ASSOCIATE EDITOR: LYNETTE C. DAWS

Serotonin and Blood Pressure Regulation

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Abstract——5-Hydroxytryptamine (5-HT; serotonin) was discovered more than 60 years ago as a substance isolated from blood. The neural effects of 5-HT have been well investigated and understood, thanks in part to the pharmacological tools available to dissect the serotonergic system and the development of the frequently prescribed selective serotonin-reuptake inhibitors. By contrast, our understanding of the role of 5-HT in the control and modification of blood pressure pales in comparison. Here we focus on the role of 5-HT in systemic blood pressure control. This review provides an in-depth study of the function and pharmacology of 5-HT in those tissues that can modify blood pressure (blood, vasculature, heart, adrenal gland, kidney, brain), with a focus on the autonomic nervous system that includes mechanisms of action and pharmacology of 5-HT within each system. We compare the change in blood pressure produced in different species by short- and long-term administration of 5-HT or selective serotonin receptor agonists. To further our understanding of the mechanisms through which 5-HT modifies blood pressure, we also describe the blood pressure effects of commonly used drugs that modify the actions of 5-HT. The pharmacology and physiological actions of 5-HT in modifying blood pressure are important, given its involvement in circulatory shock, orthostatic hypotension, serotonin syndrome and hypertension.

I. Introduction

5-Hydroxytryptamine (5-HT;[1] serotonin) is an ancient substance (Azmitia, 2001). The discovery of 5-HT is part of pharmacological history. 5-HT was recognized as a substance, isolated from blood serum (sero-), that could modify the tone of smooth muscle (-tonin) (Rapport et al., 1948; Erspamer and Asero, 1952; Page and McCubbin, 1953a,b). Just a few years later, the two original 5-HT receptors—D for dibenzyline and M for morphine—were recognized in smooth muscle preparations by Gaddum and Picarelli (1957). 5-HT pharmacology was born. Although 5-HT was discovered within the cardiovascular (CV) system, it is fair to say that the effects of 5-HT within the cardiovascular system are not well understood and integrated compared with the well established actions of 5-HT in the gastrointestinal system, and the plethora of knowledge regarding the actions of 5-HT in the central nervous system (Barnes and Sharp, 1999; Hoyer et al., 2002; Green, 2006; Berger et al., 2009).

This review represents an unbiased presentation of 5-HT as a substance that can modify blood pressure. We refer the reader to other reviews that cover different aspects of the CV system or that provide a more detailed historical perspective of 5-HT in the CV system: Kuhn et al., 1980; Marwood and Stokes, 1984; Docherty, 1988; Vanhoutte, 1991; van Zwieten et al., 1992; McCall and Clement, 1994; Yildiz et al., 1998; Nebigil and Maroteaux, 2001; Ramage, 2001; Doggrell, 2003; Côté et al., 2004; Maurer-Spurej, 2005; Watts, 2005; Villalón and Centurión, 2007; Ramage and Villalón, 2008; Nalivaiko and Sgoifo, 2009; Nichols, 2009; Nigmatullina et al., 2009; Monassier et al., 2010; and Mercado et al., 2011. We will not discuss pulmonary blood pressure or pulmonary hypertension, but refer readers to an excellent review: MacLean and Dempsie, 2009.

[1]Abbreviations: 5-CT, 5-carboxamidotryptamine; 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine (serotonin); 5-HTP, 5-hydroxytryptophan; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; AVA, arteriovenous anastomoses; CNS, central nervous system; CV, cardiovascular; DOCA, deoxycorticosterone salt; GR127935, *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-1–1′-biphenyl-4-carboxamide; HR, heart rate; IDO, indoleamine dioxygenase; IML, intermediolateral nucleus; KO, knockout; L-NNA, N^G-nitro-L-arginine; MAO, monoamine oxidase; NE, norepinephrine; NOS, nitric-oxide synthase; NTS, nucleus of the tractus solitarius; PCPA, parachlorophenylalanine; PCPAME, parachlorophenylalanine methyl ester; RVLM, rostral ventrolateral medulla; SERT, serotonin transporter; SHR, spontaneously hypertensive rat; SNRI, serotonin/norepinephrine-reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor; TCA, tricyclic antidepressant; TPH, tryptophan hydroxylase; WT, wild type.

II. 5-Hydroxytryptamine Biochemistry and Models

5-HT synthesis begins with dietary intake of l-tryptophan, an essential amino acid (Fig. 1). Foods high in L-tryptophan include egg whites, cod, chocolate, dairy products (yogurt, cheeses, milk), several meats, and nuts. The fate of tryptophan lies in the comparative activities of the enzymes indoleamine dioxygenase (IDO)/tryptophan dioxygenase and tryptophan hydroxylase (TPH). A majority

FIG. 1. Chemical schematic of the synthesis and metabolism of 5-HT.

of L-tryptophan is handled by IDO/tryptophan dioxygenase, an estimated 5 to 10% of tryptophan being shuttled through the TPH/5-HT pathway (Salter et al., 1995; Stone and Darlington, 2002). Over the past decade, the field has recognized two independent forms of TPH. TPH1 is expressed primarily in peripheral tissues, whereas TPH2 is expressed primarily in the central nervous system (Walther and Bader, 2003; Walther et al., 2003). Splice variants of TPH2 have been observed (Abumaria et al., 2008). This enzyme, dependent on the important cofactor tetrahydrobiopterin, commits tryptophan to the fate of 5-HT by converting tryptophan to 5-hydroxytryptophan

(5-HTP; Fig. 1) (Kuhn 1999). Mouse knockouts of both the TPH1 and TPH2 (Alenina et al., 2009) isoform are available, as is a double knockout of TPH1 and TPH2 (Savelieva et al., 2008). A multitude of aromatic amino acid decarboxylases can then convert 5-HTP into 5-HT. 5-HT is rapidly converted by monoamine oxidase and aldehyde dehydrogenase to 5-hydroxyindole acetic acid (5-HIAA), a stable metabolite. 5-HT itself can also be converted into melatonin (Stone and Darlington, 2002), whereas the IDO product, kynurenine, has niacin as one of its downstream products. Thus, ingestion of tryptophan is not a pure commitment to 5-HT synthesis. This is a relevant statement, given that tryptophan is sold as a dietary supplement, in an unregulated fashion, intended for use an antidepressant and sleep aid. The molecules depicted in Fig. 1 and those in the tryptophan metabolic pathway can be identified with high-pressure liquid chromatography.

In many cells, 5-HT is taken up by the serotonin transporter (SERT) and by other amine transporters. Both mouse and rat models with a nonfunctional SERT have been produced and will be further discussed in section IV.A. In each species, circulating blood 5-HT is low, but intestinal 5-HT concentration is not different in wild-type and the SERT($-/-$) animals (Chen et al., 2001; Linder et al., 2009). Thus, the ability of the body to make 5-HT is not compromised, but the ability of the platelet to carry 5-HT is significantly reduced when SERT is not functional. An outstanding question is the fate of intestinal 5-HT without the platelet. The SERT dysfunctional rodents, along with the TPH knockouts, have facilitated important in vivo investigations of the relationship between 5-HT and blood pressure, as described in succeeding sections.

III. 5-Hydroxytryptamine Receptor Pharmacology

As described above, 5-HT receptor pharmacology began with the discovery of the D receptor (dibenzyline) and M receptor (morphine) in the guinea pig ileum (Gaddum and Picarelli, 1957). The International Union of Basic and Clinical Pharmacology (IUPHAR) issues receptor nomenclature guidelines, and this was last done for 5-HT in publication form in 1994 (Hoyer et al., 1994; Martin, 1994). IUPHAR routinely updates its database; thus, the most current information, as supported by experts in 5-HT, can be found at this site: http://www.iuphar-db.org/DATABASE/FamilyMenu Forward?familyId=1. This particular site covers all 5-HT receptors except for the 5-HT$_3$ receptor, which can be found at http://www.iuphar-db.org/DATABASE/FamilyMenu Forward?familyId=68. This division recognizes that most 5-HT receptors are G protein-coupled, heptahelical proteins (class A), whereas the 5-HT$_3$ receptors are ion channels. In Table 1, we present a straightforward nomenclature scheme for 5-HT receptors. Many of the responses to 5-HT receptor activation cited in this table will be described below, and it is clear that 5-HT has significant and diverse effects throughout the cardiovascular system.

IV. Intersections of 5-Hydroxytryptamine and the Cardiovascular System that Affect Blood Pressure

Several tissues, organs, and neural circuits contribute to the control of blood pressure, and 5-HT can influence many of them. Table 1 lists the relevant locations of the various 5-HT receptors that contribute to cardiovascular regulation. Although we will briefly describe 5-HT's effects in the kidney, adrenal gland, heart, and blood, the focus of this review is on the vasculature, its control by the sympathetic nervous system, and the central nervous system pathways that determine the sympathetic nerve activity to cardiovascular tissues. We describe the presence and handling of 5-HT, the function and pharmacology of 5-HT, and give at least one example of a change in the response to 5-HT in a pathological condition that is specific to each system.

A. 5-Hydroxytryptamine in Circulating Blood: Free and Platelet-Bound

It is here that the highest peripheral levels of 5-HT are found in the cardiovascular system. Understanding the handling of 5-HT (synthesis, storage, release) in blood is critical, because it is through the blood that the circulatory system will come into contact with free, circulating 5-HT as well as 5-HT contained in platelets.

1. 5-Hydroxytryptamine Synthesis and Handling. Blood platelets do not synthesize 5-HT, but possess the SERT and acquire a high concentration of 5-HT (estimated in the millimolar range) from the intestine, where 5-HT is synthesized in enterochromaffin cells (Berger et al., 2009). Biologically active 5-HT (i.e., in contact with vasculature) is free 5-HT, existing outside of the platelet and measured as platelet free/poor 5-HT (see Table 2 for free and platelet 5-HT in humans). Rat free plasma 5-HT has been measured in the low to mid nanogram per milliliter range, largely consistent with those of the human. One to ~100 nM concentrations of 5-HT are estimated as platelet free plasma in the human (Kema et al., 2001; Monaghan et al., 2009; estimating a 5-HT molecular weight of 176 g/mol), although Brand and Anderson (2011) question the validity of 5-HT plasma measures in humans given the high variability of 5-HT concentration reported in 101 studies that they compare. The existence of whole-blood monoamine oxidase activity implies that blood, like tissues, has the ability to metabolize 5-HT to a less active substance (Celeda and Artigas, 1993) and keep circulating levels of 5-HT low. The SERT($-/-$) rat, created by Edwin Cuppen (Homberg et al., 2007), provides a unique view into other ways for 5-HT to be carried in blood. The SERT protein is truncated in this knockout such that the SERT protein, which is partially expressed, is not functional. This animal has low circulating platelet-poor and platelet-rich levels of 5-HT compared with the SERT ($+/+$) rat, which is to be expected because SERT is thought to be the primary mechanism by which 5-HT is concentrated in platelets (Linder et al., 2008a,b). However, when SERT ($-/-$) rats are infused with 5-HT, platelets do take up 5-HT (Davis et al., 2011). This

suggests either incomplete knockout of SERT or, more likely, the existence of nonSERT mechanisms to concentrate 5-HT. The SERT KO mouse has a similar reduction in blood 5-HT (Chen et al., 2001). Whether there is sufficient free 5-HT in the blood to activate vascular 5-HT receptors de-pends on the 5-HT receptor expressed by a blood ves-sel, because the affinity of 5-HT for these receptors can vary significantly (Table 1). Circulating blood is the most immediate source of 5-HT for the peripheral circulatory system.

TABLE 1
5-HT receptor pharmacology and location in the CV system

Values in parenthese are K_i values. Cloned indicates that values are only from cloned, transfected receptors. Affinity values are from averaged experiments available on http://pdsp.med.unc.edu/indexR.html. Modified from Watts, 2005.

Receptor		Agonists	Antagonists	Location and Response Relevant to Blood Pressure
Heptahelical				
Ion channel				
5-HT$_{1A}$ (2.65 nM)		8-OH-DPAT, U92016A	WAY100635, NAN190	Central nervous system (lower, raise blood pressure)
5-HT$_{1B}$ (16.01 nM)		CP-93129, sumatriptan, eletriptan (some 1D affinity)	GR-127935 (some 1D affinity), GR55562, isamoltane, SB236057	Smooth muscle (contraction); sympathetic presynaptic terminal (inhibition of NE release); sympathetic ganglia (inhibit transmission); central nervous system (lower, raise blood pressure)
5-HT$_{1D}$ (10.05 nM)		PNU-109291, alniditan, eletriptan (some 1B affinity), L-703,664	SB 272183, LY310762, BRL15572	Smooth muscle (contraction)
5-ht$_{1E}$[a] (7.00 nM, cloned)		5-CT (nonselective), BRL54443 (some 1F affinity)	None available	None identified
5-HT$_{1F}$ (67.60 nM, cloned)		LY334370, BRL54443 (1E affinity), LY344864	None available	Smooth muscle (contraction), trigeminal nerve
5-HT$_{2A}$ (970.80 nM)		DOB (2A/2B, 2C), DOI, α-methyl-5-HT (non-selective), TCB-2	R-96544, MDL100907, volinanserin	Platelet (aggregation and 5-HT release); smooth muscle (contraction); adrenal gland (epinephrine release); heart (tachycardia, contraction); central nervous system
5-HT$_{2B}$ (11.35 nM)		BW723C86	LY272015, RS127445	Endothelium (relaxation); smooth muscle (contraction); cardiac valves (proliferation)
5-HT$_{2C}$ (32.58 nM)		WAY 163909, DOI (2A, 2B, 2C), MK212, 1-methylpsilocin	RS102221, SB242084	None identified
5-HT$_3$ (splice variants) (190.33 nM)		SR57227A, 2-methyl-5-HT, phenylbiguanide	Odansetron, granisetron	Vagus nerve (bradycardia); ganglia
5-HT$_{4(short,long)}$ (117.00 nM, cloned)		RS67506, BIMU1, BIMU8, zacopride	GR113808, RS100235, SB204070	Cardiomyocyte (contraction)
5-HT$_6$ (116.53 nM, cloned)		WAY 181,187, EMD 386088	Ro 04-6790, SB 399885, SB271046	None identified

TABLE 1–Continued

Receptor		Agonists	Antagonists	Location and Response Relevant to Blood Pressure
5-HT$_{7(a-d)}$ (3.65 nM, cloned)		LP12, LP44, AS-19, 5-CT (nonselective)	SB-269970, SB-258719	Smooth muscle (relaxation); cardiomyocyte (contraction)

* No physiological response has been associated with receptor, hence lower case.

AS-19, (2S)-(+)-5-(1,3,5-trimethylpyrazol-4-yl)-2-(dimethylamino)tetralin; BIMU1, endo-N-(8-methyl-8-azabicyclo-[3.2.1] oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide; BIMU8, 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide; BRL15572, 3-[4-(4-chlorophenyl)piperazin-1-yl]-1,1-diphenyl-2-propanol; BRL54443, 5-hydroxy-3-(1-methylpiperidin-4-yl)-1H-indole; BW723C86, α-methyl-5-(2-thienylmethoxy)-1H-indole-3-ethanamine; CP-93129, 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl-5H-pyrrol[3,2-b]pyridin-5-one; DOI, 2,5-dimethoxy-4-iodoamphetamine; EMD 386088, 5-chloro-2-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole; GR113808, 1-methyl-1H-indole-3-carboxylic acid, [1-[2-[(methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl ester; GR-127935, N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-carboxamide; GR55562, 3-[3-(dimethylamino)propyl]-4-hydroxy-N-[4-(4-pyridinyl)phenyl]benzamide; L-703,664, N,N-dimethyl-5-[(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)methyl]-1H-indole-3-ethanamine; LP12, 4-(2-diphenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinehexanamide; LP44, 4-[2-(methylthio)phenyl]-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-1-piperazinehexanamide; LY272015, 1-[(3,4-dimethoxyphenyl)methy]-2,3,4,9-tetrahydro-6-methyl-1H-pyrido[3,4-b]indole; LY310762, 1-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-1,3-dihydro-3,3-dimethyl-2H-indol-2-one; LY334370, 4-fluoro-N-(1-methyl-4-piperidinyl)-1H-indol-5-yl]-benzamide; LY344864, N-[(3R)-3-(dimethylamino)-2,3,4,9-tetrahydro-1H-carbazol-6-yl]-4-fluorobenzamide; MDL100907, (2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]methanol; MK212, 6-chloro-2-(1-piperazinyl)pyrazine; NAN190, 1-(2-methoxyphenyl)-4-(4-phthalimidobutyl)piperazine; PNU-109291, (S)-3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-1H-2-benzopyran-6-carboxamide; R-96544, (2R,4R)-5-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-3-pyrrolidinol; Ro 04-6790, 4-amino-N-[2,6-bis(methylamino)-4-pyrimidinyl]-benzenesulfonamide; RS100235, 1-(5-amino-6-chloro-2,3-dihydro-1,4-benzodioxin-8-yl)-3-[1-[3-(3,4-dimethoxyphenyl)propyl]piperidin-4-yl]propan-1-one; RS102221, 8-[5-(2,4-dimethoxy-5-(4-trifluoromethylphenylsulphonamido)phenyl-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione; RS127445, 4-(4-fluoro-1-naphthalenyl)-6-(1-methylethyl)-2-pyrimidinamine; RS67506, 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-2-methylsulphonylamino)ethyl-4-piperidinyl]-1-propanone; SB204070, (1-butyl-4-piperidinyl)methyl-8-amino-7-chloro-1,4-benzodioxane-5-carboxylate; SB236057, 1′-ethyl-7-([4-[2-methyl-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]phenyl]carbonyl)-2,5,6,7-tetrahydrospiro[furo [2,3-f]indole-1,4′-piperidine]; SB242084, 6-chloro-2,3-dihydro-5-methyl-N-[6-[(2-methyl-3-pyridinyl)oxy]-3-pyridinyl]-1H-indole-1-carboxyamide dihydrochloride; SB258719, 3-methyl-N-[(1R)-1-methyl-3-(4-methyl-1-piperidinyl)propyl]-N-methylbenzenesulfonamide; SB269970, (2R)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine; SB271046, 5-chloro-N-[4-methoxy-3-(1-piperazinyl)phenyl]-3-methyl-benzo[b]thiophen-2-sulfonamide; SB272183, 5-chloro-2,3-dihydro-6-(4-methylpiperazin-1-yl)-1(4-pyridin-4-yl)napth-1-ylaminocarbonyl)-1H-indole); SB399885, N-(3,5-dichloro-2-methoxyphenyl)-4-methoxy-3-(1-piperazinyl)benzenesulfonamide; SB699551, N-[2-(dimethylamino)ethyl]-N′-[[4′-[[(2-phenylethyl)amino]methyl][1,1′-biphenyl]-4-yl]methyl]cyclopentanepropanamide; SR57227A, 1-(6-chloro-2-pyridinyl)-4-piperidinamine; U92016A, (R)-8-dipropylamino-6,7,8,9-tetrahydro-3H-benzo[e]indole-2-carbonitrile; WAY 100635, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide; WAY 163909, [(7bR, 10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1-hi]indole]; WAY 181187, 2-(1-[6-chloroimidazo[2,1-b][1,3]thiazole-5-sulfonyl)-1H-indol-3-yl)ethan-1-amine.

2. Function and 5-Hydroxytryptamine Pharmacology.

The 5-HT$_{2A}$ receptor is the dominant receptor in platelets of multiple species. Once stimulated, 5-HT$_{2A}$ receptors promote the aggregation of platelets, resulting in release of more 5-HT, ADP, and other substances. Preparations of platelets cause either contraction or relaxation of isolated arteries (Zellers et al., 1991).

3. Change in Pathological Conditions.

Platelets carry most of the blood 5-HT, so changes in platelet mechanics, fragility, and aggregation (promoted by 5-HT) can dramatically change local 5-HT concentration and, potentially, circulating 5-HT (Le Quan Sang et al., 1991; Ding et al., 1994). In 1989, Umegaki et al. demonstrated reduced content of platelet 5-HT in deoxycorticosterone salt (DOCA salt) hypertensive rats. This is a finding consistent with a number of models of

hypertension and suggests that, at least in hypertension, the platelet is "activated," in that it has a lower content of 5-HT.

B. 5-Hydroxytryptamine Presence and Function in the Vasculature

5-HT was discovered, in part, as a vasoconstrictor and this is the property for which 5-HT is best known in the cardiovascular system.

1. 5-Hydroxytryptamine Synthesis and Handling.

