen may be due to altered nerve activity or altered reflexes or alterations at the receptor level.

C. Autonomic Reflexes

1. Baroreflex. Homeostatic reflexes have evolved particularly to maintain blood flow to vital organs in hypotensive situations. The most important short-term autonomic cardiovascular reflex is the baroreflex mediated by the baroreceptors in the aortic arch and carotid sinus. The baroreceptors are mechanoreceptors that respond to changes in blood pressure. They project to the nucleus tractus solitarius in the dorsal medulla which has synaptic connections with interneurones which inhibit the vasomotor centre and stimulate the vagal cardioinhibitory centre. Baroreflex function can be altered pathologically at a variety of levels: altered sensitivity of baroreceptors to changes in blood pressure, altered central integration, altered efferent nerve activity in both sympathetic and parasympathetic nerves, and alterations in cardiovascular receptors. The baroreflex responds rapidly to maintain blood pressure near normal but quickly adapts so that the reflex begins to fade after a few hours. Long-term control of blood pressure is mainly under renal control, involving various systems including the renin-angiotensin-aldosterone system and vasopressin.

The baroreflex can be assessed in terms of the reflex bradycardia to a pressor agent or the reflex tachycardia to a depressor agent. The vagal component of the baroreflex bradycardia to the α-adrenoceptor agonist phenylephrine is reported to increase (Lo et al., 1988; Su et al., 1986) or even to decrease (Tanabe and Bunag, 1989) during maturation and to decrease with ageing (Rothbaum et al., 1974) in the rat. In humans the vagal reflex of the Valsalva manoeuvre is decreased by ageing (Oimomi et al., 1986), as is the bradycardia to phenylephrine

(Gribbin et al., 1971; Yin et al., 1978a; Elliott et al., 1982).

There are many reports that the baroreflex tachycardia to depressor agents or to postural change is decreased by ageing in humans (Elliott et al., 1982; McGarry et al., 1983; Collins et al., 1980; Dambrink and Wieling, 1987; Simpson and Wicks, 1988) and in rats (Docherty et al., 1986), although not in the anaesthetised dog (Cox et al., 1981) (table 18). Furthermore, the reduction of baroreflex function with age in nonhypertensive subjects was independent of blood pressure level, so that age is related to altered baroreflex sensitivity independent of blood pressure (Shimada et al., 1986). Similarly, the sympathetic response to cold and heat stress is reduced in aged rats (McCarty, 1985) and humans (Collins et al., 1980), although this may be partly due to a reduced response of microvessels because capillary blood flow is reduced in the nailfold circulation of the elderly (Richardson and Schwartz, 1985). In individual studies, heart rate variability decreases with age in humans (MacLennan et al., 1980; Mancia et al., 1983; Cinelli et al., 1987; Simpson and Wicks, 1988), and the difference from young was more marked in the standing position (Simpson and Wicks, 1988). Even when comparing studies, the variation between studies in heart rate for the aged is less than that for the young, both in humans (fig. 6) and conscious, but not anaesthetised, rats (fig. 7). Likewise, respiratory sinus arrhythmia decreases with ageing (Hellman and Stacy, 1976). The elderly respond to postural stress with diminished changes of heart rate and diastolic blood pressure even in the absence of postural hypotension (Collins et al., 1980; MacLennan et al., 1980; Williams et al., 1985; Vargas et al., 1986; Smith et al., 1987; Dambrink and Wieling, 1987).

2. Postural hypotension. Postural hypotension is reported to be common in the elderly, with an overall incidence of 22% (MacLennan et al., 1980) or 24% (Caird et al., 1973) in the elderly and an incidence of 24% (MacLennan et al., 1980), 30% (Caird et al., 1973), or 30–50% (Robbins and Rubenstein, 1984) in those >75 years, but other studies report a prevalence as low as 10.7% (Mader et al., 1987). Prevalence of postural hypotension was found to be as low as 6.4% in a group in which known risk factors for postural hypotension were excluded (Mader et al., 1987). However, various factors can explain differences between studies in incidence of postural hypotension, including day to day (Lipsitz, 1989), time of day, and time of measurement after standing variability (MacRae and Bulpitt, 1989). In elderly subjects with postural hypotension a failure to increase peripheral resistance sufficiently (Williams et al., 1985) or arterial rigidity (MacLennan et al., 1980) have been implicated. Postprandial hypotension is also reported to be a problem in the elderly both in a normal population (Lipsitz et al., 1983) and in a population with orthostatic hypotension (Robertson et al., 1981). Elderly subjects