A serotonergic system (uptake, synthesis, and metabolism) exists in isolated blood vessels (Ni et al., 2008). Isolated blood vessels from the mouse and rat stain for antibodies raised against 5-HT, a staining that does not depend on the presence of resident circulatory cells that might contain 5-HT. Ni et al. (2004) demonstrated the

TABLE 2
Blood 5-HT measures (whole, platelet-rich, and platelet poor) in humans

Measures of 5-HT	Comments	Reference
95–116 ng/ml	Whole blood	Jelen et al., 1979
378–518 ng/10^9 platelets	Whole platelet	Topsakal et al, 2009
65–250 ng/ml	Whole blood	Breuer et al., 1996
1–3 ng/ml	Blood diasylate	Castejon et al., 1999
0–609 ng/10^9 platelets	Platelet-rich plasma	Koch et al., 2004
350–650 ng/10^9 platelets	Platelet-rich plasma (female)	Carrasco et al., 1998
1.0–1.6 nM	Platelet rich plasma	Brenner et al., 2007
3.4–23.8 nmol/10^9 platelets	Platelet rich plasma	Kema et al., 2001
66–106 ng/10^8 platelets	Platelet rich plasma	Biondi et al., 1988
105–165 nmol/10^{11} platelets	Platelets	Kamal et al., 1984
88–246 ng/10^8 platelets	Platelets	Gujrati et al., 1994
3.4–3.5 nmol/10^9 platelets	Platelets	Fetkovska et al., 1990
12–20 ng/ml	Platelet-poor plasma (children)	Breuer et al., 1996
1–4 ng/ml	Platelet-poor plasma (female)	Carrasco et al., 1998
0.1–1 nM	Platelet-poor plasma	Brenner et al., 2007
2.5–6.1 ng/ml	Platelet-poor plasma	Biondi et al., 1988
89.5–115.5 nM	Platelet-poor plasma	Monaghan et al., 2009
5.6–23.9 ng/ml plasma	Platelet-poor plasma	Koch et al., 2004

presence of TPH1 but not TPH2 mRNA and protein in the isolated normal rat aorta and superior mesenteric artery, as well as the ability of the isolated artery to synthesize 5-HTP when arteries were incubated with exogenous tryptophan and BH_4. Isolated blood vessels—including arteries and veins—concentrate 5-HT actively through SERT (Ni et al., 2004; Linder et al., 2008a,b). Fenfluramine can release 5-HT from the blood vessel into the fluid in which the vessel is bathed (Ni et al., 2008), and this 5-HT would be near 5-HT receptors that exist within the blood vessel. Thus, there are at least two sources of 5-HT for a blood vessel: endogenously synthesized 5-HT and exogenous 5-HT. It is noteworthy that blood vessels can rapidly metabolize transported 5-HT to 5-HIAA.

2. Function and 5-Hydroxytryptamine Pharmacology. In humans and in animals, 5-HT predominantly causes direct arterial constriction, and the list of references here are just a few that report the effects of 5-HT in the isolated artery; more are included in the legend to Fig. 2: McGregor and Smirk, 1970; Docherty, 1988; Rosón et al., 1990; Vanhoutte, 1991; van Zwieten et al., 1992; Webb et al., 1992; Nishimura and Suzuki, 1995; Nishimura, 1996; Yildiz et al., 1996, 1998; Boston and Hodgson, 1997; Watts, 1997, 2002, 2005, 2009; Hutri-Kähönen et al., 1999; Ramage, 2001; Janiak et al., 2002; Doggrell, 2003; Gul et al., 2003; Côté et al., 2004; Watts and Thompson, 2004; Villalón and Centurión, 2007; Ramage and Villalón, 2008; Nichols, 2009; and Nigmatullina et al., 2009. These studies have been performed in a variety of isolated blood vessels—basilar, superior mesenteric, aortic, femoral, mesenteric resistance, for example—such that constriction cannot be attributed to a single receptor type or size of vessel. The diversity of vessel response (C = contraction, R = relaxation), species response within a vessel and 5-HT receptor subtype mediating the response (e.g., 1B, 2A) is illustrated in Fig. 2. This figure was constructed using only data from isolated vessel studies. Cerebral vessels include the meningeal, temporal and occipital arteries. Resistance vessels are included in several of the circulations (cerebral and mesenteric). Vasoconstriction is predominantly mediated by the 5-HT_{2A} receptor, but $5\text{-HT}_{1B/1D}$ receptors can also mediate constriction, exemplified by the success of the triptans, $5\text{-HT}_{1B/1D}$ agonists, in the treatment of migraine (Gilmore and Michael, 2011). Virtually every blood vessel, when mounted in a tissue bath, responds to 5-HT with contraction from baseline.

By contrast, not all blood vessels can relax to 5-HT. In the rat jugular vein and pulmonary artery and coronary arteries of rat and greyhound, 5-HT causes relaxation through activation of 5-HT_{2B} and 5-HT_7 receptors (Mylecharane, 1990; Mankad et al., 1991; Woodman and Dusting, 1994; Ellis et al., 1995; Glusa and Roos, 1996; Centurión et al., 2000, 2004; Jähnichen et al., 2005). 5-HT relaxes human umbilical arteries (Haugen et al., 1997) and dilates skeletal muscle arterioles, an important finding

with respect to blood pressure (Alsip and Harris, 1992; Alsip et al., 1996). In some cases, 5-HT receptors that mediate constriction must be blocked before unmasking or revealing 5-HT relaxant receptors (McLennan and Taylor, 1984). This raises the question of how these relaxant 5-HT receptors would be activated physiologically. Do they dampen the overall effect of 5-HT vasoconstriction? In what situation(s) can relaxant receptors be directly activated without activation of contractile receptors? In an isolated tissue bath, we may not be appropriately mimicking the group of substances that would act as the endogenous constrictors upon which 5-HT would stimulate relaxation. There are examples in which 5-HT relaxant receptors are revealed without blockade of contractile 5-HT receptors. This includes the equine coronary artery (Obi et al., 1994) and dog coronary artery (Terrón, 1996). Although no antagonists of contractile 5-HT receptors were added in the equine coronary artery studies, Terrón (1996) showed that whereas 5-HT relaxation was present naturally in the dog coronary artery, the sensitivity to 5-HT and 5-carboxamidotryptamine (5-CT) as relaxants was increased when the $5\text{-HT}_{1B/1D}$ receptor antagonist *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-1–1′-biphenyl-4-carboxamide (GR127935) was added. We note that 5-CT has affinity for 5-HT_7 receptors (Waeber and Moskowitz, 1995; Krobert et al., 2001). Thus, both contractile and relaxant receptors are in play in blood vessels, and the balance of their effects is different in different vessel types and species.

The effects of 5-HT in the vasculature become less clear when studying a system more complicated than an isolated vessel, probably because 5-HT now has the ability to stimulate multiple receptors within multiple tissue types that may act in seemingly contradictory fashion as it pertains to smooth muscle tone. We share here but a few examples. Calama et al. (2003, 2005) raise the interesting possibility that β_2 adrenergic receptors are the effectors of 5-HT-induced vasodilation in the rat hindquarters, connecting 5-HT to the adrenal medulla (epinephrine release?), because 5-HT itself does not have appreciable affinity for β-adrenergic receptors. Whether released epinephrine would also interact with α-adrenergic receptors in this situation is unknown. It is interesting to note that 5-HT itself has affinity for α-adrenergic receptors (Grandaw and Purdy, 1996). In pentobarbital-anesthetized dogs, intra-arterial 5-HT caused a vasodilation in the femoral arterial circulation that was abolished by ganglionic blockade (Phillips et al., 1985). Likewise, 5-HT increases the external carotid blood flow of the dog (Villalón et al., 1993). In the human forearm vasculature, 5-HT causes an increase in forearm blood flow, but the receptor mechanism is unclear. Blauw et al. (1988, 1991), Bruning et al. (1993, 1994), and Kemme et al. (2000) performed a number of studies to identify this receptor, and the pharmacology of the 5-HT relaxant receptor was most consistent with that of the 5-HT_3 receptor, a receptor unusual to the vasculature. Because of the inherent difficulty in performing studies in
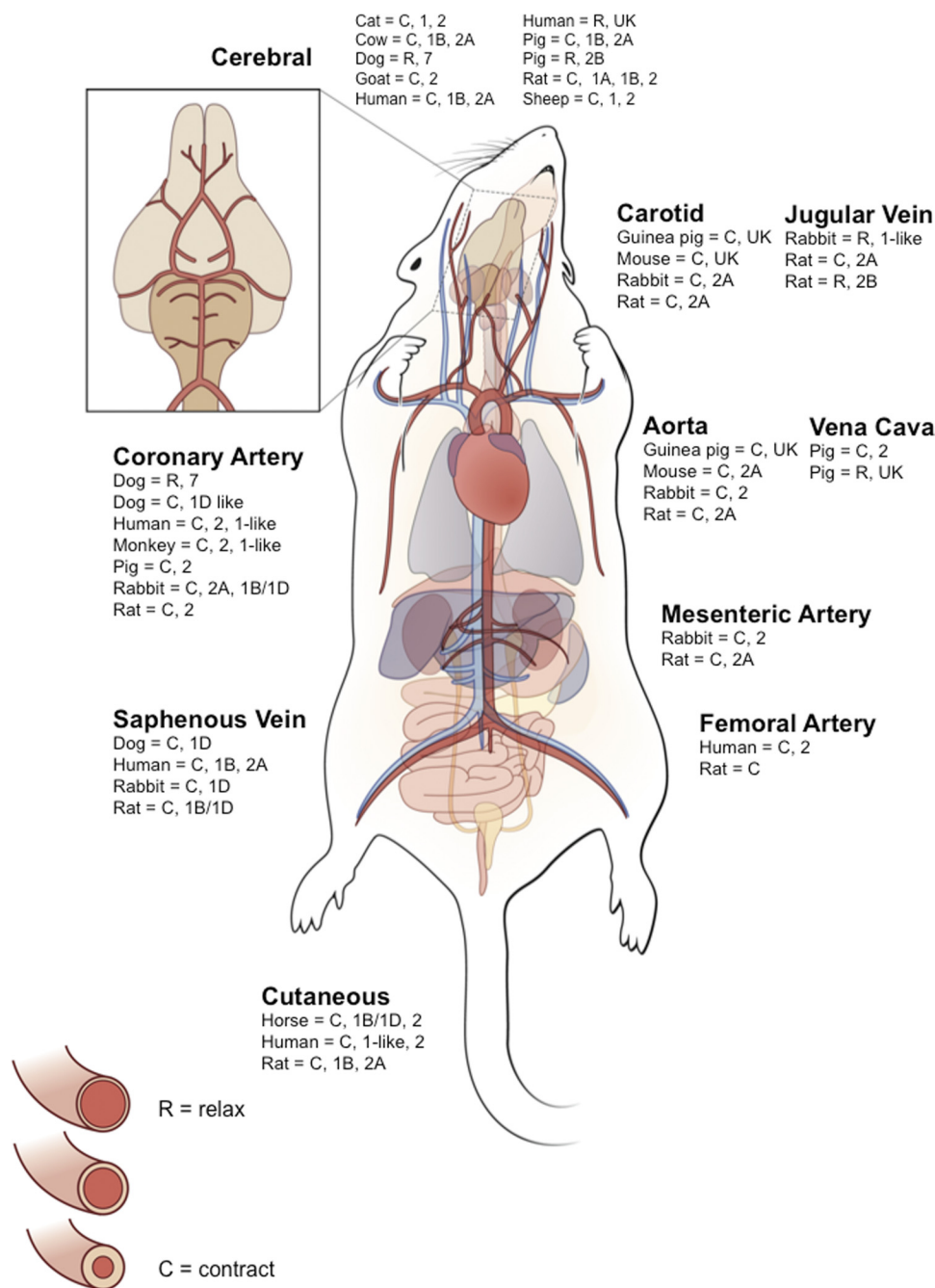
FIG. 2. Response of the vasculature to 5-HT, as depicted by using the rat vasculature as a model. Both constriction (C) and relaxation (R) may be listed for the same species if both responses were observed. Species name is listed, and the subtype of the receptor mediating the response is listed second (1B, 2A). UK, unknown receptor mechanism. Data were collected from the following references: Lemberger et al., 1984; Miller et al., 1984; Feniuk et al., 1985; Nyborg and Mikkelsen, 1985; Cohen, 1986; Leff et al., 1987; Hamel et al., 1989, 1993; Parsons et al., 1989, 1992; Bodelsson et al., 1990; Borton et al., 1990; Chester et al., 1990; Gaw et al., 1990; Mylecharane, 1990; Toda and Okamura, 1990; van Heuven-Nolsen et al., 1990; Asher et al., 1991; Lai et al., 1991; Parsons, 1991; Sumner, 1991; Cushing and Cohen, 1992a,b, 1993; Dorigo et al., 1992; Eglen et al., 1992; Weiner et al., 1992; Bax et al., 1993; Glusa and Müller-Schweinitzer, 1993; Jansen et al., 1993; Cushing et al., 1994, 1996; Yildiz and Tuncer, 1994; Fujiwara and Chiba, 1995; Miranda et al., 1995; Schmuck et al., 1996; Terrón, 1996; Valentin et al., 1996; Verheggen et al., 1996, 1998, 2004, 2006; Zwaveling et al., 1996; Ellwood and Curtis, 1997; Parsons et al., 1998; Nilsson et al., 1999; Roon et al., 1999; Terrón and Falcón-Neri, 1999; Bouchelet et al., 2000; Galzin et al., 2000; Geerts et al., 2000; Ishida et al., 2001; Lamping and Faraci, 2001; McKune and Watts, 2001; Schöning et al., 2001; Razzaque et al., 2002; Teng et al., 2002; van den Broek et al., 2002; Froldi et al., 2003, 2008; Edvinsson et al., 2005; Nagai et al., 2007; Zerpa et al., 2007; Masu et al., 2008; Linder et al., 2010; Radenkoviä et al., 2010.

humans, the breadth of the pharmacology used to verify and identify this response has not been as wide as that in animal models.

The ability of 5-HT to alter arteriovenous anastomoses (AVA)—present in the skin, fingers, lips, and ears—has

been studied. Saxena and Verdouw (1982) reported increases in arteriolar blood flow in pig ears and skin, observed as a "pinking" of the tissue after injection of 5-HT ($1\text{--}10\ \mu g \cdot kg^{-1} \cdot min^{-1}$) into the carotid artery of the pig, an event that decreased the blood pressure of the animals.

This increased flow, presumably in the capillaries or nutritive vessels, was considered to occur at the expense of non-nutrient or AVA blood flow. Experiments were also performed in the cat, which similarly responded with a decrease in blood pressure to intra-arterial 5-HT, but tissue blood flow did not change significantly. In the human, intra-arterial 5-HT decreased AVA blood flow and increased capillary skin blood flow (Blauw et al., 1991). Likewise, the 5-HT$_{1A}$ agonist 8-OH-DPAT decreased AVA blood flow in the anesthetized pig (Bom et al., 1989) and caused cutaneous vasoconstriction in the canine forelimb (Dobbins et al., 1983). The affinity of 8-OH-DPAT for the 5-HT$_7$ receptor complicates the attribution of such an event to a single receptor (Wood et al., 2000; Sprouse et al., 2004). In the rat tail, 5-HT has the interesting effect of causing an increase in tail temperature—indicative of dilation in this cutaneous circulation—that was associated with a decrease in blood pressure (Key and Wigfield, 1992). Similar results were observed with the administration of the 5-HT releaser fenfluramine in the rat (Subramanian and Vollmer, 2004). Thus, a cutaneous vasodilation in the rat may play a role in the decrease in blood pressure in response to 5-HT, but the mechanisms of such dilation are not known. A discussion of the relative contribution of the cutaneous circulation to changes in systemic blood pressure is beyond the scope of this review but is an interesting idea in light of the discussion of whether temperature homeostasis or blood pressure homeostasis has primacy in the body (Blankfield, 2006).

3. Change in Pathological Conditions. Hyper-reactivity (or enhanced vasoconstriction) to 5-HT is a hallmark of vascular damage. This is observed experimentally as a lower threshold for 5-HT to cause contraction, an increased potency of 5-HT, and/or an increased efficacy of 5-HT compared with a normotensive control. One of the best-studied changes in vascular response to 5-HT has been in vessels from humans and animals with high blood pressure (hypertension). Hyper-reactivity occurs in arteries and in veins in hypertension, in a number of different vascular beds and differently sized vessels (Cummings et al., 1986; Thompson and Webb, 1987; Huzoor-Akbar et al., 1989; Dohi and Lüscher, 1991; Webb et al., 1992; Moreno et al., 1996). In several models of experimental hypertension, up-regulation of 5-HT$_{2B}$ receptors in the smooth muscle is one mechanism by which 5-HT becomes hyper-reactive (Watts et al., 1995, 1996; Watts, 1997; Watts and Fink, 1999; Banes and Watts, 2002, 2003; Russell et al., 2002). Mineralocorticoids can directly stimulate expression of the 5-HT$_{2B}$ receptor (Banes and Watts, 2002, 2003) such that an up-regulated receptor enables a more sensitive contraction. It should be noted that the 5-HT$_{2B}$ receptor is expressed in arterial smooth muscle of a normotensive animal. This receptor does not seem to be functionally coupled to contraction as it is in hypertension. Thus, there may be more than one event in hypertension—up-regulation of the receptor and/or signaling element—

that allows for vessels to be hyperresponsive to 5-HT. This is but one example of the change in vascular responsiveness to 5-HT in a pathological state.

C. 5-Hydroxytryptamine Presence and Function in the Heart

The effects of 5-HT on the heart are complex, and important work has been performed, in particular by Kaumann and Levy (2006) and Nebigil and Maroteaux (2001).

1. 5-Hydroxytryptamine Synthesis and Handling. 5-HT has been found in the heart (Sole et al., 1979), and Ikeda et al. (2005) demonstrated the ability of neonatal rat cardiomyocytes to synthesize 5-HT. 5-HT is a survival factor for cardiomyocytes, as demonstrated by Nebigil et al. (2003a). SERT expression has also been observed in cultured cardiac myocytes (Sari and Zhou, 2003) and heart valves (Pavone et al., 2008). Loss of TPH in the mouse resulted in abnormal cardiac activity, suggesting that peripheral 5-HT—from within or outside of the heart—is important to cardiac function (Côté et al., 2003) and development.

2. Function and 5-Hydroxytryptamine Receptor Pharmacology. Kaumann and Levy (2006) have provided a focus for 5-HT receptors in the human cardiovascular system, demonstrating that 5-HT increases atrial function and arrhythmias as well as positive inotropic, lusitropic, and arrhythmic effects in the ventricle, primarily through activation of 5-HT$_4$ receptors. The work of Nebigil and Maroteaux (2001) strongly supports the role of the 5-HT$_{2B}$ receptor (originally the stomach fundus 5-HT receptor) in normal heart development and function. These researchers and others have shown that receptors for 5-HT exist directly on cardiac myocytes and on the vagus and sympathetic nerves. Stimulation of 5-HT$_3$ receptors on the vagus nerves (cardiac vagal afferents) accounts for the bradycardia elicited by activation of the Bezold-Jarisch reflex. 5-HT can also act as a sympatholytic through activation of 5-HT$_1$ receptors on sympathetic nerve terminals, inhibiting norepinephrine release. Both of these mechanisms contribute to a reduced cardiac output, which would be associated with a decrease in blood pressure. However, 5-HT can also activate the heart. The receptor mechanism for 5-HT to increase heart rate (positive chronotropy) is species-dependent. For example, this occurs through activation of 5-HT$_{2A}$ receptors in the rat, 5-HT$_4$ receptors in the pig and human, and 5-HT$_7$ receptors in the cat (Saxena and Villalón, 1991; Villalón et al., 1997; Côté et al., 2004). In isolated cardiomyocytes, 5-HT stimulates mitogenesis, and the 5-HT$_{2B}$ receptor is critical for development of the heart in the mouse (Nebigil and Maroteaux, 2001). 5-HT stimulates hypertrophy in cardiac myocytes, and Bianchi et al. (2005) suggested the provocative hypothesis that 5-HT may be used as a substrate for monoamine oxidase (MAO), ultimately providing the hydrogen peroxide that activates hypertrophic pathways.

Thus, the cardiac effects of 5-HT are complex and species-dependent; collectively, these studies suggest that 5-HT could both increase and decrease blood pressure through its actions in the heart.

3. Change in Pathological Conditions. Up-regulation and stimulation of the 5-HT$_{2B}$ receptor within the heart leads to cardiac hypertrophy (Nebigil et al., 2003b), such that mice lacking the 5-HT$_{2B}$ receptor are protected from cardiac hypertrophy. Significant interest has been paid to the expression of 5-HT receptors on aortic valves (especially the 5-HT$_{2B}$ receptor), because the 5-HT releaser and weight-loss drug fenfluramine causes valvular dysfunction (Roth, 2007; Huang et al., 2009; Hajjo et al., 2010). Finally, SERT KO mice demonstrate cardiac fibrosis (Pavone et al., 2009).

D. 5-Hydroxytryptamine Presence and Function in the Kidney

1. 5-Hydroxytryptamine Synthesis and Handling. The proximal tubules of the kidney are a site of synthesis for 5-HT (Stier and Itskovitz, 1985; Sole et al., 1986; Stier et al., 1986; Itskovitz et al., 1989; Hafdi et al., 1996). As a positively charged molecule, 5-HT is excreted by SERT and other cation transporters within the nephron, where it may reduce the inhibitory effect of parathyroid hormone-induced inhibition of sodium-phosphate transport (Hafdi et al., 1996).

2. Function and 5-Hydroxytryptamine Pharmacology. 5-HT has two notable effects on renal function, both of which would promote the elevation of blood pressure. First, when administered to the isolated, perfused kidney, 5-HT causes an elevation in perfusion pressure, a response supported by renal vasoconstriction. The 5-HT receptor of the main renal artery is exquisitely sensitive to 5-HT, and the pharmacology of this interesting response has yet to be defined, most closely resembling a 5-HT$_2$-like receptor in the rat (Watts and Thompson, 2004). Second, when 5-HT is given to rats or cats in vivo or in vitro to cortical tubules, sodium excretion is reduced (Fastier and Waal, 1957; Frandsen and Nielsen, 1966; Soares-da-Silva, 1996). In the cat (Fastier and Waal, 1957), 5-HT caused a decrease in blood pressure. In the human, the prodrug γ-L-glutamyl-5-hydroxy-L-tryptophan was given (16.6 μg · kg^{-1} · min^{-1} i.v.) over 60 min. The authors state that there was no difference in blood pressure and pulse rate on the days of experimentation, but the data are not presented (Li Kam Wa et al., 1994). Sodium and volume retention would keep blood volume elevated. In the dog, the picture is less clear, because 5-HT has been reported to increase (Shoji et al., 1989) or more commonly decrease (Blackmore, 1958; Park et al., 1968) urinary excretion of sodium. Overall, these findings suggest 5-HT has antinatriuretic/antidiuretic effects within the kidney that increase blood volume and support blood pressure.

3. Change in Pathological Condition. Serotonin syndrome, which results from an elevated level of 5-HT typically caused by ingestion of foods and drugs, can result in renal failure (Rajapakse et al., 2010). 5-HT has also been implicated in the nephropathies that accompany diabetes (Doggrell, 2003).

E. 5-Hydroxytryptamine Presence and Function in the Adrenal Gland

The adrenal gland is a significantly understudied tissue with respect to 5-HT.

1. 5-Hydroxytryptamine Synthesis and Handling. When animals are infused with 5-HT for 1 week via a minipump (ALZET Osmotic Pumps, Cupertino, CA), the adrenal gland accumulates a significant amount of 5-HT (Linder et al.,
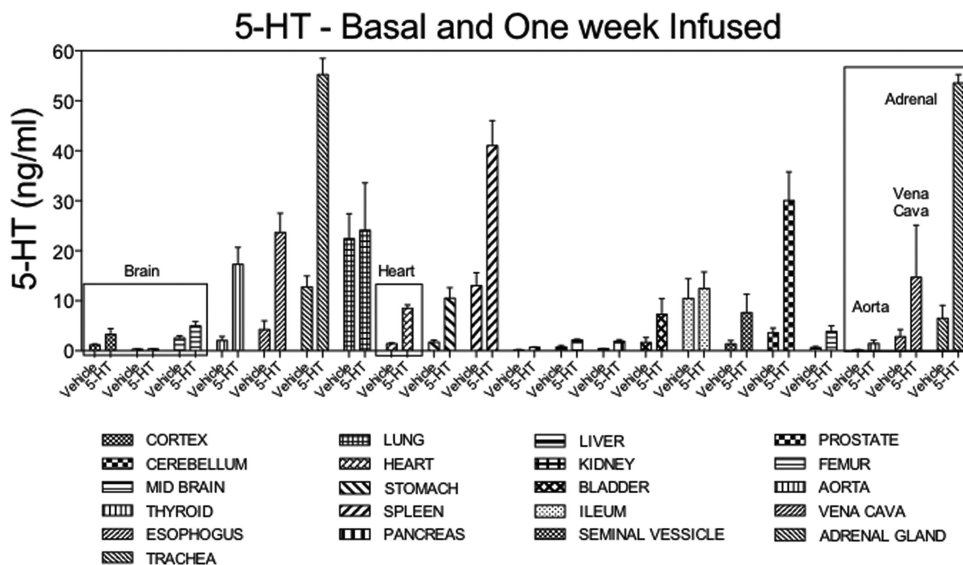
FIG. 3. Distribution of 5-HT in organs when infused with vehicle or 5-HT at a dose of 25 μg · kg^{-1} · min^{-1} in the rat for one week. Vehicle animals receive saline. Bars represent means ± S.E.M. for $n = 6$. Boxes highlight organs that are of cardiovascular interest. [Adapted from Linder AE, Beggs KM, Burnett RJ, and Watts SW (2009) Body distribution of infused serotonin in rats. *Clin Exp Pharmacol Physiol* **36:**599–601 Copyright © 2009 John Wiley & Sons, Inc. Used with permission.

2009), and Fig. 3 illustrates that the adrenal gland becomes one of the most concentrated reservoirs of 5-HT in the body. The uptake of 5-HT by the adrenal gland was virtually abolished in the SERT($-/-$) rat, demonstrating the importance of SERT to the adrenal accumulation of 5-HT. It is noteworthy that endogenous 5-HT has also been located in the adrenal medulla, with evidence that 5-HT is synthesized within the chromaffin cells in the frog and rat (Csaba and Sudár, 1978; Verhofstad and Jonsson, 1983; Holzwarth et al., 1984; Brownfield et al., 1985; Holzwarth and Brownfield, 1985; Delarue et al., 1992). However, it is not clear whether the adrenal gland—cortex or medulla—can synthesize 5-HT. In the human, TPH was not detected immunohistochemically in the adrenal cortex (Meyer and Brinck 1999). An interesting connection between adrenal gland and brain 5-HT synthesis was made by Miller et al. (1980), who demonstrated that brain tryptophan utilization was determined by the presence or absence of the adrenal gland. GTP cyclohydrolase is present in the adrenal gland, and this makes the tetrahydrobiopterin that is a necessary cofactor of the tyrosine, tryptophan, and phenylalanine hydroxylases (Nagatsu et al., 1995). Thus, there is potential for 5-HT to modify blood pressure through actions in the adrenal gland.

2. Function and 5-Hydroxytryptamine Pharmacology. 5-HT can act as a sympathomimetic in the sympathetic nerves of the blood vessels (Kawasaki and Takasaki, 1984), and 5-HT stimulates adrenal medullary epinephrine release through mechanisms that are both receptor-dependent and -independent (Bagdy et al., 1989; Sugimoto et al., 1996). 5-HT also has effects within the adrenal cortex. The role of the 5-HT$_4$ receptor in the normal human adrenal gland includes stimulation of cortisol (Louiset et al., 2004), whereas 5-HT$_7$ receptors are associated with an increase in adenylate cyclase activity that leads to aldosterone production (Contesse et al., 1999; Lenglet et al., 2002), suggesting an important mechanism in water and salt retention.

3. Change in Pathological Condition. Little is known in this regard. 5-HT$_4$ receptors are located in the adrenal gland (Brudeli et al., 2010), and elevated levels of the transcript of this receptor are detected in the adrenal glands of patients with unilateral aldosterone-producing adenoma (Cartier et al., 2005; Ye et al., 2007), but it is not known how or whether the up-regulated 5-HT$_4$ receptor contributes to

the disease. The ability of the adrenal gland to concentrate 5-HT to levels that are 2 to 3 times that in another tissue in the body (rat) raises the question of what 5-HT does in this tissue and how this is modified in disease.

F. 5-Hydroxytryptamine Influence on the Autonomic Control of Blood Pressure

5-HT has a multitude of effects on the peripheral nervous system that can ultimately modify the effects of sympathetic activity. Figure 4 depicts various places within the nervous system where 5-HT might act to affect blood pressure, and we begin at the level of the sympathetic-vascular junction.

1. Peripheral Effects of 5-Hydroxytryptamine at the Sympathetic-Vascular Junction. The arterial vascular system, including resistance arterioles, is innervated by the sympathetic nervous system. Sympathetic nerve terminals release the sympathetic neurotransmitters—norepinephrine (NE), neuropeptide Y, and ATP—to contract vascular smooth muscle. The norepinephrine transporter (NET) is also present on the sympathetic terminal to facilitate reuptake of NE. Neurotransmitter release is regulated locally by feedback inhibition through autoreceptors (adrenergic receptors that inhibit further NE release), and feedback inhibition of NE release can occur as a result of other chemicals, including 5-HT. Feuerstein (2008) published a comprehensive review of presynaptic receptors for dopamine, histamine, and 5-HT. Although autoinhibition of serotonergic nerves through 5-HT receptors makes intuitive sense, the finding of 5-HT receptors on adrenergic nerves is less intuitive. The 5-HT$_{1B/1D}$ receptor class has been found on sympathetic nerve terminals (Feniuk et al., 1979; Shepherd and Vanhoutte, 1985; Göthert et al., 1986, 1991; Molderings et al., 1990). Activation of these receptors results in a reduced NE release from the terminal such that the overall effect is reduced contractile tone.

Likewise, the presence of NET in sympathetic terminals is reasonably understood. Whether SERT has also been localized to the vascular sympathetic terminal remains in question. The promiscuity of these transporters—SERT taking up NE, NET taking up 5-HT—is recognized (Daws, 2009). This promiscuity can have physiological relevance. In a fascinating study, Kawasaki and Takasaki (1984) demonstrated that 5-HT could be taken up and released
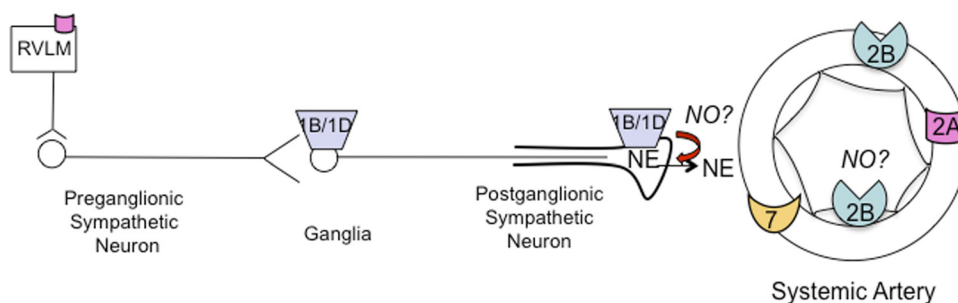
FIG. 4. Schematic of the potential sites at which 5-HT could interact to lower blood pressure within the context of the sympathetic nervous system. Small geometric shapes represent individual classes of 5-HT receptors; semicircular red arrow indicates inhibition.

from sympathetic terminals in the vasculature. This raises the intriguing possibility that 5-HT may be coreleased with NE in normal transmission; this is especially important when recognizing that 5-HT has the ability to potentiate the contractile response of arteries to endogenous hormones such as NE (MacLennan et al., 1993; Yildiz et al., 1998). In mesenteric arteries, 5-HT-like immunoreactive nerves have been reported (Gale and Cowen, 1988). Although circulating levels of 5-HT are typically low as a result of platelet uptake of 5-HT via SERT, a thrombotic event that would cause platelet aggregation could lead to a local increase of 5-HT, such that NET would take it up and it would be either metabolized or repackaged. Whether this can happen in all sympathetic nerves remains in question.

Morán et al. (2010) demonstrated that 5-HT inhibits the pressor effect of sympathetic stimulation in long-term diabetic pithed rats. They have suggested that both the $5-HT_{1A}$ and $5-HT_2$ receptors are involved in this response. This would implicate a variety of receptors—$5-HT_{1A}$, $5-HT_{1B/1D}$, $5-HT_2$—in the inhibition of sympathetic activity independent of the central nervous system.

2. Peripheral Effects of 5-Hydroxytryptamine on Sympathetic Ganglionic Transmission.

a. 5-Hydroxytryptamine synthesis and handling. The enzymes for dedicated 5-HT synthesis—tryptophan hydroxylase and an aromatic acid amino decarboxylase—exist in sympathetic ganglia. 5-HT has been immunohistochemically localized in sympathetic ganglia (Verhofstad and Jonsson, 1983; Dun et al., 1984; Häppölä, 1988; Päivärinta et al., 1989; Karhula et al., 1995). mRNA for SERT (Nishimura et al., 1999) and multiple 5-HT receptors (Newberry et al., 1996; Pierce et al., 1996; Watkins and Newberry, 1996) are present in ganglia. Removal of celiac superior mesenteric ganglion results in a loss of 5-HT-like immunoreactive nerves around mesenteric blood vessels. All of these data point to the ganglia as a site of 5-HT synthesis, uptake, and possible release. Given the integral nature of the ganglia to autonomic neurotransmission, understanding the role of 5-HT in this site is important.

b. Function and 5-hydroxytryptamine pharmacology. Many studies using an in vitro preparation have shown that 5-HT can facilitate transmission within autonomic ganglia. Hertzler (1961) reported 5 decades ago that 5-HT decreased the threshold and increased the amplitude of the rat stellate ganglionic responses to preganglionic stimulation. Wallis and Dun (1987) demonstrated that 5-HT induced depolarization of the guinea pig celiac ganglion. Meehan and Kreulen (1991) and Cai et al. (1999) later extended this observation to include depolarization of the inferior mesenteric ganglion. Meehan and Kreulen (1991) found that this effect was dependent on activation of $5-HT_3$ receptors. In the superior cervical ganglion, 5-HT causes a depolarization and enhanced transmission (Watkins and Newberry 1996) by acting at more than one 5-HT receptor subtype, including $5-HT_{2A}$ and $5-HT_3$ receptors. Thus, there seems to be an overall ability of 5-HT to stimulate ganglionic transmission, but there are exceptions to this generalization. There is evidence from a few in vitro studies to implicate an inhibitory role of 5-HT in ganglionic transmission. Gilbert and Newberry (1987) showed that 5-HT acts on $5-HT_1$-like receptors to hyperpolarize the cervical ganglion of the rat. Dun and Karczmar (1981) showed that 5-HT inhibited ganglionic transmission by a presynaptic mechanism (i.e., by reducing acetylcholine release from the presympathetic nerve terminal).

Only a few investigators have used an in vivo model to study the effects of 5-HT on ganglionic transmission. Jones et al. (1995) showed that $5-HT_{1D}$ receptors mediate inhibition of sympathetic ganglionic transmission in anesthetized cats.

c. Changes in Pathological Condition. Most recently, $5-HT_3$ receptors have been suggested to contribute to long-term potentiation in sympathetic ganglia, and inhibition of 5-HT receptors with the antagonist odansetron decreases blood pressure in obese Zucker rats (Gerges et al., 2002). Likewise, tropisetron and odansetron ($5-HT_3$ receptor antagonists) prevented the hypertension caused by psychosocial stress (Alkadhi et al., 2005); the authors suggest that the long-term potentiation facilitated by 5-HT facilitates the increased sympathetic drive that is the basis of the hypertension.

3. Central Effects of 5-Hydroxytryptamine Influencing the Sympathetic Neural Control of Blood Pressure

a. Crossing the blood-brain barrier. The extent to which 5-HT in the systemic circulation has access to 5-HT receptors on cells within the brain is a significant consideration in understanding the role of 5-HT in regulating blood pressure. In this regard, many of the populations of central neurons controlling the autonomic neural outflows to the heart, vasculature, and kidney have 5-HT receptors and receive inputs from the extensive serotonergic pathways within the CNS or from serotonergic primary afferent neurons (Fig. 5). Thus, depending on the extent to which and the site at which circulating 5-HT crosses the blood-brain barrier, it could influence blood pressure by altering the discharge of 5-HT receptor-expressing neurons in cardiovascular regulatory pathways. In contrast with its precursor, 5-HTP, which moves freely across the blood-brain barrier, the current consensus is that 5-HT does not cross the blood-brain barrier (Hardebo and Owman, 1980; Ohtsuki, 2004; Afergan et al., 2008; Ueno, 2009; Pozdzik et al., 2010). However, a study in 1968 demonstrated that intravenous 5-HT administration results in higher levels of 5-HT and its primary metabolite, 5-HIAA, in the brain (Bulat and Supek, 1968). Moreover, with the finding that SERT is on the capillary endothelial cells that comprise the blood-brain barrier (Brust et al., 2000; Wakayama et al., 2002), and that 5-HT can be transported by these cells (Roux and Couraud, 2005), it is possible for 5-HT to move in and out of the CNS. Nakatani et al.
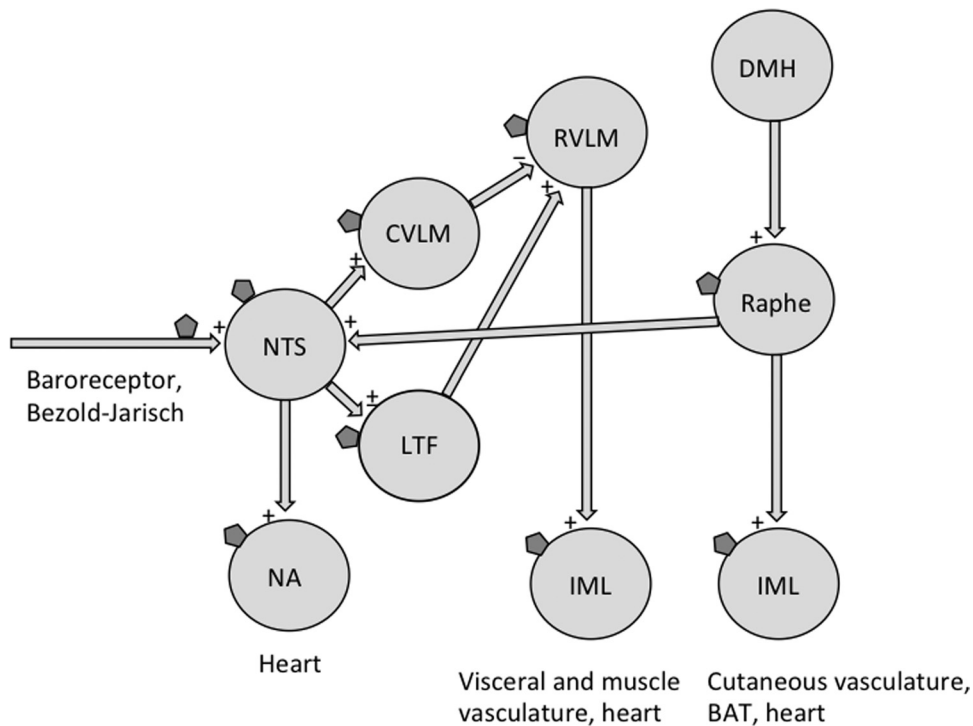
FIG. 5. Central autonomic circuits and potential central sites of action of systemically administered serotonin. The excitatory (+), inhibitory (−), or mixed (±) connections shown between the various autonomic nuclei are based on data described by Barman and Gebber (2000), Guyenet (2006), and Morrison (2004). The solid pentagon symbols show locations of 5-HT receptors. BAT, brown adipose tissue; CVLM, caudal ventrolateral medulla; DMH, dorsomedial hypothalamus; LTF, lateral tegmental field; NA, nucleus ambiguus; NTS, nucleus of the tractus solitarius.

(2008) described the ability of 5-HT to pass from the CNS to the periphery. Westergaard (1975, 1978) demonstrated more than 30 years ago that 5-HT itself can modify blood-brain barrier function, whereas 5-HT may also increase the permeability of the barrier under heat stress (Sharma and Dey, 1984). 5-HT has been localized in the circumventricular organs of the rat (Takeuchi and Sano, 1983). Finally, Alenina et al. (2009) demonstrated that 5-HT was still detectable in the brains of the TPH2(−/−) mouse. This can be interpreted in three ways: 1) that TPH2 knockout is not complete, but there is little other evidence to suggest this is true; 2) there is another source for 5-HT synthesis (such as TPH1 or phenylalanine hydroxylase) that is revealed upon removal of the primary 5-HT synthetic source in the CNS (TPH2); and 3) it is possible that the 5-HT detected in the brain of the TPH2(−/−) mouse is made by TPH1 (located in the periphery), and this 5-HT moves from the periphery to the brain. Bagale et al. (2011) reported the use of ethylamine-functionalized fluorophores that can be used to visualize SERT in living tissues. Thus, it remains possible that systemic 5-HT could have effects on blood pressure by binding to 5-HT receptors on CNS neurons, and we have tools to test this idea. The potential effects of systemic 5-HT acting within the brain can be appreciated from a review of the role of central serotonergic effects on the principal blood pressure-controlling pathways within the brain.

b. Central 5-hydroxytryptamine influences on blood pressure. The central neural networks regulating blood pressure are primarily those that control the level of sympathetic activities to cardiovascular tissues. Figure 5 shows some of the major neural circuits known to regulate blood pressure and heart rate (Barman and Gebber, 2000; Morrison, 2004; Guyenet, 2006). The sympathetic ganglion cells innervating the heart, blood vessels, adrenal medulla, and kidney receive their principal excitation from sympathetic preganglionic neurons in the intermediolateral nucleus (IML) in the thoracolumbar spinal cord. The sympathetic preganglionic neurons, although influenced by a network of spinal interneurons, receive their primary glutamatergic drive from supraspinal populations of sympathetic premotor neurons, including the major group of cardiovascular regulatory neurons in the rostral ventrolateral medulla (RVLM). The activity of these sympathetic premotor neurons is determined, in turn, by connections from pontine, hypothalamic, and limbic areas and by brainstem inputs from cardiovascular baroreceptor and chemoreceptor reflex circuits. The baroreceptor reflex, for instance, is initiated by sensory input from stretch receptors in the carotid sinus and aortic arch that project to the nucleus of the tractus solitarius (NTS), in a negative feedback fashion, to alter cardiac output and vascular resistance to compensate for externally imposed changes in blood pressure. NTS neurons excite neurons in the caudal ventrolateral medulla that in turn inhibit RVLM sympathoexcitatory neurons. A reduction in baroreceptor activity mediates the sympathetic activation that increases heart rate, cardiac contractility, venous stiff-

ness, and vasoconstriction to compensate for the decrease in blood pressure that occurs upon standing when gravity pulls blood toward the lower extremities. Likewise, baroreceptor sensory neurons in the NTS provide the parasympathetic premotor drive to the cardiac vagal preganglionic neurons in the medulla that drive cardiac vagal nerve activity to slow the heart.