TABLE 18
*Effects of maturation or ageing on autonomic reflexes**

Species	Effects of maturation	Effects of ageing	Reference
Human			
Baroreflex		↓	Gribbin et al., 1971; Yin et al., 1978a; Elliott et al., 1982; McGarry et al., 1983; Collins et al., 1980
Postural stress		↓	Collins et al., 1980; McLennan et al., 1980; McGarry et al., 1983; Williams et al., 1985; Smith et al., 1987
Cold stress		↓	Collins et al., 1980
Valsalva		↓	Oimomi et al., 1986
Heart rate variability		↓	McLennan et al., 1980; Mancia et al., 1983; Cinelli et al., 1987; Simpson & Wicks, 1988
Respiratory sinus arrhythmia		↓	Hellman & Stacy, 1976
Rat			
Baroreflex		↓	Rothbaum et al., 1974; Docherty et al., 1986
	↓		Tanabe & Bunag, 1989
	↑		Lo et al., 1988; Su et al., 1986
Cold stress		↓	McCarty, 1985
Dog baroreflex		↔	Cox et al., 1981

* Symbols: ↑, increased; ↔, unchanged; ↓, decreased response in maturation or ageing.

responded to the postprandial decrease in systolic pressure with insufficient tachycardia and therefore failed to compensate adequately for the pooling of blood in the splanchnic circulation during digestion.

3. Depressor responses. The hypotensive actions of the α_1-adrenoceptor antagonist prazosin and the nonselective antagonist phentolamine are reported to be unchanged by ageing in humans, and the hypotensive actions of prazosin are unchanged in the rat and rabbit (table 8). Although the ability of ketanserin (a 5-HT$_2$ and α_1-adrenoceptor antagonist: Cohen, 1984; Marwood and Stokes, 1984) to decrease blood pressure increases with age in humans (table 8; Breckenridge, 1988), this is not true of the selective 5-HT$_2$ antagonist ritanserin (table 8). The vasodilator sodium nitroprusside is more effective at decreasing blood pressure in old than in young humans (McGarry et al., 1983; Irvine and Shepherd, 1984) and conscious rats (Docherty et al., 1986), presumably due to a diminished baroreflex compensation, because the depressor response to sodium nitroprusside was little affected by age in pentobarbitone-anaesthetised rats in which the baroreflex is markedly attenuated (Docherty, 1990).

4. Diminished reflexes. Diminished reflex responses to pressor or depressor agents, diminished response to heat or cold, postural hypotension, and postprandial hypotension are all manifestations of a reduced ability to respond appropriately to changes in blood pressure or blood flow. Diminished heart rate variability and decreased respiratory sinus arrhythmia may be partly due to baroreflex alterations but may additionally invoke diminished sympathetic control of heart rate. Other factors are involved in some of these changes such as decreased responsiveness of cutaneous veins to temperature change.

D. Cardiac Changes

1. Stroke volume. At rest in healthy human subjects, stroke volume and cardiac output are unaltered (Ehrsam

et al., 1983; Rodeheffer et al., 1984) or decreased by ageing (Conway et al., 1971). Stroke volume at rest is reported to be unchanged by ageing in the conscious rat (Rothbaum et al., 1974; Tuma et al., 1985) and unchanged (Tuma et al., 1985) or decreased (Frolkis et al., 1988) by ageing in the anaesthetised rat and decreased by ageing in the rat isolated heart (Friberg et al., 1985). Stroke volume and cardiac output at rest are also reported to be decreased by ageing in the anaesthetised dog, cat, and rabbit (Frolkis et al., 1988). Hence, both human and animal studies confirm that stroke volume is little changed by ageing at least at rest. During dynamic exercise, the maximum cardiac output and oxygen consumption is reported to decline with age (Conway et al., 1971; Gerstenblith et al., 1976), although it is difficult to rule out disease-related changes because the incidence of heart disease is increased by ageing (Tejada et al., 1968). However, in some studies of subjects without overt coronary disease, cardiac output at rest and during exercise was unaffected by age, although maintained by a slower heart rate (Kostis et al., 1982) and greater stroke volume during exercise in elderly individuals (Rodeheffer et al., 1984; Lakatta, 1987): a cardiac output of 15 litres/min was achieved by a heart rate of approximately 135 beats/min and a stroke volume of 115 ml in young and by a heart rate of 115 beats/min and a stroke volume of 135 ml in the elderly group (values estimated from fig. 5 of Rodeheffer et al., 1984). Maximum exercise heart rate is reduced in the elderly as is exercise tolerance (Kostis et al., 1982). This increased stroke volume in the elderly during exercise is associated with an increase in end-diastolic volume by the Frank-Starling relationship (Rodeheffer et al., 1984; Lakatta, 1987). Increases in left ventricular end-diastolic pressure have also been reported in older, as compared to younger, patients with mitral regurgitation (Clancy et al., 1985). However, higher filling pressures in the elderly lead to a tendency

for breathlessness to occur in exercise (Riesenberg, 1986).