Central serotonergic influences on blood pressure arise from stimulation of serotonin receptors on neurons within these neural circuits that determine sympathetic and vagal outflows (Fig. 5 and Table 3). Not only is there a myriad of central sites at which 5-HT could influence blood pressure, but there are several 5-HT receptor subtypes with differing effects on neuronal activity. Further complicating the interpretation of experimental data is the lack of specificity of many experimental designs in which cardiovascular parameters were measured after administration of 5-HT or related compounds into the cerebral ventricles or into the systemic circulation. Thus, serotonergic drugs can have access to a wide spectrum of 5-HT receptors on diverse populations of neurons. Although this drug delivery approach has relevance to investigations of a compound's therapeutic potential, it is not likely to mimic the normal physiological release of 5-HT from specific subpopulations of 5-HT neurons onto restricted sets of target neurons. It is also apparent, on the basis of the preceding description, that through different receptor populations, 5-HT could have divergent effects on different populations of neurons in the serially connected organization of the central pathways determining the sympathetic and vagal outputs controlling blood pressure. Thus, if 5-HT has simultaneous access to inhibitory 5-HT receptors (such as 5-HT_{1A} receptors) on sympathetic premotor neurons and stimulatory 5-HT receptors (such as 5-HT_{2A} receptors) on sympathetic preganglionic neurons, it is not surprising that administration of serotonin can either inhibit or stimulate preganglionic sympathetic nerves (Lewis and Coote, 1990). Moreover, Pickering et al. (1994) showed that perfusion of a spinal cord slice preparation with 5-HT induced rhythmic activity in sympathetic preganglionic neurons.

Central stimulation of 5-HT_{1A}-receptors reduces vasoconstrictor sympathetic nerve activity and increases cardiac vagal nerve activity, both leading to a decrease in blood pressure (Ramage, 2001). This may occur through inhibition of vasomotor premotor neurons in the RVLM (McCall and Clement, 1994), although a potential role of adrenergic receptors in this effect has been suggested (Nosjean and Guyenet, 1991), or of their antecedent sympathoexcitatory neurons in the lateral tegmental field (McCall and Clement, 1994). As shown in Fig. 5, sympathetic premotor neurons controlling cutaneous vasoconstriction are located in the rostral medullary raphe, where a local injection of a 5-HT_{1A}-receptor agonist elicits a cutaneous vasodilation (Ootsuka and Blessing, 2006). Because the cutaneous vasculature is strongly constricted at normal ambient temperatures, inhibition of the skin sympathetic outflow could contribute significantly to a 5-HT_{1A}-receptor

agonist-evoked decrease in blood pressure. 5-HT_{1A}-receptor agonists in the spinal IML can, however, elicit a sympathoexcitation as a result of increased responsiveness to glutamatergic inputs (Madden and Morrison, 2006), potentially through inhibition of local GABA neurons.

Central stimulation of 5-HT_{2A}-receptors can lead to an increase in blood pressure, partly through increased vasoconstrictor sympathetic outflow arising from activation of sympathetic premotor neurons in the RVLM (Ramage and Daly, 1998) but also from the contribution of vasopressin release (Saydoff et al., 1996). Intravenous administration of a 5-HT_{2A}-receptor agonist facilitates the cutaneous sympathetic outflow (Blessing and Seaman, 2003), potentially at the IML site of sympathetic preganglionic neurons (Ootsuka and Blessing, 2005), and thus could contribute to an elevated arterial pressure in response to central 5-HT_{2A}-receptor agonist administration.

The NTS is the site of termination of primary sensory neurons, including those from the baroreceptors, chemoreceptors, and cardiopulmonary receptors that participate in reflex regulation of blood pressure. The NTS receives serotonergic inputs from serotonergic neurons in the nodose ganglia and from neurons in the medullary raphe nuclei (Thor and Helke, 1987; Nosjean et al., 1990) (Fig. 5), and 5-HT_{1A}, 5-HT_{1B}, 5-HT_2, 5-HT_3, and 5-HT_4 receptors have been identified within the NTS, including on vagal afferent nerve terminals (Laguzzi, 2003).

Microinjection of 5-HT into the NTS can elicit either depressor or pressor responses (Feldman and Galiano, 1995; Nosjean et al., 1995; Callera et al., 1997; Laguzzi, 2003) that could arise from facilitatory or inhibitory effects of 5-HT on the NTS circuitry involved in integrating the baroreceptor and other cardiovascular reflexes. Chemical destruction of serotonergic neuronal elements in the NTS by microinjection of the neurotoxin 5,7-dihydroxytryptamine led to a transient (over 6 days) increase in blood pressure (Orer et al., 1991). Selective activation of 5-HT_{2A} receptors in the NTS by microinjection of DOI significantly enhanced the cardiovagal component of the baroreceptor reflex (Laguzzi, 2003), consistent with the possibility that, under physiological conditions, 5-HT released from the projections originating in the nodose ganglia and/or nucleus raphe pallidus might trigger the 5-HT_{2A} receptor-mediated reflex responses.

On the other hand, microinjection of 5-HT or the selective 5-HT_3 receptor agonist 1-(m-chlorophenyl)-biguanide into the rat NTS increases lumbar sympathetic nerve activity and blood pressure (Nosjean et al.,1995), which was prevented by prior microinjection of zacopride, a 5-HT_3 receptor antagonist. Because the gain of the sympathetic component of the baroreceptor reflex was not changed, they concluded that activation of 5-HT_3 receptors in the NTS causes sympathoexcitation by a mechanism independent of the baroreceptor reflex. In this regard, 5-HT_3 receptor activation excites neurons in the NTS and in the dorsal motor nucleus of the vagus, directly adjoining the NTS, by a glutamate-dependent mechanism (Jordan,

TABLE 3
Effect of acutely administered 5-HT or serotonergic agonist on blood pressure and heart rate in a variety of species

Leftmost column list species or agonist, status of model consciousness, surgical or pharmacological agents on board during experimentation.

5-HT or Agonist and Species	Site of Administration	Dose	Effect on Blood Pressure	Effect on Heart Rate	Time Point	Reference
5-HT						
Rat, conscious	IV	$2\ \mu g$/rat	Decrease	Decrease	Minutes	Callera et al., 2005
Rat, conscious (female)	SC	2 mg/kg	Decrease		Minutes	Barney et al., 1981
Rat, conscious	ICV	<10 nmol	Increase	Increase	Minutes	Dedeoğlu and Fisher, 1991
Rat, conscious	ICV	>10 nmol	Increase	Decrease	Minutes	Dedeoğlu and Fisher, 1991
Rat, conscious	ICV	4 nmol/kg	Increase	Decrease	Minutes	Anderson et al., 1996
Rat, conscious	ICV	$10\ \mu g$	Increase	Decrease	Minutes	Saydoff et al., 1996
Rat, vagotomized and pithed, ketanserin	IV	10^{-9}–10^{-5} mol/kg	Decrease			Terrón, 1997
Rat, vagotomized, anesthetized, ritanserin	IV	1–$10\ \mu g \cdot kg^{-1} \cdot min^{-1}$	Decrease		Minutes	De Vries et al., 1999
Rat, anesthetized, vagosympathecto-mized, ketanserin	IV	1–$30\ \mu g$/kg	Decrease		Minutes	Centurión et al., 2004
Rat, pithed	IV	5–$20\ \mu g$/kg	Increase		Minutes	Cavero et al., 1981
Rat, syrosingopine and mianserin	IV	$20\ \mu g$/kg	Decrease		Minutes	Cavero et al., 1981
Rat, anesthetized	IR, IMes	1–$3\ \mu g$/min	Increase	Increase	Minutes	Janssen et al., 1989
Rat, anesthetized	ICV	$20\ \mu g$	Increase	Decrease	5 min	Montes and Johnson, 1990
Rat, anesthetized	ICV	$20\ \mu g$	Decrease	Decrease	10 min	Montes and Johnson, 1990
Rat, anesthetized	ICV	40, 120 nmol/kg	Increase	Decrease	Minutes	Anderson et al., 1992
Rat, anesthetized	RVLM	5–50 nmol	Decrease	Decrease	Minutes	Key and Wigfield, 1992
Cat, anesthetized	Fourth ventricle	20–640 nmol/kg	Decrease	Decrease	Minutes	Shepheard et al., 1994
Dog, anesthetized	IV	$8\ \mu g \cdot kg^{-1} \cdot min^{-1}$	Decrease	Increase	Minutes-hours	Carlson et al., 1967.
Dog, anesthetized	IV	$20\ \mu g \cdot kg^{-1} \cdot min^{-1}$	Decrease	Increase	Minutes	Martinez and Lokhandwala, 1980
Calf, metrenperone	IV	0.05 mg $\cdot kg^{-1} \cdot min^{-1}$	Decrease	Decrease, then increase	Minutes	Linden et al., 1999
Human, conscious	IV	2–$4\ \mu g \cdot kg^{-1} \cdot min^{-1}$	Variable		Minutes–hours	Carlson et al., 1967
Human, conscious	IV	20 nmol $\cdot kg^{-1} \cdot min^{-1}$	No Change	No Change	Minutes	Hansen et al., 2008
Human, conscious	IL	2.5–250 nmol	No Change	No Change	Minutes	Hansen et al., 2008
Human, conscious	IA (forearm)	10–80 ng $\cdot kg^{-1} \cdot min^{-1}$	No change	No change	Minutes	Blauw et al., 1988
8-OH-DPAT						
Rat, anesthetized	IV	8–$128\ \mu g$/kg	Decrease	Decrease	Minutes-hours	Fozard et al., 1987
Rat, anesthetized	IV	1 mg/kg	Decrease	Decrease	Minutes	Helke et al., 1993
Rat, conscious	IP	0.05–0.25 mg/kg	Decrease		Minutes	van den Buuse and Wegener, 2005
Rat, conscious, hemorrhaged	ICV, IV	48 nmol/kg	Increase		Minutes	Scrogin, 2003
Rat, conscious, hemorrhaged	IV	30 nmol/kg	Increase		Minutes	Tiniakov et al., 2007
Rat, conscious	ICV	<10 nmol	Increase	Increase	Minutes	Dedeoğlu and Fisher, 1991
Rat, conscious	ICV	>10 nmol	Decrease	Decrease	Minutes	Dedeoğlu and Fisher, 1991
Rat, hemorrhaged	ICV	10 nmol	Increase	Increase	Minutes	Jochem et al., 2009
Rat, anesthetized	Ventral medulla	$0.1\ \mu g$/0.1 μl	Decrease	Decrease	Minutes	Valenta and Singer, 1990
Rat, anesthetized	ICV	3 nmol/kg	Increase	Increase	Minutes	Anderson et al., 1992
Rat, anesthetized	Ventral medulla	20–50 ng	Decrease	Decrease	Minutes	Helke et al., 1993
Rabbit, hypovolemic conscious	Fourth ventricle	10–30 nmol	Increase		Minutes	Evans et al., 1993
Cat, anesthetized	IV	1–$100\ \mu g$/kg	Decrease	Decrease	Minutes	Ramage and Fozard, 1987
Cat, anesthetized	Fourth ventricle	2.5–40 nmol/kg	Decrease	Decrease	Minutes	Shepheard et al, 1994
Pig	IA	0.3–$10\ \mu g \cdot kg^{-1} \cdot min^{-1}$	None	Decrease	Minutes	Bom et al., 1989
Dog	IV	10–$300\ \mu g$/kg	Decrease	No change	Minutes	Dabiré et al., 1990
Dog	VA	0–$3\ \mu g$/kg	Decrease	Decrease	Minutes	Dabiré et al., 1990
Dog	VLPA	$0.2\ \mu g$/site	Decrease	Decrease		Dabiré et al., 1990
Buspirone						
Rat, conscious	IP	0.1/0.5 mg/kg	Decrease/increase		Minutes	van den Buuse and Wegener, 2005

TABLE 3–*Continued*

5-HT or Agonist and Species	Site of Administration	Dose	Effect on Blood Pressure	Effect on Heart Rate	Time Point	Reference
5-CT						
Rat, anesthetized, vagotomized. ketanserin	IV	0.01–0.3 μg/kg	Decrease		Minutes	Centuriónetal,2004
Rat, vagotomized, pithed, ketanserin	IV	10^{-11}-10^{-7} mol/kg	Decrease		Minutes	Terrón, 1997
Rat, anesthetized	ICV	3 nmol/kg	Increase	Increase	Minutes	Anderson et al., 1992
Cat, anesthetized	Fourth ventricle	2.5–40 nmol/kg	Decrease	No change	Minutes	Shepheard et al, 1994
DP-5-CT						
Rat, anesthetized	ICV	3 nmol/kg	Increase	Increase	Minutes	Anderson et al., 1992
Cat, anesthetized	Fourth ventricle	2.5–40 nmol/kg	Decrease	Decrease	Minutes	Shepheard et al., 1994
Rizatriptan						
Rat, anesthetized	IV	0.63–2500 μg/kg	Decrease	Decrease	Minutes	Pagniez et al., 1998
Sumatriptan						
Rat, anesthetized	IV	0.63–2500 μg/kg	Decrease	Decrease	Minutes	Pagniez et al., 1998
Cat, anesthetized	Fourth ventricle	10–160 nmol/kg	Decrease	No change	Minutes	Shepheard et al., 1994
α-Methyl-5-HT						
Rat	IV	3–30 μg	Increase		Minutes	Dalton et al., 1986
5-Methoxytryptamine						
Rat, vagotomized, pithed, ketanserin	IV	10^{-9}–10^{-5} mol/kg	Decrease		Minutes	Terrón, 1997
DOI						
Rat, anesthetized	ICV	40, 120 nmol/kg	Increase	Decrease	Minutes	Anderson et al., 1992
Rat, anesthetized	Intra-NTS	0.05–1 pmol	Decrease	Decrease	Minutes	Comet et al., 2007
Rat, anesthetized	ICV	2 μmol/kg	Increase	Increase	Minutes	Knowles and Ramage, 1999
DOB						
Rat, anesthetized	Intra-NTS	0.025–0.5 pmol	Decrease	Decrease	Minutes	Merahi and Laguzzi, 1995
m-CPBG						
Rat, anesthetized	Third ventricle	80–320 nmol	Decrease	No change	Minutes	Ferreira et al., 2004
2-Methyl-5-HT						
Rat, anesthetized	IV	3–30 μg	Decrease	Decrease	Minutes	Dalton et al., 1986
m-CPP						
Rat, anesthetized	Third ventricle	80–320 nmol	Increase	Decrease then increase	$\leq$30 min	Ferreira et al., 2005
Quipazine						
Rat, anesthetized	ICV	2 μmol/kg	Increase	Increase	Minutes	Knowles and Ramage, 1999
5-HTP						
Rat, conscious	IV	2–40 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}	Decrease		24 h	Echizen and Freed, 1982
Cat, anesthetized	IV	5–10 mg/kg	Decrease		Hours	Flórez and Armijo, 1974
Tryptophan						
Rat, SHR, conscious	IP	1–100 mg/kg	Decrease		Hours	Sved et al., 1982
Rat, conscious	IV	2–40 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}	No change		24 h	Echizen and Freed, 1982

5-HTP, 5-hydroxytryptophan; DOB, 2,5-dimethoxy-4-bromoamphetamine hydrochloride; DOI, ($\pm$)-2,5-dimethoxy-4-iodoamphetamine; DP-5-CT, dipropyl-5-carboxamido-tryptamine; IA, intraarterial; ICV, intracerebroventricular; IL, intraluminal (intestinal); IMes, intramesenteric artery; IP, intraperitoneal; IR, intrarenal artery; IV, intravenous; m-CPBG, m-chlorophenylbiguanidine; m-CPP, 1-(3-chlorophenyl)piperazine hydrochloride; VA, vertebral artery; VLPA, ventrolateral pressor area.

2005), and 5-HT$_3$ receptor blockade reduces excitatory amino acid transmission in NTS (Wan and Browning, 2008). Vagal afferents expressing 5-HT$_3$ receptors arise not only from the gut but also from the heart, mediating the Bezold-Jarish reflex. Activation of 5-HT$_3$ receptors on vagal afferents could influence blood pressure through a reduction in the effectiveness of the arterial chemoreceptor reflex (Moreira et al., 2007). Thus, the effects on blood pressure of 5-HT administration into the NTS and its effects on specific reflexes that influence blood pressure is complex, varying with factors such as anesthesia, species, and relative prominence of or exposure to various 5-HT receptor subtypes. The existence of 5-HT receptors on both the sensory and synaptic terminals of primary afferents suggests that transmission in these pathways could be influenced both by the levels of circulating 5-HT and by 5-HT released within the NTS from the terminals of raphe neurons.

V. Effect of 5-Hydroxytryptamine on Blood Pressure: Whole-Animal Studies

A. Effects of 5-Hydroxytryptamine and Serotonergic Agonists on Blood Pressure

1. Short-Term. When 5-HT is administered intravenously to anesthetized rodents over the course of seconds to minutes, a classic triphasic response is observed (Dalton et al., 1986; Hardcastle and Hardcastle, 1999) (Fig. 6A). There is 1) a depressor response attributed to

a reduction in heart rate (HR) by activation of the Bezold-Jarisch reflex followed by 2) a significant elevation in blood pressure. This pressor response is thought to be mediated by 5-HT$_2$ receptors in the vasculature. After this transient pressor response, there is 3) a slow vasodepressor response that has been attributed to activation of both 5-HT$_7$ and 5-HT$_{1B/1D}$ receptors (Terrón et al., 2007). In studies of anesthetized animals, this response can be observed up to 60 min after 5-HT administration and a decrease in blood pressure to 5-HT can continue for at least a week with continued 5-HT administration.

Table 3 compiles responses to 5-HT administered in a number of different ways, but all in an acute (seconds to minute) time frame. Multiple investigators have demonstrated the ability of 5-HT, given either subcutaneously or intravenously, to decrease blood pressure in either rodents or dogs. In a pithed rat model, administration of 5-HT results in an increase in blood pressure (Cavero et al.,

FIG. 6. A, classic triphasic (1, 2, 3) effect of 5-HT (75 μg/kg bolus) on blood pressure in the anesthetized rat. Time base below traces is 1 s/division. Total time base is 75 s. B, effect of 5-HT (25 μg · kg^{-1} · min^{-1}, subcutaneous pump) on blood pressure (top) and heart rate (bottom) in the conscious rat over the course of 30 h. Dashed vertical line indicates implantation of pump. Points represent means ± S.E.M. for the number of animals in parentheses.

1981), suggesting that the interaction with the central sympathetic nervous system may be key for the mechanism of blood pressure decrease. There are few reports of the response of the human to 5-HT (intravenous), and in one study that addressed directly the effect of 5-HT on blood pressure in man, the effects of 5-HT on blood pressure were variable (Carlson et al., 1967). 5-HT (0.1–50 ng · kg^{-1} · min^{-1}, intra-arterial) caused a dose-dependent increase in forearm blood flow in humans, but this alone was insufficient to decrease blood pressure, which is somewhat expected given the restriction of circulating substances in the assay used (Blauw et al., 1988).

The effect of serotonergic agonists other than 5-HT on blood pressure are tabulated in the lower part of Table 3. In the conscious rat, the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT causes variable effects on blood pressure when given intraperitoneally or intravenously but overall reduces blood pressure (van den Buuse and Wegener, 2005). By contrast, in the hemorrhaged rat, 8-OH-DPAT produces a significant pressor response and is described as rescuing blood pressure from the effects of hemorrhage (Tiniakov et al., 2007). In the cat (anesthetized), 8-OH-DPAT (intravenous) causes a decrease in blood pressure (Ramage and Fozard, 1987). 5-CT has a significantly greater affinity for more of the 5-HT$_1$ receptor subtypes and causes a decrease in blood pressure (Terrón et al., 2007), with the caveat that 5-CT also has significant affinity for the 5-HT$_7$ receptor (Waeber and Moskowitz, 1995; Krobert et al., 2001). These animals, however, were anesthetized, vagotomized, and treated with ketanserin to unmask a 5-HT-stimulated relaxation/depressor response (Terrón, 1997; Centurión et al., 2004), so, as with isolated arteries, the physiological relevance of such a response remains in question. Sumatriptan and rizatriptan (intravenous), 5-HT$_{1B/1D}$ receptor agonists, also caused a decrease in blood pressure, but this effect may not be peripheral. Pagniez et al. (1998) have suggested that this effect is due to central 5-HT$_{1A}$ receptor activation. In contrast to these studies, in which serotonergic agonists were clearly depressors when given peripherally, 5-HT$_2$ receptor agonists such as α-methyl-5-HT and (±)-2,5-dimethoxy-4-iodoamphetamine elevate blood pressure. Because it is unclear whether these agonists—including 5-HT—cross the blood-brain barrier or interact with the area postrema, we cannot exclude the idea that the effects observed on blood pressure are at least partially centrally mediated.

2. Long-Term. Because of our interest in the role of 5-HT in blood pressure, we studied prolonged elevation of 5-HT in the normal rat and followed blood pressure using radiotelemetry. The time period of 5-HT infusion was over the course of a week. Although many of the studies described in Table 3 suggest that 5-HT is largely a depressor agent in short-term peripheral administration, the knowledge that 1) 5-HT is a direct vasoconstrictor, 2) blood vessels from hypertensive animals are hyper-responsive to 5-HT, and 3) circulating levels of free 5-HT are elevated in hypertension suggested to us that
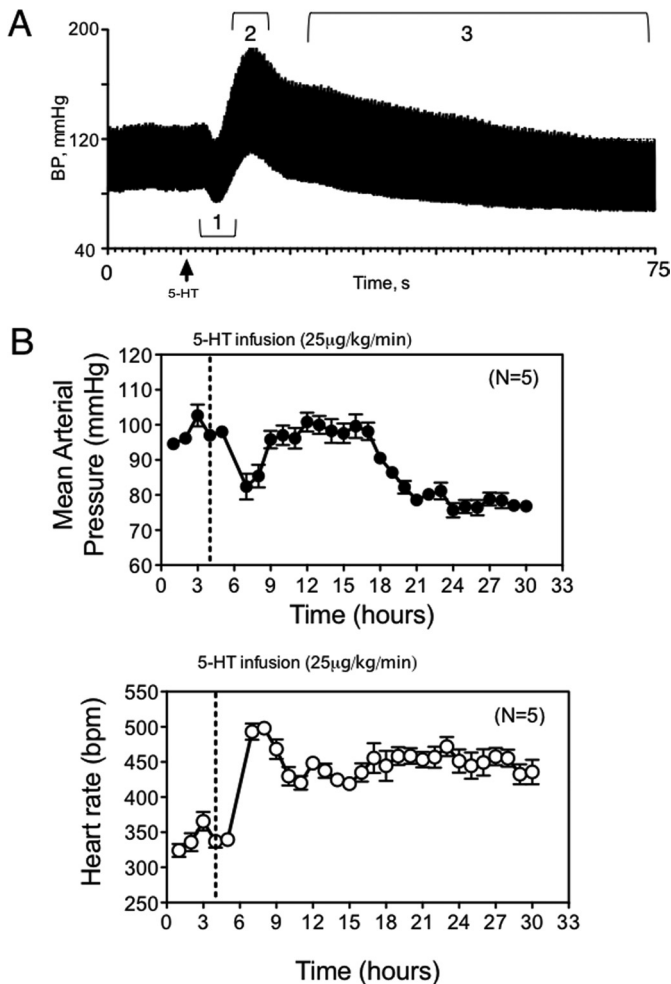
5-HT could be a pathogenic factor in hypertension, contributing to an elevation in blood pressure. Contrary to these ideas, we observed that 5-HT caused a decrease in blood pressure in the conscious sham and DOCA-salt hypertensive rats (Diaz et al., 2008). In these studies, 5-HT was given in an Alzet miniosmotic pump ($25 \ \mu g \cdot kg^{-1} \cdot min^{-1}$) placed subcutaneously and with an antioxidant. On day 7, plasma 5-HT (free) was elevated from 2.7 ± 0.03 (vehicle) to 47.1 ± 13.18 ng/ml (5-HT; 17-fold increase) in a sham rat. This is within the range of that found in experimental and genetic hypertensive rats (25–60 ng/ml or ~125 nM 5-HT). Measures of *human* 5-HT have been carefully re-evaluated using liquid chromatography–tandem mass spectrometry. Estimated 5-HT concentrations in platelet-depleted plasma were 89.5 to 115.5 nM in 18 healthy subjects (Monaghan et al., 2009). Thus, the rat is a good model to use because the levels of 5-HT we achieve in this model are physiological and comparable with what is found in human. Stunningly, 5-HT nearly normalized the blood pressure of the DOCA-salt hypertensive rat (Table 4), dropping blood pressure by over 50 mm Hg and maintaining a lower pressure for the entire week. Platelet free 5-HT levels were increased 10- to 15-fold in the experiments represented in these tables. This was the first study to demonstrate that, unlike the effects of 5-HT in minutes of infusion, 5-HT continues to exert its antihypertensive effects over days. It is possible but not proven that with the longer-term infusion, we are extending phase 3 of the response to 5-HT (Fig. 6A, phase 3). To investigate this possibility, we tracked changes in blood pressure and heart rate within the first 30 h after 5-HT administration in normal male Sprague-Dawley rats (Fig. 6B, conscious). Our findings suggest that there are at least two hypotensive phases upon long-term 5-HT administration: one within the first 3 h and a second, more stable decrease after nearly 20 h of administration. Heart rate remains elevated during these first 30 h. Thus, it is unlikely that the long-term (1 week) decrease in blood pressure to 5-HT is simply an extension of the decrease observed within the first hour. We do not know whether these different phases of changes in blood pressure have the same mechanism. In Fig. 7, we demonstrate the ability of 5-HT [Alzet miniosmotic pump (25
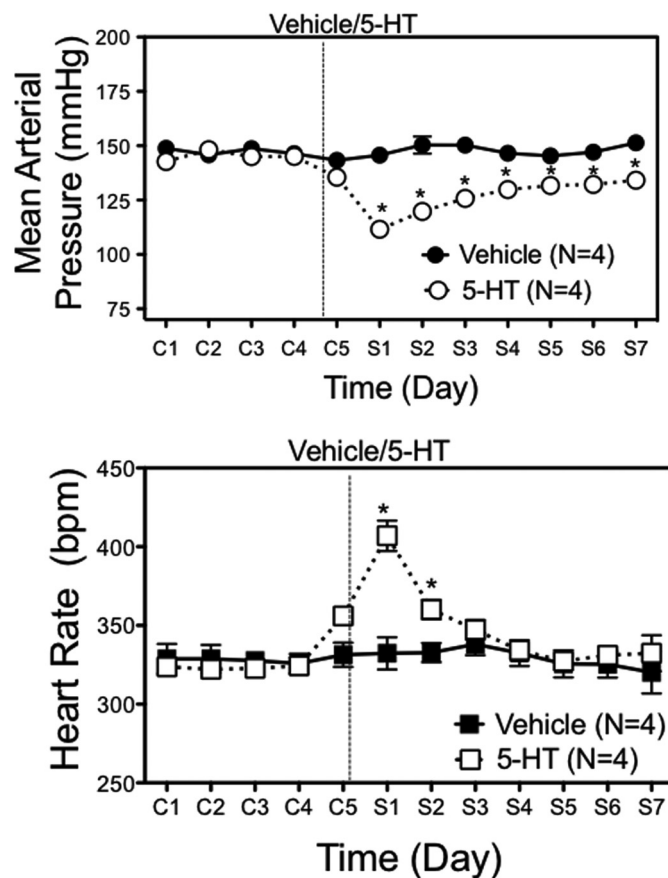

FIG. 7. Top, ability of 5-HT ($25 \ \mu g \cdot kg^{-1} \cdot min^{-1}$, subcutaneous pump) to lower blood pressure of a male SHR. Bottom, concomitant heart rate measures. Dashed vertical line indicates implantation of the pump. Points are means $\pm$ S.E.M. for the number of animals in parentheses. *, $p < 0.05$, significantly different from vehicle time point.

$\mu g \cdot kg^{-1} \cdot min^{-1}$)] to lower blood pressure in the spontaneously hypertensive rat (SHR) over 1 week. Blood pressure was significantly reduced within the first 2 days of delivery, during which time the HR was elevated. HR returned to normal levels, whereas blood pressure remained reduced by day 7. This suggests that although the baroreceptor reflex is intact, it cannot completely correct for the decrease in pressure. Table 4 compiles the results of experiments from our laboratory investigating the response to a 1-week infusion of 5-HT [Alzet miniosmotic pump ($25 \ \mu g \cdot kg^{-1} \cdot min^{-1}$)] on

TABLE 4
Effect of long-term administration of 5-HT ($25 \ \mu g \cdot kg^{-1} \cdot min^{-1}$, 1-week administration, subcutaneous) on blood pressure in the rat

Rat Group (All $n > 4$)	Control BP	Nadir BP	Time Point	Reference
	mm Hg		*h*	
Male SD (CRiver)	101 ± 2	86 ± 1	24	Diaz et al., 2008
Male SD (CRiver)	102 ± 3	79 ± 2	48	Diaz et al., 2008
Male DOCA-salt SD (CRiver)	166 ± 7	112 ± 3	48	Diaz et al., 2008
Male SD (Harlan)	103 ± 3	83 ± 3	24	Diaz et al., 2008
Male L-NNA SD (Harlan)	161 ± 4	153 ± 5	72	Diaz et al., 2008
Male SERT(+/+) (Wistar)	107 ± 11	84 ± 1	24	Davis et al., 2011
Male SERT(−/−) (Wistar)	103 ± 2	88 ± 4	24	Davis et al., 2011
Female SERT(+/+) (Wistar)	111 ± 3	89 ± 2	24	Davis et al., 2011
Female SERT(−/−) (Wistar)	109 ± 2	94 ± 3	24	Davis et al., 2011

BP, blood pressure; CRiver, Charles River Laboratories; SD, Sprague Dawley.

blood pressure in several rodent models, and these studies support the ability of 5-HT to reduce rodent blood pressure.

Potential mechanisms contributing to the 5-HT-induced decrease in blood pressure in the chronic setting include a role for NOS and for the SERT. The NOS inhibitor L-NNA abolished the ability of 5-HT to cause a decrease in blood pressure in both normal and DOCA-salt rats given L-NNA. We have validated this finding in a study using newly available iPrecio pumps (Primetech Corp., Tokyo, Japan), which allow for programmable release of infusions over time. We conducted a dose-response curve to 5-HT within normal rats and demonstrated a dose-dependent decrease in blood pressure, one that could be prevented with administration of L-NNA (Tan et al., 2011). Thus, 5-HT is interacting with NOS somewhere to effect the decrease in blood pressure. The decrease in 5-HT is not physiologically antagonized by L-NNA, which elevated the initial blood pressure, because 5-HT readily reduces the blood pressure of the DOCA-salt and SHRs (Diaz et al., 2008; Fig. 4). 5-HT can increase NO production from several different types of cells and tissues (Arima et al., 1996; Manivet et al., 2000; Borgdorff et al., 2002; Bellou et al., 2003; Borgdorff and Tangelder, 2006; García et al., 2006; Chanrion et al., 2007). Hoffmann et al. (1990) described 5-HT receptors as mediating the long-lasting decrease in blood pressure after exercise and implicated $5-HT_1$ and $5-HT_2$ receptors in mediating this response. Use of the SERT dysfunctional rat also suggests that SERT function is important to 5-HT-induced decrease in blood pressure because the magnitude of the blood pressure decrease induced by 5-HT was reduced by 50% in the SERT dysfunctional mice compared with the male wild-type mice (Davis et al., 2011). SERT function is important in the concentration of 5-HT by blood vessels (Ni et al., 2004), but the presence of SERT expression on the blood-brain barrier suggests the possibility that 5-HT crosses the blood-brain barrier to cause a decrease in blood pressure.

This work with long-term 5-HT administration comes approximately 30 years after a series of elegant studies done using 5-HTP and investigating the effect of this 5-HT precursor on blood pressure. 5-HTP but *not* tryptophan lowered blood pressure in a prolonged (24–48 h) fashion (Echizen and Freed, 1982; Fregly et al., 1987a; Ding et al., 1989; Itskovitz et al., 1989; Baron et al., 1991) (Table 3). 5-HTP is dedicated to 5-HT synthesis, whereas only 5 to 10% of tryptophan is dedicated to 5-HT. A study by Sved et al. (1982) differs in that tryptophan (intraperitoneal) was able to reduce blood pressure of SHRs over the course of hours. Likewise, Fregly et al. (1987b) demonstrated that tryptophan administration inhibited the development of DOCA-salt hypertension in the rat. 5-HTP also inhibited the development of DOCA-salt hypertension (Fregly et al., 1987a) and thus raises the possibility that 5-HT is able to reduce the activity of mechanisms responsible for the elevation of blood pressure. Like tryptophan, 5-HTP is relevant because of the enormous concern of the side effects of

unregulated administration of 5-HTP for aide in a multitude of disorders, including depression, fibromyalgia, obesity, insomnia, and headache (Birdsall, 1998; Das et al., 2004; Turner et al., 2006).

C. Effect of Removal of 5-Hydroxytryptamine on Blood Pressure

Another way to ask the question of the importance of 5-HT to blood pressure is to investigate the outcome of removing 5-HT from the body or preventing its synthesis. This has been done in two ways: pharmacological inhibition of TPH by use of parachlorophenylalanine (PCPA) and removal of the TPH gene. *p*-Chlorophenylalanine methyl ester (PCPAME) was used for decades as a tool to inhibit TPH. In 1976, Buckingham et al. demonstrated that PCPAME (400 mg/kg) caused a significant decrease in blood pressure that lasted for at least 8 days in the male DOCA-salt hypertensive rat, with the reduction in blood pressure observed on the first day of administration. Although this decrease was present in the normal animal, it did not reach the magnitude of decrease reached in the DOCA-rat and was observed only after 5 days of treatment (a latent response). Brainstem 5-HT was depleted by PCPAME, but circulating 5-HT was not measured. These findings suggest that 5-HT promotes a rise in blood pressure by an unknown mechanism, and this is not consistent with the findings just presented in which long-term 5-HT exposure caused a reduction in blood pressure. By contrast, other studies suggest that depletion of 5-HT centrally (primarily brainstem) results in an elevation in blood pressure. Central PCPA administration to Wistar rats was accompanied by elevated blood pressure under anesthesia (Althaus et al., 1985), and central depletion of 5-HT was again associated with an elevated blood pressure in awake rats (Kellett et al., 2005).

Similarly conflicting outcomes have been observed when 5-HT synthesis is removed genetically. TPH1 knockout mice have been created; this isoform of TPH is primarily responsible for peripheral 5-HT, and these mice have normal central 5-HT levels. Systemic arterial pressure (carotid catheterization) was measured in halothane-anesthetized TPH1 KO mice and, compared with WT, TPH1 KO mice showed a significant elevation in basal arterial pressure, where pressure was taken in anesthetized mice (Morecroft et al., 2007). This implies that peripheral 5-HT acts to lower blood pressure or inhibits a mechanism that supports blood pressure. It would have been ideal to measure blood pressure using telemetry, given that anesthetics themselves typically lower blood pressure. Significantly more work has been done with the TPH2 KO mouse, a mouse in which removal of 5-HT is primarily in the central nervous system, and peripheral 5-HT is largely normal. Blood pressure measured telemetrically in TPH2 KO mice was significantly lower than that of the wild type, especially during late afternoon and evening (Alenina et al., 2009). A caveat of this study is that activity was not measured, and because decreased activity

(as may be seen with extended sleep) is associated with a decreased blood pressure, the blood pressure data are somewhat difficult to interpret. Brain 5-HT was not abolished in the TPH2 KO mice but significantly reduced. Taken together, 5-HT seems to have different roles in regulating blood pressure by acting in the periphery (lower) versus central compartment (elevation), at least in the mouse. Mice in which both TPH1 and TPH2 are knocked out have been created (Savelieva et al., 2008), but blood pressure in these animals was not measured. As expected, TPH1 KO but not TPH2 KO mice show dramatically reduced levels of circulating 5-HT. It is noteworthy that measures of peripheral levels of 5-HT in the blood were not zero in mice in which both TPH1 and TPH2 were knocked out. The fact that 5-HT levels were not zero in these animals is interesting, and it has been proposed that enzymes such as phenylalanine hydroxylase may serve to produce 5-HT (Savelieva et al., 2008).

VI. 5-Hydroxytryptamine, Pharmaceutical Compounds and Clinical Situations

A. Pharmaceuticals

Drugs that modify 5-HT concentration are frequently prescribed. These drugs prevent either the uptake or the metabolism of 5-HT, both of which would promote the elevation of 5-HT concentration. As such, study of the effects of these drugs on blood pressure may give additional insights into the potential actions of 5-HT in modifying blood pressure. To our knowledge, no drugs that inhibit 5-HT production are currently used therapeutically. A selective serotonin-reuptake enhancer has been described—tianeptine—but it is the only one of its class and its effectiveness as an enhancer of SERT has been questioned. Lexicon Pharmaceuticals (The Woodlands, TX) currently has the tryptophan hydroxylase inhibitor telotristat etiprate (LX1032) in phase 2 clinical trials for carcinoid tumors, a condition in which 5-HT is made in inappropriately high amounts by slow-growing tumors of the enterochromaffin cells in the intestine. It is noteworthy that hypotension is one of the presenting symptoms of patients with this type of tumor.

The various classes of drugs that modify 5-HT concentration include the selective serotonin-reuptake inhibitors (SSRI), serotonin/norepinephrine-reuptake inhibitors (SNRI), and MAO A/B monoamine oxidase. The oldest class of drugs is the tricyclic antidepressants (TCAs). A preponderance of these drugs are/were used in the treatment of depression and some related mood disorders. Table 5 compiles data from a number of studies, animal and human, in which mean arterial blood pressure was measured as one endpoint. Blood pressure was either the focus of the study cited or a variable measured within a trial. Relatively clear patterns emerge from the gathering of these studies. Use of TCAs—still prescribed—has been associated directly with a decrease in blood pressure and/or a decreased tolerance for blood pressure changes associated

with moving from a supine to standing posture (orthostatic hypotension). This finding was consistent in multiple species tested, including dog, rabbit, and human. MAO inhibitors have also been used clinically; they, too, are associated with a decrease in blood pressure or orthostatic hypotension (Stahl and Felker, 2008). Some of the later compounds, such as rasagiline, seem to exert less of an effect on blood pressure.

With the introduction of zimeldine, indalpine, fluvoxamine, and fluoxetine in the mid- to late 1980s, the class of SSRIs was born. Zimeldine was the first developed SSRI (Carlsson and Wong, 1997), and fluoxetine (Prozac; Eli Lilly & Co., Indianapolis, IN) is the best-known SSRI. There is little information as to the effect of fluoxetine, or a related compound fluvoxamine, on blood pressure except for reports in the rat, in which fluoxetine causes hypertension (Tsai and Lin, 1986; Lazartigues et al., 2000). By contrast, fluoxetine reduced blood pressure in the SHR (Sved et al., 1982). It is noteworthy that fluoxetine has been cited for use in the treatment of orthostatic hypotension, the very syndrome caused by TCAs and MAO inhibitors (Grubb et al., 1994). Thus, fluoxetine has divergent effects on blood pressure. Other compounds in this class— citalopram, paroxetine, sertraline, and zimeldine—have varied effects on blood pressure, no effect being the most common outcome. This differs significantly from the effect of SNRIs. Table 5 lists some of the reports that suggest this class of drugs has a more pronounced effect on blood pressure, elevating blood pressure in many cases. A number of meta-analyses have been performed in this regard (Thase, 1998; Kim et al., 2003; de Lemos et al., 2008; Johansson et al., 2010). Because these compounds inhibit reuptake of NE as well as 5-HT, one can understand their potential to elevate blood pressure, because the SNRI would prolong the effect of NE (and 5-HT) at the vascular junction to promote an increase in total peripheral resistance. The SNRI sibutramine was a drug prescribed for medical management of weight loss but was pulled from the market in 2010 because of concerns over cardiovascular side effects that include an elevation in blood pressure. It is less clear how SNRIs would reduce blood pressure, but such a result has been observed in humans for both venlafaxine and duloxetine.