2. Ventricular hypertrophy. There is a modest degree of left ventricular hypertrophy with age in humans in response to the increased afterload caused by increased systolic blood pressure, but a decreased myocardial contractility and decreased stroke volume may develop (e.g., poor left ventricular filling due to myocardial stiffness: Wikstrand, 1986) in the long term, activating homeostatic factors including the adrenergic, renin-angiotensin, and vasopressin systems to maintain blood pressure in the face of declining cardiac output, further increasing the afterload on the heart. This vicious circle leads to the clinical syndrome of congestive heart failure. Left ventricular hypertrophy is an independent risk factor for ventricular arrhythmias and sudden death (Frohlich, 1987).

E. Treatment of Hypertension in the Elderly

Because the European Working Party on Hypertension in the Elderly study (Amery et al., 1985) has demonstrated the benefits of treating hypertension in the elderly, interest has focused on which class of drug might be especially beneficial to decrease blood pressure in the elderly. Agents with direct vasodilator actions might be expected to be more effective at lowering blood pressure in the elderly, due to diminished reflex compensation, although postural problems must be considered. Ketanserin (De Cree et al., 1985) and calcium entry blockers but not β-blockers (Buhler, 1983) are claimed to be especially effective in the elderly. However, it is perhaps less important to find agents that are more effective at lowering pressure in the elderly as compared to young hypertensives than to find useful antihypertensive agents effective in the elderly whether or not they are more or less effective in the young. Angiotensin-converting enzyme inhibitors (Jenkins et al., 1985; Cox et al., 1989), β-blockers (Coope and Warrender, 1986), α-methyldopa (Amery et al., 1985), verapamil (Cox et al., 1988), and thiazide diuretics (Amery et al., 1985; Hulley et al., 1985) have also been shown to be beneficial as antihypertensive agents in the elderly.

Side effects may make effective antihypertensive agents less useful in the elderly: postural hypotension may make vasodilators less useful; cardiodepressant actions may make β-blockers and some calcium entry blockers unsuitable in those with congestive heart failure; centrally acting agents may be less useful due to sedation (Davidson, 1989, Robertson, 1989). Glomerular filtration rate decreases with age and this decline is accompanied by a decrease in the renal elimination of drugs as has been demonstrated for digoxin (Cusack et al., 1979), resulting in a need to prescribe lower doses in the elderly. In a study of prescribing patterns in general practice in Ireland, β-blockers were prescribed approximately twice as often in those <65 years of age than those >65 years (Nolan and O'Malley, 1987). Because

left ventricular hypertrophy is associated with morbidity in the elderly, therapeutic regimens have been sought that can regress myocardial hypertrophy. Several antihypertensive therapies may be effective in reducing left ventricular hypertrophy including weight loss, methyldopa, β-blockers, angiotensin-converting enzyme inhibitors, and calcium entry blockers (Frohlich, 1987; Mace et al., 1985).

F. Synopsis

Our knowledge of the effects of ageing on the cardiovascular system is clearly incomplete, and we are left with so much apparently contradictory findings due to tissue differences, species and strain differences, and differences between drugs. One can make the simple observation that ageing tends to cause a loss, rather than an improvement, of responsiveness. Increased response in the elderly usually reflects diminished reflex compensation as is the case with depressor agents.

At the isolated tissue level, there is little evidence that altered responsiveness to, or altered plasma levels of, vasoactive agents with age has any marked influence on overall cardiovascular control. It seems overall that any reduction in the response to a vasoconstrictor is likely to be largely matched by a reduction in the response to a vasodilator. This does not mean that changes in responsiveness to vasoactive agents do not have implications, but more information is required on how ageing alters the local control of blood flow and on the integrity of the endothelium. On the aged myocardium, a diminished response to β-adrenoceptor agonists probably reflects diminished response to a variety of agents, sug-
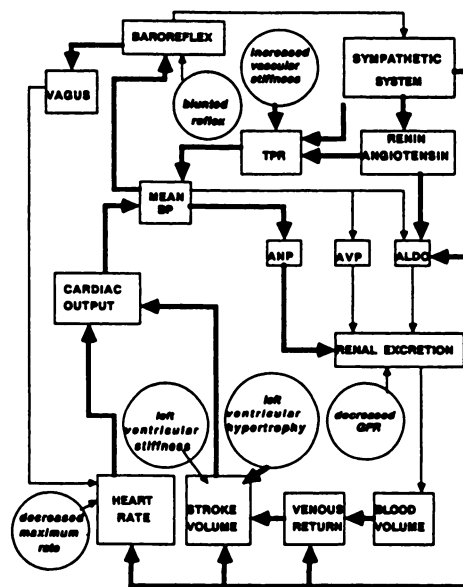