On the whole, it is difficult to attribute the effects of any of the MAOIs, SSRIs, SNRIs, or TCAs to inhibition of metabolism or uptake of 5-HT because of the importance of MAO and uptake systems to norepinephrine and epinephrine. MAO metabolizes both amines as well as 5-HT, and the transport systems are known to be imperfect in their selectivity, such that NET can take up 5-HT and vice versa (Daws, 2009). Moreover, whereas these compounds each elevate 5-HT concentration, their effects are not absolutely specific for 5-HT. For example, more than a dozen publications describe the ability of fluoxetine and its metabolite norfluoxetine to inhibit multiple classes of potassium channels that operate in the cardiovascular system (exemplified by Tytgat et al., 1997). Given our experimental findings of

TABLE 5
Effect of serotonergic compounds on blood pressure of different species

Compound	Species	Effect on Blood Pressure	Dose	Reference
TCAs				
Imipramine	Human	Orthostatic hypotension	1–5 g/kg/day	Giardina et al., 1985
Imipramine	Human	Orthostatic hypotension	100 mg/day	Thayssen et al., 1981
Imipramine	Human	Orthostatic hypotension	~225 mg/day	Glassman et al., 1979
Imipramine	Rabbit	Decrease	29 mg/kg	Hughes and Radwan, 1979
Imipramine	Dog	Decrease	0.1–10 mg/kg	Kato et al., 1974
Imipramine	Dog	Decrease	1–10 mg/kg	Yokota et al., 1987
Imipramine	Human	Orthostatic hypotension	200 mg/day	Guelfi et al., 1983
Imipramine	Dog	Decrease	$0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	Lindbom et al., 1982
Nortriptyline	Human	Orthostatic hypotension	0.5–3.5 mg/kg/day	Giardina et al., 1985
Nortriptyline	Human	No change	40 mg/day	Thayssen et al., 1981
Amitriptyline	Rabbit	Decrease	15 mg/kg	Hughes and Radwan, 1979
Amitriptyline	Dog	Decrease	0–20 mg/kg	Lindbom et al., 1982
Amitriptyline	Dog	Decrease	1–10 mg/kg	Yokota et al., 1987
Amitriptyline	Dog	Decrease	0.1–10 mg/kg	Kato et al., 1974
Amitriptyline	Human	Decrease	25 mg/day	Ogura et al., 1983
Amitriptyline	Human	No change	75 mg/day	Penttilä et al., 2001
Maprotiline	Rabbit	Decrease	34 mg/kg	Hughes and Radwan, 1979
Clomipramine	Dog	Decrease	1–10 mg/kg	Yokota et al., 1987
Clomipramine	Human	Orthosatic hypotension	150 mg/day	Christensen et al., 1985
Clomipramine	Dog	Decrease	0–20 mg/kg	Lindbom et al., 1982
Desmethylimipramine	Human	Increase	100 mg	Ross et al,. 1983
Desipramine	Human	No change	100 mg/day	Chalon et al., 2003
MAO Inhibitors				
Rasagiline	Rat	No change	0.2–1 mg/kg	Finberg et al., 2006
Rasagiline	Rat	No change	1 mg/kg	Abassi et al., 2004
Rasagiline	Rat	Decrease	10 mg/kg	Abassi et al., 2004
Selegiline	Rat	No change	1–5 mg/kg	Finberg et al., 2006
Selegiline	Human	Orthostatic hypotension	10 mg/day	Turkka et al., 1997
Selegiline	Rat	No change	1 mg/kg	Abassi et al., 2004
Selegiline	Rat	Decrease	10 mg/kg	Abassi et al., 2004
L-Deprenyl	Rat	No change	5 mg/kg	Stevens et al., 1998
L-Deprenyl	Rat	Increase	25 μg/100 g	Kerecsen and Bunag, 1989
Clorgyline	Rat	No change	2 mg/kg	Finberg et al., 2006
Clorgyline	Rat	No change/decrease	25 μg/100g	Kerecsen and Bunag, 1989
Clorgyline	Human	Decrease	28 mg/day	Murphy et al., 1979
Harmaline	Rat	Decrease	20 mg/kg	Marwood et al., 1985
Pargyline	Rat	Decrease	100 mg/kg	Marwood et al., 1985
Pargyline	Rat	Decrease	10 mg/kg	Fuentes et al., 1979
Pargyline	Human	Decrease	87 mg/day	Murphy et al., 1979
Tranylcypromine	Rat	Decrease	10 mg/kg	Marwood et al., 1985
Tranylcypromine	Rat	Decrease	5 mg/kg	Ashkenazi et al., 1983
Tranylcypromine	Human	Orthostatic hypotension	20–100 mg/day	Nolen et al., 1993
Tranylcypromine	Rat	Increase	25 mg/kg	Finberg et al., 2006
Isoniazid	Rat	Decrease	30–300 mg/kg	Vidrio et al., 2000
Brofaromine	Human	Orthostatic hypotension	50–250 mg/day	Nolen et al., 1993
SSRIs				
Citalopram	Human	No change	40 mg/day	Christensen et al., 1985
Citalopram	Human	No change	40–60 mg/day	Pedersen et al., 1982
Citalopram	Human	No change	20 mg/day	Penttilä et al., 2001
Fluvoxamine	Human	No change	300 mg/day	Guelfi et al., 1983
Fluoxetine	Rat	Increase	10–50 μg i.c.v.	Lazartigues et al., 2000
Fluoxetine	Rat	Decrease	10 mg/kg	Sved et al., 1982
Fluoxetine	Human	Increase	20 mg/day	Amsterdam et al., 1999
Paroxetine	Dog	Increase/ Decrease	0.1–10 mg/kg	Yokota et al., 1987
Sertraline	Human, adolescent	No change	Up to 200 mg/day	Wilens et al., 1999
Sertraline	Human	No change	Up to 400 mg/day	Saletu et al., 1986
Zimeldine	Dog	Decrease	1–20 mg/kg	Lindbom et al., 1982
Zimeldine	Human	No change	100 mg/day	Saletu et al., 1986
SNRIs				
Milnacipran	Human	Increase	0.2–0.8 mg/kg	Caron et al., 1993
Venlafaxine	Human	Increase	75–225 mg/day	Perahia et al., 2008
Venlafaxine	Human	Decrease	75–225 mg/day	Alexandrino-Silva et al., 2008
Venlafaxine	Human	Increase	225–525 mg/day	Mbaya et al., 2007
Duloxetine	Rat	Decrease	30 mg/day	Chudasama and Bhatt, 2009
Duloxetine	Human	Increase	120–400 mg/day	Derby et al., 2007
Duloxetine	Human	No change	60–120 mg/day	Perahia et al., 2008
Duloxetine	Human	No change	40–120 mg/day	Bailey et al., 2006
Duloxetine	Human	Increase	80 mg/day	Chalon et al., 2003
Sibutramine	Human	Decrease	10–15 mg/day	Sharma et al., 2009
Sibutramine	Human	Basal increase, decrease in sympathetic stimulation	15 mg/day	Birkenfeld et al., 2005
Sibutramine	Rat	No change	5 mg/day	Chudasama and Bhatt, 2009
Sibutramine	Human	Decrease	10–15 mg/day	Gaciong and Placha, 2005
Sibutramine	Human	Increase	5–20 mg/day	McMahon et al., 2000

the ability of 5-HT to reduce blood pressure in the long term, it is tempting to speculate that the decrease in blood pressure observed in response to these drugs is due specifically to inhibition of 5-HT metabolism or uptake, but the caveats described make it difficult to do so. Alternatively, we have to question what an elevation in blood pressure in response to these compounds means if 5-HT is a purported antihypertensive agent.

B. Clinical Situations

1. Circulatory Shock. The involvement of 5-HT in shock, a condition of near cardiovascular collapse because of significant blood loss, is interesting and complicated. With the loss of blood, the body loses a significant portion of its 5-HT, because platelets are the primary source of circulating 5-HT. Shock is a 5-HT-reduced condition. Scrogin (2003) and Tiniakov et al. (2007) have done elegant work in demonstrating that activation of the 5-HT$_{1A}$ receptor centrally can reverse the profound reduction in total peripheral resistance in shock that is due to hemorrhage and can rescue blood pressure. The 5-HT$_{1A}$ receptor has markedly complex roles in blood pressure regulation, as outlined in Table 3. Depending on the site of injection and the dose, 8-OH-DPAT (which has significant affinity for 5-HT$_1$ and 5-HT$_7$ receptors) can either elevate or reduce blood pressure in the rat, the species in which the greatest amount of work has been performed. The 5-HT$_{1A}$ receptor clearly serves multiple purposes, but in shock, the 5-HT$_{1A}$ receptor supports blood pressure.

2. Orthostatic Hypotension. Orthostatic hypotension (postural hypotension) is defined clinically as a ≥ 20 mm Hg decrease of systolic blood pressure or ≥ 10 mm Hg decrease of diastolic blood pressure upon standing (Medow et al., 2008). The dizziness experienced, associated with fainting, can limit the use of these medications, which occurs with a majority of the TCAs. The association of orthostatic hypotension with multiple types of serotonergic inhibitors raises the question of the involvement of 5-HT in this event. We cannot explain how SSRIs such as fluoxetine are used to treat orthostatic hypotension whereas TCAs cause hypotension, but it is logical to believe 5-HT is not at the root cause of either event.

3. Serotonin Syndrome. More aptly named serotonin toxicity or serotonin toxidrome, this situation occurs with an overdose or interaction of drugs that promote an elevation of 5-HT (Skop et al., 1994; Mason et al., 2000; Boyer and Shannon, 2005). This is best recognized with ingestion of foods rich in tryptophan taken with MAO inhibitors, TCAs, SSRIs, SNRIs, or sometimes a combination of these drugs. This has also been observed with alternative, nonregulated therapies, such as St. John's wort and tryptophan. 5-HT toxicity presents with a multitude of symptoms that include central, gastrointestinal, muscular, autonomic, and cardiovascular symptoms. Of these, an elevation in temperature is notable.

Hypertension is also associated with 5-HT toxicity. Obviously, 5-HT has a multitude of physiological effects that make its ability to reduce blood pressure, as we observed in infusions, obfuscated by other activated pathways.

4. Hypertension. The role played by 5-HT in hypertension is still unclear. With the discovery of 5-HT in blood, it made sense that 5-HT would be regarded as a pathological factor in hypertension, promoting an increase in total peripheral resistance. Indeed, arteries isolated from both human and experimental models of hypertension show a classic hyper-reactivity to 5-HT that would support this activity. However, the action of 5-HT in vivo is far more complex. In the human, free circulating 5-HT is elevated, and the uptake of 5-HT appears to be impaired in the platelet of the hypertensive human such that the platelet appears "activated" (Kamal et al., 1984; Persson et al., 1988; Fetkovska et al., 1990a,b; Carrasco et al., 1998; Brenner et al., 2007).

By contrast, in pregnancy-induced hypertension, platelet content of 5-HT is increased and release of 5-HT is reduced (Gujrati et al., 1994) or shown to be unchanged (Jelen et al., 1979). Filshie et al. (1992) found that urinary 5-HIAA was not elevated in women with pregnancy-induced hypertension compared with women with normal pregnancy. Thus, there is no clear-cut association between platelet 5-HT content and blood pressure. The association of a reduced level of circulating 5-HT with elevated blood pressure in the human was suggested by Topsakal et al. (2009). In patients with hypertension who do not show the normal decrease in nocturnal blood pressure ("nondippers"), thrombocyte 5-HT levels were lower compared with "dippers" and control dubjects. We made an attempt to address this question of whether there is a correlative relationship between circulating 5-HT levels (free and platelet-bound) and blood pressure. For this purpose, we performed a regressive correlation of the free plasma and platelet-rich measures of 5-HT circulating in the rodent, along with telemetric measures of systolic blood pressure taken at the end of a 1-week infusion of 5-HT [Alzet miniosmotic pump ($25\ \mu g \cdot kg^{-1} \cdot min^{-1}$)]. These results were retrieved from our published articles and represent only male rats—both normotensive and hypertensive—that received 5-HT (Diaz et al., 2008; Davis et al., 2011; $25\ \mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 week). The 5-HT values in Fig. 8 represent the 5-HT concentration measured on the last day of infusion. Using these values, there is no linear relationship between either platelet-poor (free) or platelet-rich (plasma) and mean arterial blood pressure in the rat. As such, it is difficult to describe changes in circulating 5-HT as causal or a result of elevated blood pressure.

The pathogenic effect of 5-HT was initially supported by studies reported decades ago that showed the ability of the 5-HT$_{2A/2C}$ receptor antagonist ketanserin to reduce blood pressure in the human and in experimental models of hypertension (Nelson et al., 1987; Liu et al., 1991; Azzadin et al., 1995; Krygicz et al., 1996; van Schie et al., 2002), but
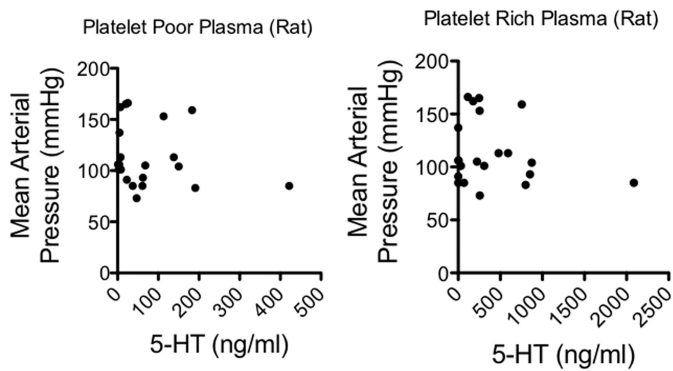
FIG. 8. Correlation between platelet poor plasma (*x*-axis, left) and rich plasma (right) with mean arterial blood pressure (telemetric) taken from conscious rats at the end of a 1-week infusion of 5-HT.

this effect was later attributed to α-adrenergic receptor blockade (Vanhoutte 1991; Wenting et al., 1982; Cohen et al., 1983a; Vanhoutte et al., 1988; van Zwieten et al., 1992). Other 5-HT$_{2A}$ receptor antagonists such as ritanserin and 6-methyl-1-(1-methylethyl)ergoline-8â-carboxylic acid 2-hydroxy-1-methylpropyl ester (LY53857) have not proven effective in reducing blood pressure (Cohen et al., 1983b; Gradin et al., 1985; Dalton et al., 1986; Nelson et al., 1987; Frishman et al., 1988; Stott et al., 1988; Docherty, 1989), making the effect of 5-HT on blood pressure equivocal. In the human, one report suggests that polymorphism of the 5-HT$_{2A}$ receptor is associated with elevation of blood pressure (Halder et al., 2007), but the mechanism of contribution of this polymorphism to blood pressure is not understood.

VII. Conclusions and Outstanding Questions

The role of 5-HT in modifying blood pressure is complex. We present both in vitro and in vivo evidence that argues 5-HT does have effects on blood pressure, many times opposite in nature in in vitro versus in vivo settings. These studies have raised a number of important questions that are the basis for future studies:

- What is the mechanism of 5-HT-induced long-term depression of blood pressure? Time and again, it has been demonstrated that 5-HT causes a long-term decrease in blood pressure. This decrease seems to be completely dependent on 5-HT stimulation of NOS activity, because the NOS inhibitor L-NNA abolishes the effect of 5-HT. Where in the body does 5-HT stimulate NOS? The vascular endothelial cell and neuron are the best candidates.

- Does 5-HT cross the blood-brain barrier? This question is important to answer given the long-held belief that 5-HT does not cross the blood-brain barrier, a belief held despite data, though decades old, that suggest the opposite. This knowledge would help us include or eliminate the central nervous system as a target for 5-HT in reducing blood pressure during

prolonged exposure.

- How are temperature and blood pressure linked by 5-HT? In several studies, 5-HT decreases blood pressure while causing heat loss. The ability of 5-HT to modify temperature itself, but also change temperature through cutaneous vasodilation, is interesting. Studies that investigate the primacy of temperature versus blood pressure homeostasis and whether 5-HT is a 'connector' to these two important physiological endpoints would be fascinating.

- Does intracellular 5-HT modify cardiovascular function? The possibility that intracellular 5-HT can modify proteins has been raised. This is carried out by the enzyme transglutaminase to change the function of proteins such as the small G protein Rho. Paulmann et al. (2009) made the important observation that 5-HT regulates insulin secretion from pancreatic β cells by serotonylating (e.g., adding 5-HT to a protein covalently) GTPases. All the work cited above considers the biological activities of 5-HT as being exerted *external* to the cell through classic receptor stimulation. This particular article points to the idea that we may need to reconsider whether 5-HT also exerts biological effects *internal* to the cell.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Watts, Morrison, Davis and Barman.

References

Abassi ZA, Binah O, and Youdim MB (2004) Cardiovascular activity of rasagiline, a selective and potent inhibitor of mitochondrial monoamine oxidase B: comparison with selegiline. *Br J Pharmacol* **143:**371–378.
Abumaria N, Ribic A, Anacker C, Fuchs E, and Flügge G (2008) Stress upregulates TPH1 but not TPH2 mRNA in the rat dorsal raphe nucleus: identification of two TPH2 mRNA splice variants. *Cell Mol Neurobiol* **28:**331–342.
Afergan E, Epstein H, Dahan R, Koroukhov N, Rohekar K, Danenberg HD, and Golomb G (2008) Delivery of serotonin to the brain by monocytes following phagocytosis of liposomes. *J Control Release* **132:**84–90.
Alenina N, Kikic D, Todiras M, Mosienko V, Qadri F, Plehm R, Boyé P, Vilianovitch L, Sohr R, Tenner K, et al. (2009) Growth retardation and altered autonomic control in mice lacking brain serotonin. *Proc Natl Acad Sci USA* **106:**10332–10337.
Alexandrino-Silva C, Nadalini Mauá FH, de Andrade AG, and de Toledo Ferraz Alves TC (2008) Hypotension caused by therapeutic doses of venlafaxine: case report and proposed pathophysiological mechanisms. *J Psychopharmacol* **22:**214–216.
Alkadhi KA, Alzoubi KH, Aleisa AM, Tanner FL, and Nimer AS (2005) Psychosocial stress-induced hypertension results from in vivo expression of long-term potentiation in rat sympathetic ganglia. *Neurobiol Dis* **20:**849–857.
Alsip NL and Harris PD (1992) Serotonin-induced dilation of small arterioles is not mediated via endothelium-derived relaxing factor in skeletal muscle. *Eur J Pharmacol* **229:**117–124.
Alsip NL, Schuschke DA, and Miller FN (1996) Microvascular responses in the skeletal muscle of the diabetic rat. *J Lab Clin Med* **128:**429–437.
Althaus JS, Beckman JJ, and Miller ED Jr (1985) Central serotonin depletion: effect on blood pressure during anesthesia. *Anesth Analg* **64:**1163–1170.
Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, and Beasley C (1999) Blood pressure changes during short-term fluoxetine treatment. *J Clin Psychopharmacol* **19:**9–14.
Anderson IK, Martin GR, and Ramage AG (1992) Central administration of 5-HT activates 5-HT$_{1A}$ receptors to cause sympathoexcitation and 5-HT$_2$/5-HT$_{1C}$ receptors to release vasopressin in anaesthetized rats. *Br J Pharmacol* **107:**1020–1028.
Anderson IK, Ramage AG, and Gardiner SM (1996) Cardiovascular effects of serotonin and DP-5-CT in conscious Long-Evans and Brattleboro rats. *Am J Physiol* **271:**R455–R463.
Arima T, Ohshima Y, Mizuno T, Kitamura Y, Segawa T, and Nomura Y (1996) Cyclic GMP elevation by 5-hydroxytryptamine is due to nitric oxide derived from endog-

enous nitrosothiol in NG108–15 cells. *Biochem Biophys Res Commun* **227:**473–478.

Asher EF, Alsip NL, Zhang PY, and Harris PD (1991) Halothane attenuates small arteriole vasodilation to serotonin (5-HT) in skeletal muscle. *Anesth Analg* **73:**583–589.

Ashkenazi R, Finberg JP, and Youdim MB (1983) Effects of LM 5008, a selective inhibitor of 5-hydroxytryptamine uptake, on blood pressure and responses to sympathomimetic amines. *Br J Pharmacol* **79:**915–922.

Azmitia EC (2001) Modern views on an ancient chemical: serotonin effects on cell proliferation, maturation, and apoptosis. *Brain Res Bull* **56:**413–424.

Azzadin A, Mysliwiec J, Wollny T, Mysliwiec M, and Buczko W (1995) Serotonin is involved in the pathogenesis of hypertension developing during erythropoietin treatment in uremic rats. *Thromb Res* **77:**217–224.

Bagale SM, Brown AS, Gonzalez MM, Vitores A, Micotto TL, Kumar NS, Hentall ID, and Wilson JN (2011) Fluorescent reporters of monoamine transporter distribution and function. *Bioorg Med Chem Lett* **21:**7387–7391.

Bagdy G, Calogero AE, Murphy DL, and Szemeredi K (1989) Serotonin agonists cause parallel activation of the sympathoadrenomedullary system and the hypothalamo-pituitary-adrenocortical axis in conscious rats. *Endocrinology* **125:**2664–2669.

Bailey RK, Mallinckrodt CH, Wohlreich MM, Watkin JG, and Plewes JM (2006) Duloxetine in the treatment of major depressive disorder: comparisons of safety and efficacy. *J Natl Med Assoc* **98:**437–447.

Banes AK and Watts SW (2002) Upregulation of arterial serotonin 1B and 2B receptors in deoxycorticosterone acetate-salt hypertension. *Hypertension* **39:**394–398.

Banes AK and Watts SW (2003) Arterial expression of 5-HT$_{2B}$ and 5-HT$_{1B}$ receptors during development of DOCA-salt hypertension. *BMC Pharmacology* **3:**12.

Barman SM and Gebber GL (2000) "Rapid" rhythmic discharges of sympathetic nerves: sources, mechanisms of generation, and physiological relevance. *J Biol Rhythms* **15:**365–379.

Barnes NM and Sharp T (1999) A review of central 5-HT receptors and their function. *Neuropharmacology* **38:**1083–1152.

Barney CC, Threatte RM, Kikta DC, and Fregly MJ (1981) Effects of serotonin and L-5-hydroxytryptophan on plasma renin activity in rats. *Pharmacol Biochem Behav* **14:**895–900.

Baron A, Riesselmann A, and Fregly MJ (1991) Reduction in the elevated blood pressure of Dahl salt-sensitive rats treated chronically with L-5-hydroxytryptophan. *Pharmacology* **42:**15–22.

Bax WA, Renzenbrink GJ, Van Heuven-Nolsen D, Thijssen EJ, Bos E, and Saxena PR (1993) 5-HT receptors mediating contractions of the isolated human coronary artery. *Eur J Pharmacol* **239:**203–210.

Bellou A, Lambert H, Gillois P, Montémont C, Gerard P, Vauthier E, Sainte-Laudy J, Longrois D, Guéant JL, and Mallié JP (2003) Constitutive nitric oxide synthase inhibition combined with histamine and serotonin receptor blockade improves the initial ovalbumin-induced arterial hypotension but decreases the survival time in brown norway rat anaphylactic shock. *Shock* **19:**71–78.

Berger M, Gray JA, and Roth BL (2009) The expanded biology of serotonin. *Ann Rev Med* **60:**355–366.

Bianchi P, Pimentel DR, Murphy MP, Colucci WS, and Parini A (2005) A new hypertrophic mechanism of serotonin in cardiac myocytes: receptor-independent ROS generation. *FASEB J* **19:**641–643.

Biondi ML, Marasini B, Bianchi E, and Agostoni A (1988) Plasma free and intraplatelet serotonin in patients with Raynaud's phenomenon. *Int J Cardiol* **19:**335–339.

Birdsall TC (1998) 5-Hydroxytryptophan: a clinically-effective serotonin precursor. *Altern Med Rev* **3:**271–280.

Birkenfeld AL, Schroeder C, Pischon T, Tank J, Luft FC, Sharma AM, and Jordan J (2005) Paradoxical effect of sibutramine on autonomic cardiovascular regulation in obese hypertensive patients–sibutramine and blood pressure. *Clin Auton Res* **15:**200–206.

Blackmore WP (1958) Effect of serotonin on renal hemodynamics and sodium excretion in the dog. *Am J Physiol* **193:**639–643.

Blankfeld RP (2006) The thermoregulatory-vascular remodeling hypothesis: an explanation for essential hypertension. *Med Hypotheses* **66:**1174–1178.

Blauw G, Bom AH, van Brummelen P, Camps J, Arndt JW, Verdouw PD, Chang PC, van Zwieten PA, and Saxena PR (1991) Effects of 5-hydroxytryptamine on capillary and arteriovenous anastomotic blood flow in the human hand and forearm and in the pig hind leg. *J Cardiovasc Pharmacol* **17:**316–324.

Blauw GJ, van Brummelen P, Chang PC, Vermeij P, and van Zwieten PA (1988) Regional vascular effects of serotonin and ketanserin in young, healthy subjects. *Hypertension* **11:**256–263.

Blessing WW and Seaman B (2003) 5-Hydroxytryptamine(2A) receptors regulate sympathetic nerves constricting the cutaneous vascular bed in rabbits and rats. *Neuroscience* **117:**939–948.

Bodelsson M, Arneklo-Nobin B, and Törnebrandt K (1990) Effect of cooling on smooth muscle response to 5-hydroxytryptamine in human hand veins. *Acta Physiol Scand* **140:**331–339.

Bom AH, Verdouw PD, and Saxena PR (1989) Carotid haemodynamics in pigs during infusions of 8-OH-DPAT: reduction in arteriovenous shunting is mediated by 5-HT1-like receptors. *Br J Pharmacol* **96:**125–132.

Borgdorff P, Fekkes D, and Tangelder GJ (2002) Hypotension caused by extracorporeal circulation: serotonin from pump-activated platelets triggers nitric oxide release. *Circulation* **106:**2588–2593.

Borgdorff P and Tangelder GJ (2006) Pump-induced platelet aggregation with subsequent hypotension: its mechanism and prevention with clopidogrel. *J Thorac Cardiovasc Surg* **131:**813–821.

Borton M, Neligan M, Wood F, Dervan P, Goggins K, and Docherty JR (1990) Contractions to 5-hydroxytryptamine in human coronary artery and human saphenous vein. *Br J Clin Pharmacol* **30 (Suppl 1):**107S–108S.

Boston PC and Hodgson WC (1997) Changes in reactivity towards 5-hydroxytrypta-

mine in the renal vasculature of the diabetic spontaneously hypertensive rat. *J Hypertens* **15:**769–774.

Bouchelet I, Case B, Olivier A, and Hamel E (2000) No contractile effect for 5-HT1D and 5-HT1F receptor agonists in human and bovine cerebral arteries: similarity with human coronary artery. *Br J Pharmacol* **129:**501–508.

Boyer EW and Shannon M (2005) The serotonin syndrome. *N Engl J Med* **352:**1112–1120.

Brand T and Anderson GM (2011) The measurement of platelet-poor plasma serotonin: a systematic review of prior reports and recommendations for improved analysis. *Clin Chem* **57:**1376–1386.

Brenner B, Harney JT, Ahmed BA, Jeffus BC, Unal R, Mehta JL, and Kilic F (2007) Plasma serotonin levels and the platelet serotonin transporter. *J Neurochem* **102:**206–215.

Breuer J, Georgaraki A, Sieverding L, Baden W, and Apitz J (1996) Increased turnover of serotonin in children with pulmonary hypertension secondary to congenital heart disease. *Pediatr Cardiol* **17:**214–219.

Brownfield MS, Poff BC, and Holzwarth MA (1985) Ultrastructural immunocytochemical co-localization of serotonin and PNMT in adrenal medullary vesicles. *Histochemistry* **83:**41–46.

Brudeli B, Moltzau LR, Andressen KW, Krobert KA, Klaveness J, and Levy FO (2010) Synthesis and pharmacological properties of novel hydrophilic 5-HT$_4$ receptor antagonists. *Bioorg Med Chem* **18:**8600–8613.

Bruning TA, Chang PC, Blauw GJ, Vermeij P, and van Zwieten PA (1993) Serotonin-induced vasodilatation in the human forearm is mediated by the "nitric oxide-pathway": no evidence for involvement of the 5-HT3-receptor. *J Cardiovasc Pharmacol* **22:**44–51.

Bruning TA, van Zwieten PA, Blauw GJ, and Chang PC (1994) No functional involvement of 5-hydroxytryptamine1A receptors in nitric oxide-dependent dilatation caused by serotonin in the human forearm vascular bed. *J Cardiovasc Pharmacol* **24:**454–461.

Brust P, Friedrich M, Krizbai IA, Bergmann R, Roux F, Ganapathy V, and Johannsen B (2000) Functional expression of the serotonin transporter in immortalized rat brain microvessel endothelial cells. *J Neurochem* **74:**1241–1248.

Buckingham RE, Hamilton TC, and Moore RA (1976) Prolonged effects of p-chlorophenylalanine on the blood pressure of conscious normotensive and DOCA/saline hypertensive rats. *Br J Pharmacol* **56:**69–75.

Bulat M and Supek Z (1968) Passage of 5-hydroxytryptamine through the blood-brain barrier, its metabolism in the brain and elimination of 5-hydroxyindoleacetic acid from the brain tissue. *J Neurochem* **15:**383–389.

Cai SR, Wang LC, Kong DH, Huang ZX, and Ma RC (1999) Substance P- and 5-hydroxytryptamine-mediated depolarization in sympathetic ganglion neurons. *Acta Physiol Sinica* **51:**585–587.

Calama E, García M, Jarque MJ, Morán A, Martín ML, and San Román L (2003) 5-Hydroxytryptamine-induced vasodilator responses in the hindquarters of the anaesthetized rat, involve beta2 adrenoceptors. *J Pharm Pharmacol* **55:**1371–1378.

Calama E, Ortíz de Urbina AV, Morán A, Martín ML, and San Román L (2005) Effect of 5-hydroxytryptamine on neurogenic vasoconstriction in the isolated, autoperfused hindquarters of the rat. *Clin Exp Pharmacol Physiol* **32:**894–900.

Callera JC, Bonagamba LG, Sévoz C, Laguzzi R, and Machado BH (1997) Cardiovascular effects of microinjection of low doses of serotonin into the NTS of unanesthetized rats. *Am J Physiol* **272:**R1135–R1142.

Callera JC, Colombari E, De Luca LA Jr, and Menani JV (2005) The bradycardic and hypotensive responses to serotonin are reduce by activation of GABA$_A$ receptors in the nucleus tractus solitarius of awake rats. *Braz J Med Biol Res* **38:**1123–1131.

Carlson LA, Ekelund LG, and Orö L (1967) Metabolic and cardio-vascular effects of serotonin. *Life Sci* **6:**261–271.

Carlsson A and Wong DT (1997) Correction: a note on the discovery of selective serotonin reuptake inhibitors. *Life Sci* **61:**1203.

Caron J, Libersa C, Hazard JR, Lacroix V, Facq E, Guedon-Moreau L, Fautrez V, Solles A, Puozzo C, and Kacet S (1993) Acute electrophysiological effects of intravenous milnacipran, a new antidepressant agent. *Eur Neuropsychopharmacol* **3:**493–500.

Carrasco G, Cruz MA, Gallardo V, Miguel P, Lagos M, and González C (1998) Plasma and platelet concentration and platelet uptake of serotonin in normal and preeclamptic pregnancies. *Life Sci* **62:**1323–1332.

Cartier D, Jégou S, Parmentier F, Lihrmann I, Louiset E, Kuhn JM, Bastard C, Plouin PF, Godin M, Vaudry H, et al. (2005) Expression profile of serotonin4 (5-HT4) receptors in adrenocortical aldosterone-producing adenomas. *Eur J Endocrinol* **153:**939–947.

Castejon AM, Paez X, Hernandez L, and Cubeddu LX (1999) Use of intravenous microdialysis to monitor changes in serotonin release and metabolism induced by cisplatin in cancer patients: comparative effects of granisetron and ondansetron. *J Pharmacol Exp Ther* **291:**960–966.

Cavero I, Lefèvre-Borg F, and Roach AG (1981) Effects of mianserin, desipramine and maprotiline on blood pressure responses evoked by acetylcholine, histamine and 5-hydroxytryptamine in rats. *Br J Pharmacol* **74:**143–148.

Centurión D, Glusa E, Sánchez-López A, Valdivia LF, Saxena PR, and Villalón CM (2004) 5-HT$_7$, but not 5-HT$_{2B}$, receptors mediate hypotension in vagosympathectomized rats. *Eur J Pharmacol* **502:**239–242.

Centurión D, Sánchez-López A, Ortiz MI, De Vries P, Saxena PR, and Villalón CM (2000) Mediation of 5-HT-induced internal carotid vasodilatation in GR127935- and ritanserin-pretreated dogs by 5-HT$_7$ receptors. *Naunyn Schmiedebergs Arch Pharmacol* **362:**169–176.

Chalon SA, Granier LA, Vandenhende FR, Bieck PR, Bymaster FP, Joliat MJ, Hirth C, and Potter WZ (2003) Duloxetine increases serotonin and norepinephrine availability in healthy subjects: a double-blind, controlled study. *Neuropsychopharmacology* **28:**1685–1693.

Chanrion B, Mannoury la Cour C, Bertaso F, Lerner-Natoli M, Freissmuth M, Millan MJ, Bockaert J, and Marin P (2007) Physical interaction between the serotonin

transporter and neuronal nitric oxide synthase underlies reciprocal modulation of their activity. *Proc Natl Acad Sci USA* **104:**8119–8124.

Chen JJ, Li Z, Pan H, Murphy DL, Tamir H, Koepsell H, and Gershon MD (2001) Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: abnormal intestinal motility and the expression of cation transporters. *J Neurosci* **21:**6348–6361.

Chester AH, Martin GR, Bodelsson M, Arneklo-Nobin B, Tadjkarimi S, Tornebrandt K, and Yacoub MH (1990) 5-Hydroxytryptamine receptor profile in healthy and diseased human epicardial coronary arteries. *Cardiovasc Res* **24:**932–937.

Christensen P, Thomsen HY, Pedersen OL, Gram LF, and Kragh-Sørensen P (1985) Orthostatic side effects of clomipramine and citalopram during treatment for depression. *Psychopharmacology* **86:**383–385.

Chudasama HP and Bhatt PA (2009) Evaluation of anti-obesity activity of duloxetine in comparison with sibutramine along with its anti-depressant activity: an experimental study in obese rats. *Can J Physiol Pharmacol* **87:**900–907.

Cohen ML, Fuller RW, and Kurz KD (1983a) Evidence that blood pressure reduction by serotonin antagonists is related to alpha receptor blockade in spontaneously hypertensive rats. *Hypertension* **5:**676–681.

Cohen ML, Fuller RW, and Kurz KD (1983b) LY53857, a selective and potent serotonergic (5-HT$_2$) receptor antagonist, does not lower blood pressure in the spontaneously hypertensive rat. *J Pharmacol Exp Ther* **227:**327–332.

Cohen RA (1986) Contractions of isolated canine coronary arteries resistant to S2-serotonergic blockade. *J Pharmacol Exp Ther* **237:**548–552.

Comet MA, Bernard JF, Hamon M, Laguzzi R, and Sévoz-Couche C (2007) Activation of nucleus tractus solitarius 5-HT$_{2A}$ but not other 5-HT$_2$ receptor subtypes inhibits the sympathetic activity in rats. *Eur J Neurosci* **26:**345–354.

Contesse V, Lenglet S, Grumolato L, Anouar Y, Lihrmann I, Lefebvre H, Delarue C, and Vaudry H (1999) Pharmacological and molecular characterization of 5-hydroxytryptamine(7) receptors in the rat adrenal gland. *Mol Pharmacol* **56:**552–561.

Côté F, Fligny C, Fromes Y, Mallet J, and Vodjdani G (2004) Recent advances in understanding serotonin regulation of cardiovascular function. *Trends Mol Med* **10:**232–238.

Côté F, Thévenot E, Fligny C, Fromes Y, Darmon M, Ripoche MA, Bayard E, Hanoun N, Saurini F, Lechat P, et al. (2003) Disruption of the nonneuronal tph1 gene demonstrates the importance of peripheral serotonin in cardiac function. *Proc Natl Acad Sci USA* **100:**13525–13530.

Csaba G and Sudár F (1978) Localization of radioactively labelled serotonin in the nucleus of adrenal medulla cells. *Acta Anat* **100:**237–240.

Cummings SA, Groszmann RJ, and Kaumann AJ (1986) Hypersensitivity of mesenteric veins to 5-hydroxytryptamine- and ketanserin-induced reduction of portal pressure in portal hypertensive rats. *Br J Pharmacol* **89:**501–513.

Cushing DJ, Baez M, Kursar JD, Schenck K, and Cohen ML (1994) Serotonin-induced contraction in canine coronary artery and saphenous vein: role of a 5-HT1D-like receptor. *Life Sci* **54:**1671–1680.

Cushing DJ and Cohen ML (1992a) Serotonin-induced relaxation in canine coronary artery smooth muscle. *J Pharmacol Exp Ther* **263:**123–129.

Cushing DJ and Cohen ML (1992b) Comparison of the serotonin receptors that mediate smooth muscle contraction in canine and porcine coronary artery. *J Pharmacol Exp Ther* **261:**856–862.

Cushing DJ and Cohen ML (1993) Serotonin-induced contraction in porcine coronary artery: use of ergolines to support vascular 5-hydroxytryptamine2-receptor heterogeneity. *J Pharmacol Exp Ther* **264:**193–200.

Cushing DJ, Zgombick JM, Nelson DL, and Cohen ML (1996) LY215840, a high-affinity 5-HT$_7$ receptor ligand, blocks serotonin-induced relaxation in canine coronary artery. *J Pharmacol Exp Ther* **277:**1560–1566.

Dabiré H, Laubie M, and Schmitt H (1990) Hypotensive effects of 5-HT$_{1A}$ receptor agonists on the ventrolateral medullary pressor area in dogs. *J Cardiovasc Pharmacol* **15 (Suppl 7):**S61–S67.

Dalton DW, Feniuk W, and Humphrey PP (1986) An investigation into the mechanisms of the cardiovascular effects of 5-hydroxytryptamine in conscious normotensive and DOCA-salt hypertensive rats. *J Auton Pharmacol* **6:**219–228.

Das YT, Bagchi M, Bagchi D, and Preuss HG (2004) Safety of 5-hydroxy-L-tryptophan. *Toxicol Lett* **150:**111–122.

Davis RP, Linder AE, and Watts SW (2011) Lack of the serotonin transporter (SERT) reduces the ability of 5-hydroxytryptamine to lower blood pressure. *Naunyn Schmiedebergs Arch Pharmacol* **383:**543–546.

Daws LC (2009) Unfaithful neurotransmitter transporters: focus on serotonin uptake and implications for antidepressant efficacy. *Pharmacol Ther* **121:**89–99.

de Lemos HP Jr, Atallah AN, and de Lemos AL (2008) Can sibutramine alter systemic blood pressure in obese patients? Systematic review and meta-analysis. *Sao Paulo Med J* **126:**342–346.

De Vries P, De Visser PA, Heiligers JP, Villalón CM, and Saxena PR (1999) Changes in systemic and regional haemodynamics during 5-HT$_7$ receptor-mediated depressor responses in rats. *Naunyn-Schmiedebergs Arch Pharmacol* **359:**331–338.

Dedeoğlu A and Fisher LA (1991) Central nervous actions of serotonin and a serotonin1A receptor agonist: cardiovascular excitation at low doses. *J Pharmacol Exp Ther* **257:**425–432.

Delarue C, Becquet D, Idres S, Hery F, and Vaudry H (1992) Serotonin synthesis in adrenochromaffin cells. *Neuroscience* **46:**495–500.

Derby MA, Zhang L, Chappell JC, Gonzales CR, Callaghan JT, Leibowitz M, Ereshefsky L, Hoelscher D, Leese PT, and Mitchell MI (2007) The effects of a supratherapeutic doses of duloxetine on blood pressure and pulse rate. *J Cardiovasc Pharmacol* **49:**384–393.

Diaz J, Ni W, Thompson J, King A, Fink GD, and Watts SW (2008) 5-Hydroxytryptamine lowers blood pressure in normotensive and hypertensive rats. *J Pharmacol Exp Ther* **325:**1031–1038.

Ding XR, Stier CT Jr, and Itskovitz HD (1989) Serotonin and 5-hydroxytryptophan on blood pressure and renal blood flow in anesthetized rats. *Am J Med Sci* **297:**290–293.

Ding YA, Chou TC, and Huan R (1994) Are platelet cytosolic free calcium, serotonin

concentration and blood viscosity different between hypertensive and normotensive subjects? *Cardiology* **85:**76–81.

Dobbins DE, Adamski SW, Lokhandwala MF, and Grega GJ (1983) Evidence that serotonin receptors mediate the cutaneous vasoconstriction produced by 5-hydroxytryptamine in canine forelimbs. *Circ Res* **53:**473–481.

Docherty JR (1988) Investigation of cardiovascular 5-hydroxytryptamine receptor subtypes in the rat. *Naunyn Schmiedebergs Arch Pharmacol* **337:**1–8.

Docherty JR (1989) An investigation of the effects of intravenous injection of the 5-hydroxytryptamine 2 receptor antagonists ketanserin and LY 53857 on blood pressure in anesthetized spontaneously hypertensive rats. *J Pharmacol Exp Ther* **248:**736–740.

Doggrell SA (2003) The role of 5-HT on the cardiovascular and renal systems and the clinical potential of 5-HT modulation. *Expert Opin Investig Drugs* **12:**805–823.

Dohi Y and Lüscher TF (1991) Altered intra- and extraluminal effects of 5-hydroxytryptamine in hypertensive mesenteric resistance arteries: contribution of the endothelium and smooth muscle. *J Cardiovasc Pharmacol* **18:**278–284.

Dorigo P, Belluco P, Corradi L, Gaion RM, and Maragno I (1992) Vasodilatory activity of etozoline in rat and guinea-pig isolated aorta: study of the mechanism of action. *Arch Int Pharmacodyn Ther* **315:**63–78.

Dun NJ and Karczmar AG (1981) Evidence for a presynaptic inhibitory action of 5-hydroxytryptamine in a mammalian sympathetic ganglion. *J Pharmacol Exp Ther* **217:**714–718.

Dun NJ, Kiraly M, and Ma RC (1984) Evidence for a serotonin-mediated slow excitatory potential in the guinea-pig coeliac ganglia. *J Physiol* **351:**61–76.

Echizen H and Freed CR (1982) Long-term infusion of L-5-hydroxytryptophan increases brain serotonin turnover and decreases blood pressure in normotensive rats. *J Pharmacol Exp Ther* **220:**579–584.

Edvinsson L, Uddman E, Wackenfors A, Davenport A, Longmore J, and Malmsjö M (2005) Triptan-induced contractile (5-HT1B receptor) responses in human cerebral and coronary arteries: relationship to clinical effect. *Clin Sci* **109:**335–342.

Eglen RM, Perkins LA, Walsh LK, and Whiting RL (1992) Agonist action of indole derivatives at 5-HT1-like, 5-HT3, and 5HT4 receptors in vitro. *J Auton Pharmacol* **12:**321–333.

Ellis ES, Byrne C, Murphy OE, Tilford NS, and Baxter GS (1995) Mediation by 5-hydroxytryptamine$_{2B}$ receptors of endothelium-dependent relaxation in rat jugular vein. *Br J Pharmacol* **114:**400–404.