FIG. 8. Cardiovascular control mechanisms. *Bold arrows* indicate positive or stimulatory actions, and *thin arrows* indicate negative or inhibitory actions. Items enclosed in *circles* indicate possible age-related changes in cardiovascular control. *BP*, blood pressure; *TPR*, total peripheral resistance; *AVP*, arginine vasopressin; *ALDO*, aldosterone; *GFR*, glomerular filtration rate.

gesting that "run down" of response in both heart and vasculature may reflect a decline in signal transduction mechanisms rather than alterations at the receptor level. There is no clear evidence that altered plasma levels of vasoactive agents during ageing results in a compensatory inverse alteration in receptor number.

A decline in prejunctional α_2-adrenoceptor-mediated inhibition of transmitter release and of neuronal NA uptake may serve to maintain cardiovascular function in face of declining neurotransmitter content and declining postjunctional response. Hence, the cardiac response to the endogenous neurotransmitter NA may be largely unaffected by ageing despite diminished response to agents such as isoprenaline which are not substrates for reuptake. The increased plasma levels of NA found in the elderly may be a consequence of decreased reuptake of NA.

In fig. 8 the major mechanisms involved in the short- and long-term control of blood pressure and the sites at which age-related pharmacological changes can alter homeostasis are illustrated. Diminished baroreflex compensation is responsible for the failure to respond appropriately to rapid changes in blood pressure, whereas increased vascular stiffness and diminished glomerular filtration rate may be responsible for the gradual increase in blood pressure, particularly systolic, which occurs with age. A decreased maximum tachycardia with age results in a need to rely more on increased stroke volume to increase cardiac output during exercise, and additionally the increased afterload on the heart results in left ventricular hypertrophy. Increased left ventricular stiffness may slow diastolic filling and result in an inability to reach the desired cardiac output and may lead to heart failure. The aged cardiovascular system probably functions normally at rest, but under stress, diminished autonomic reflexes cause problems, and in exercise, a given cardiac output is maintained by a larger stroke volume and slower heart rate in the elderly. Drug therapy may have more marked effects on the cardiovascular system of the elderly, both due to diminished compensatory reflexes and diminished renal excretion of drugs.

Finally, because the elderly are becoming an increasing proportion of the population in Westernised countries, putting an increasing burden on health services, it is of increasing importance to establish whether .diet or change of lifestyle can slow down the changes in the cardiovascular system with ageing and which drugs are especially suited for the treatment of cardiovascular disease in the elderly.

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Errata

In the September 1989 issue of Pharmacological Reviews (Vol. 41, No. 3), in the article, "IV. Pharmacological Properties in Vivo," by Jean F. Borel, the following changes should be noted:

p. 240: fig. 2 (With permission from ref. 6)

p. 277: ref. 449 = 448

p. 282: ref. 317 = 316

p. 284/285 table 4. Corrections of selected references:

3rd line: ref. 874 = 873

    7th line: ref. 223 = 222

    9th line: ref. 260 = 259

    13th line: ref. 203 = 282

    21st line: ref. 151 = 150

    26th line: ref. 652 = 646

    31st line: ref. 633 = 632

p. 285 (continued)

    4th line: ref. 78 = 79

    5th line: ref. 222 = 224

    33rd line: ref. 540 = 539

p. 286: ref. 106 = 100

p. 287: ref. 649 = 648; ref. 628 = 629

p. 289: ref. 785 = 785a

p. 290: ref. 627 = 628

p. 291: ref. 866 = 886

    ref. 150 = 151

p. 306: ref. 601 = 602

p. 319 table 6, Corrections of selected references:

    26th line: ref. 629 = 627

    35th line: ref. 288 = 286

p. 329: on the right, 23rd line: days −7 to 60 or 7 to 60 . . .

p. 333: ref. 287 = 286

p. 334: ref. 538 = 540

    on the right, 14th line from below: this dose of CS marked

p. 342: on the right, 3rd and 4th lines from below:

    . . . protection of lethal and by the intracerebral route, infected mice, . . .

p. 345: ref. 677 = 676

p. 347: ref. 446 = 449

p. 365: ref. 707a: . . . uveoretinitis induced with autologous retina. J. ocul. Pharmacol . . . .