Ellwood AJ and Curtis MJ (1997) Involvement of 5-HT$_{(1B/1D)}$ and 5-HT$_{2A}$ receptors in 5-HT-induced contraction of endothelium-denuded rabbit epicardial coronary arteries. *Br J Pharmacol* **122:**875–884.

Erspamer V and Asero B (1952) Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature* **169:**800–801.

Evans RG, Haynes JM, and Ludbrook J (1993) Effects of 5-HT-receptor and alpha 2-adrenoceptor ligands on the haemodynamic response to acute central hypovolaemia in conscious rabbits. *Br J Pharmacol* **109:**37–47.

Fastier FN and Waal H (1957) The antidiuretic action of 5-hydroxytryptamine in cats in relation to the production of certain chemoreflexes. *Br J Pharmacol Chemother* **12:**484–488.

Feldman PD and Galiano FJ (1995) Cardiovascular effects of serotonin in the nucleus of the solitary tract. *Am J Physiol* **269:**R48–R56.

Feniuk W, Humphrey PP, and Watts AD (1979) Presynaptic inhibitory action of 5-hydroxytryptamine in dog isolated saphenous vein. *Br J Pharmacol* **67:**247–254.

Feniuk W, Humphrey PP, Perren MJ, and Watts AD (1985) A comparison of 5-hydroxytryptamine receptors mediating contraction in rabbit aorta and dog saphenous vein: evidence for different receptor types obtained by use of selective agonists and antagonists. *Br J Pharmacol* **86:**697–704.

Ferreira HS, de Castro e Silva E, Cointeiro C, Oliveira E, Faustino TN, and Fregoneze JB (2004) Role of central 5-HT$_3$ receptors in the control of blood pressure in stressed and non-stressed rats. *Brain Res* **1028:**48–58.

Ferreira HS, Oliveira E, Faustino TN, Silva Ede C, and Fregoneze JB (2005) Effect of the activation of central 5-HT$_{2C}$ receptors by the 5-HT$_{2C}$ agonist mCPP on blood pressure and heart rate in rats. *Brain Res* **1040:**64–72.

Fetkovska N, Amstein R, Ferracin F, Regenass M, Bühler FR, and Pletscher A (1990a) 5-Hydroxytryptamine kinetics and activation of blood platelets in patients with essential hypertension. *Hypertension* **15:**267–273.

Fetkovska N, Pletscher A, Ferracin F, Amstein R, and Buhler FR (1990b) Impaired uptake of 5 hydroxytryptamine platelet in essential hypertension: clinical relevance. *Cardiovasc Drugs Ther* **4 (Suppl 1):**105–109.

Feuerstein TJ (2008) Presynaptic receptors for dopamine, histamine, and serotonin. *Handb Exp Pharmacol* **184:**289–338.

Filshie GM, Maynard P, Hutter C, Cooper JC, Robinson G, and Rubin P (1992) Urinary 5-hydroxyindole acetate concentration in pregnancy induced hypertension. *BMJ* **304:**1223.

Finberg JP, Gross A, Bar-Am O, Friedman R, Loboda Y, and Youdim MB (2006) Cardiovascular responses to combined treatment with selective monoamine oxidase type B inhibitors and L-DOPA in the rat. *Br J Pharmacol* **149:**647–656.

Flórez J and Armijo JA (1974) Effect of central inhibition of the 1-amino acid decarboxylase on the hypotensive action of 5-HT precursors in cats. *Eur J Pharmacol* **26:**108–110.

Fozard JR, Mir AK, and Middlemiss DN (1987) Cardiovascular response to 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in the rat: site of action and pharmacological analysis. *J Cardiovasc Pharmacol* **9:**328–347.

Frandsen P and Nielsen AT (1966) The antidiuretic effect of 5-hydroxytryptamine in the rat after subcutaneous injection of 'physiological' doses. *Acta Pharmacol Toxicol (Copenh)* **24:**50–54.

Fregly MJ, Lockley OE, and Sumners C (1987a) Chronic treatment with L-5-hydroxytryptophan prevents the development of DOCA-salt-induced hypertension in rats. *J Hypertens* **5:**621–628.

Fregly MJ, Lockley OE, van der Voort J, Sumners C, and Henley WN (1987b) Chronic dietary administration of tryptophan prevents the development of deoxycorticosterone acetate salt induced hypertension in rats. *Can J Physiol Pharmacol* **65:**753–764.

Frishman WH, Okin S, and Huberfeld S (1988) Serotonin antagonism in the treatment of systemic hypertension: the role of ketanserin. *Med Clin North Am* **72:**501–522.

Froldi G, Montopoli M, Zanetti M, Dorigo P, and Caparrotta L (2008) 5-HT_1B receptor subtype and aging in rat resistance vessels. *Pharmacology* **81:**70–78.

Froldi G, Nicoletti P, Caparrotta L, and Ragazzi E (2003) 5-HT receptors mediating contraction in the rat-tail artery. *Adv Exp Med Biol* **527:**665–670.

Fuentes JA, Ordaz A, and Neff NH (1979) Central mediation of the antihypertensive effect of pargyline in spontaneously hypertensive rats. *Eur J Pharmacol* **57:**21–27.

Fujiwara T and Chiba S (1995) Augmented responses to 5-HT2-receptor-mediated vasoconstrictions in atherosclerotic rabbit common carotid arteries. *J Cardiovasc Pharmacol* **26:**503–510.

Gaciong Z and Placha G (2005) Efficacy and safety of sibutramine in 2225 subjects with cardiovascular risk factors: short-term, open-label, observational study. *J Hum Hypertens* **19:**737–743.

Gaddum JH and Picarelli ZP (1957) Two kinds of tryptamine receptor. *Br J Pharmacol* **12:**323–328.

Gale JD and Cowen T (1988) The origin and distribution of 5-hydroxytryptamine-like immunoreactive nerve fibres to major mesenteric blood vessels of the rat. *Neuroscience* **24:**1051–1059.

Galzin AM, Delahaye M, Hoornaert C, McCort G, and O'Connor SE (2000) Effects of SL 65.0472, a novel 5-HT receptor antagonist, on 5-HT receptor mediated vascular contraction. *Eur J Pharmacol* **404:**361–368.

García M, Morán A, Luisa Martín M, Barthelmebs M, and San Román L (2006) The nitric oxide synthesis/pathway mediates the inhibitory serotoninergic responses of the pressor effect elicited by sympathetic stimulation in diabetic pithed rats. *Eur J Pharmacol* **537:**126–134.

Gaw AJ, Wadsworth RM, and Humphrey PP (1990) Pharmacological characterisation of postjunctional 5-HT receptors in cerebral arteries from the sheep. *Eur J Pharmacol* **179:**35–44.

Geerts IS, De Meyer GR, and Bult H (2000) Collar-induced elevation of mRNA and functional activity of 5-HT(1B) receptor in the rabbit carotid artery. *Br J Pharmacol* **131:**1723–1731.

Gerges NZ, Aleisa AM, Alhaider AA, and Alkadhi KA (2002) Reduction of elevated arterial blood pressure in obese Zucker rats by inhibition of ganglionic long-term potentiation. *Neuropharmacology* **43:**1070–1076.

Giardina EG, Johnson LL, Vita J, Bigger JT Jr, and Brem RF (1985) Effect of imipramine and nortriptyline on left ventricular function and blood pressure in patients treated for arrhythmias. *Am Heart J* **109:**992–998.

Gilbert MJ and Newberry NR (1987) A 5-HT1-like receptor mediates a sympathetic ganglionic hyperpolarization. *Eur J Pharmacol* **144:**385–388.

Gilmore B and Michael M (2011) Treatment of acute migraine headache. *Am Fam Physician* **83:**271–280.

Glassman AH, Bigger JT Jr, Giardina EV, Kantor SJ, Perel JM, and Davies M. (1979) Clinical characteristics of imipramine-induced orthostatic hypotension. *Lancet* **1:**468–472.

Glusa E and Müller-Schweinitzer E (1993) Heterogeneity of 5-HT receptor subtypes in isolated human femoral and saphenous veins. *Naunyn Schmiedebergs Arch Pharmacol* **347:**133–136.

Glusa E and Roos A (1996) Endothelial 5-HT receptors mediate relaxation of porcine pulmonary arteries in response to ergotamine and dihydroergotamine. *Br J Pharmacol* **119:**330–334.

Göthert M, Molderings GJ, Fink K, and Schlicker E (1991) Heterogeneity of presynaptic serotonin receptors on sympathetic neurones in blood vessels. *Blood Vessels* **28:**11–18.

Göthert M, Schlicker E, and Kollecker P (1986) Receptor-mediated effects of serotonin and 5-methoxytryptamine on noradrenaline release in the rat vena cava and in the heart of the pithed rat. *Naunyn Schmiedebergs Arch Pharmacol* **332:**124–130.

Gradin K, Pettersson A, Hedner T, and Persson B (1985) Chronic 5-HT_2 receptor blockade with ritanserin does not reduce blood pressure in the spontaneously hypertensive rat. *J Neural Transm* **64:**145–149.

Grandaw PP and Purdy RE (1996) Serotonin-induced vasoconstriction in rabbit femoral artery: mediation by both 5-HT2 serotonergic and alpha 1-adrenoceptors. *J Cardiovasc Pharmacol* **27:**854–860.

Green AR (2006) Neuropharmacology of 5-hydroxytryptamine. *Br J Pharmacol* **147:**S145–S152.

Grubb BP, Samoil D, Kosinski D, Wolfe D, Lorton M, and Madu E (1994) Fluoxetine hydrochloride for the treatment of severe refractory orthostatic hypotension. *Am J Med* **97:**366–368.

Guelfi JD, Dreyfus JF, and Pichot P (1983) A double-blind controlled clinical trial comparing fluvoxamine with imipramine. *Br J Clin Pharmacol* **15:**411S–417S.

Gujrati VR, Goyal A, Gaur SP, Singh N, Shanker K, and Chandravati (1994) Relevance of platelet serotonergic mechanisms in pregnancy induced hypertension. *Life Sci* **55:**327–335.

Gul H, Yildiz O, Simsek A, Balkan M, Ersoz N, Cetiner S, Isimer A, and Sen D (2003) Pharmacologic characterization of contractile serotonergic receptors in human isolated mesenteric artery. *J Cardiovasc Pharmacol* **41:**307–315.

Guyenet PG (2006) The sympathetic control of blood pressure. *Nat Rev Neurosci* **7:**335–346.

Hafdi Z, Couette S, Comoy E, Prie D, Amiel C, and Friedlander G (1996) Locally formed 5-hydroxytryptamine stimulates phosphate transport in cultured opossum kidney cells and in rat kidney. *Biochem J* **320:**615–621.

Hajjo R, Grulke CM, Golbraikh A, Setola V, Huang XP, Roth BL, and Tropsha A (2010) Development, validation, and use of quantitative structure-activity relationship models of 5-hydroxytryptamine (2B) receptor ligands to identify novel receptor binders and putative valvulopathic compounds among common drugs. *J Med Chem* **53:**7573–7586.

Halder I, Muldoon MF, Ferrell RE, and Manuck SB (2007) Serotonin receptor 2A (HTR2A) gene polymorphisms are associated with blood pressure, central adiposity, and the metabolic syndrome. *Metab Syndr Relat Disord* **5:**323–330.

Hamel E, Grégoire L, and Lau B (1993) 5-HT_1 receptors mediating contraction in bovine cerebral arteries: a model for human cerebrovascular '5-HT1D beta' receptors. *Eur J Pharmacol* **242:**75–82.

Hamel E, Robert JP, Young AR, and MacKenzie ET (1989) Pharmacological properties of the receptor(s) involved in the 5-hydroxytryptamine-induced contraction of the feline middle cerebral artery. *J Pharmacol Exp Ther* **249:**879–889.

Hansen MB, Arif F, Gregersen H, Bruusgaard H, and Wallin L (2008) Effect of serotonin on small intestinal contractility in healthy volunteers. *Physiol Res* **57:**63–71.

Häppölä O (1988) 5-Hydroxytryptamine-immunoreactive neurons and nerve fibers in the superior cervical ganglion of the rat. *Neuroscience* **27:**301–307.

Hardcastle J and Hardcastle PT (1999) Effects of 5-hydroxytryptamine on the transintestinal electrical activity and cardiovascular function of fawn-hooded rats in-vivo. *J Pharm Pharmacol* **51:**1415–1421.

Hardebo JE and Owman C (1980) Barrier mechanisms for neurotransmitter monoamines and their precursors at the blood-brain interface. *Ann Neurol* **8:**1–31.

Haugen G, Mellembakken J, and Stray-Pedersen S (1997) Characterization of the vasodilatatory response to serotonin in human umbilical arteries perfused in vitro. The influence of the endothelium. *Early Hum Dev* **47:**185–193.

Helke CJ, McDonald CH, and Phillips ET (1993) Hypotensive effects of 5-HT_1A receptor activation: ventral medullary sites and mechanisms of action in the rat. *J Auton Nerv Syst* **42:**177–188.

Hertzler EC (1961) 5-Hydroxytryptamine and transmission in sympathetic ganglia. *Br J Pharmacol* **17:**406–413.

Hoffmann P, Carlsson S, Skarphedinsson JO, and Thorén P (1990) Role of different serotonergic receptors in the long-lasting blood pressure depression following muscle stimulation in the spontaneously hypertensive rat. *Acta Physiol Scand* **139:**305–310.

Holzwarth MA and Brownfield MS (1985) Serotonin coexists with epinephrine in rat adrenal medullary cells. *Neuroendocrinology* **41:**230–236.

Holzwarth MA, Sawetawan C, and Brownfield MS (1984) Serotonin-immunoreactivity in the adrenal medulla: distribution and response to pharmacological manipulation. *Brain Res Bull* **13:**299–308.

Homberg JR, Olivier JD, Smits BM, Mul JD, Mudde J, Verheul M, Nieuwenhuizen OF, Cools AR, Ronken E, Cremers T, et al. (2007) Characterization of the serotonin transporter knockout rat: a selective change in the functioning of the serotonergic system. *Neuroscience* **146:**1662–1676.

Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, Saxena PR, and Humphrey PP (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev* **46:**157–203.

Hoyer D, Hannon JP, and Martin GR (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* **71:**533–554.

Huang XP, Setola V, Yadav PN, Allen JA, Rogan SC, Hanson BJ, Revankar C, Robers M, Doucette C, and Roth BL (2009) Parallel functional activity profiling reveals valvulopathogens are potent 5-hydroxytryptamine(2B) receptor agonists: implications for drug safety assessment. *Mol Pharmacol* **76:**710–722.

Hughes IE and Radwan S (1979) The relative toxicity of amitriptyline, imipramine, maprotiline and mianserin in vivo. *Br J Pharmacol* **65:**331–338.

Hutri-Kähönen N, Kähönen M, Wu X, Sand J, Nordback I, Taurio J, and Pörsti I (1999) Control of vascular tone in isolated mesenteric arterial segments from hypertensive patients. *Br J Pharmacol* **127:**1735–1743.

Huzoor-Akbar, Chen NY, Fossen DV, and Wallace D (1989) Increased vascular contractile sensitivity to serotonin in spontaneously hypertensive rats is linked with increased turnover of phosphoinositide. *Life Sci* **45:**577–583.

Ikeda K, Tojo K, Otsubo C, Udagawa T, Kumazawa K, Ishikawa M, Tokudome G, Hosoya T, Tajima N, Claycomb WC, et al. (2005) 5-Hydroxytryptamine synthesis in HL-1 cells and neonatal rat cardiocytes. *Biochem Biophys Res Commun* **328:**522–525.

Ishida T, Kawashima S, Hirata Ki, Sakoda T, Shimokawa Y, Miwa Y, Inoue N, Ueyama T, Shiomi M, Akita H, et al. (2001) Serotonin-induced hypercontraction through 5-hydroxytryptamine 1B receptors in atherosclerotic rabbit coronary arteries. *Circulation* **103:**1289–1295.

Itskovitz HD, Werber JL, Sheridan AM, Brewer TF, and Stier CT Jr (1989) 5-Hydroxytryptophan and carbidopa in spontaneously hypertensive rats. *J Hypertens* **7:**311–315.

Jähnichen S, Glusa E, and Pertz HH (2005) Evidence for 5-HT_2B and 5-HT_7 receptor-mediated relaxation in pulmonary arteries of weaned pigs. *Naunyn-Schmiedebergs Arch Pharmacol* **371:**89–98.

Janiak P, Lainée P, Grataloup Y, Luyt CE, Bidouard JP, Michel JB, O'Connor SE, and Herbert JM (2002) Serotonin receptor blockade improves distal perfusion after lower limb ischemia in the fatty Zucker rat. *Cardiovasc Res* **56:**293–302.

Jansen I, Olesen J, and Edvinsson L (1993) 5-Hydroxytryptamine receptor characterization of human cerebral, middle meningeal and temporal arteries: regional differences. *Acta Physiol Scand* **147:**141–150.

Janssen BJ, van Essen H, Struyker Boudier HA, and Smits JF (1989) Hemodynamic effects of activation of renal and mesenteric sensory nerves in rats. *Am J Physiol* **257:**R29–R36.

Jelen I, Fananapazir L, and Crawford TB (1979) The possible relation between late pregnancy hypertension and 5-hydroxytryptamine levels in maternal blood. *Br J Obstet Gynaecol* **86:**468–471.

Jochem J, Zak A, Rybczyk R and Irman-Florjanc T (2009) Interactions between the serotonergic and histaminergic systems in the central cardiovascular regulation in haemorrhage-shocked rats: involvement of 5-HT(1A) receptors. *Inflamm Res* **58 (Suppl 1):**38–40.

Johansson K, Sundström J, Neovius K, Rössner S, and Neovius M (2010) Long-term changes in blood pressure following orlistat and sibutramine treatment: a meta-analysis. *Obes Rev* **11:**777–791.

Jones JF, Martin GR, and Ramage AG (1995) Evidence that 5-HT_1D receptors mediate inhibition of sympathetic ganglionic transmission in anaesthetized cats. *Br J Pharmacol* **116:**1715–1717.

Jordan D (2005) Vagal control of the heart: central serotonergic (5-HT) mechanisms. *Exp Physiol* **90:**175–181.

Kamal LA, Le Quan-Bui KH, and Meyer P (1984) Decreased uptake of 3H-serotonin and endogenous content of serotonin in blood platelets in hypertensive patients. *Hypertension* **6:**568–573.

Karhula T, Soinila S, Lakomy M, Majewski M, Kaleczyk J, and Häppölä O (1995) 5-Hydroxytryptamine-immunoreactive nerve fibers in the rat and porcine vertebral sympathetic ganglia: effect of precursor loading and relation to catecholaminergic neurons. *Neurosci Lett* **194:**85–88.

Kato H, Noguchi Y, and Takagi K (1974) Comparison of cardiovascular toxicities induced by dimetacrine, imipramine and amitriptyline in isolated guinea pig atria and anesthetized dogs. *Jpn J Pharmacol* **24:**885–891.

Kaumann AJ and Levy FO (2006) 5-Hydroxytryptamine receptors in the human cardiovascular system. *Pharmacol Ther* **111:**674–706.

Kawasaki H and Takasaki K (1984) Vasoconstrictor response induced by 5-hydroxytryptamine released from vascular adrenergic nerves by periarterial nerve stimulation. *J Pharmacol Exp Ther* **229:**816–822.

Kellett DO, Stanford SC, Machado BH, Jordan D, and Ramage AG (2005) Effect of 5-HT depletion on cardiovascular vagal reflex sensitivity in awake and anesthetized rats. *Brain Res* **1054:**61–72.

Kema IP, Meijer WG, Meiborg G, Ooms B, Willemse PH, and de Vries EG (2001) Profiling of tryptophan-related plasma indoles in patients with carcinoid tumors by automated, on-line, solid-phase extraction and HPLC with fluorescence detection. *Clin Chem* **47:**1811–1820.

Kemme MJ, Burggraaf J, Schoemaker RC, Cohen AF, and Blauw GJ (2000) No evidence for functional involvement of 5-HT$_{2B}$ receptors in serotonin-induced vasodilatation in the human forearm. *J Cardiovasc Pharmacol* **36:**699–703.

Kerecsen L and Bunag RD (1989) Selective pressor enhancement by monoamine oxidase inhibitors in conscious rats. *J Pharmacol Exp Ther* **251:**645–649.

Key BJ and Wigfield CC (1992) Changes in the tail surface temperature of the rat following injection of 5-hydroxytryptamine into the ventrolateral medulla. *Neuropharmacology* **31:**717–723.

Kim SH, Lee YM, Jee SH, and Nam CM (2003) Effect of sibutramine on weight loss and blood pressure: a meta-analysis of controlled trials. *Obes Res* **11:**1116–1123.

Knowles ID and Ramage AG (1999) Evidence for a role for central 5-HT$_{2B}$ as well as 5-HT$_{2A}$ receptors in cardiovascular regulation in anaesthetized rats. *Br J Pharmacol* **128:**530–542.

Koch CA, Lasho TL, and Tefferi A (2004) Platelet-rich plasma serotonin levels in chronic myeloproliferative disorders: evaluation of diagnostic use and comparison with the neutrophil PRV-1 assay. *Br J Haematol* **127:**34–39.

Krobert KA, Bach T, Syversveen T, Kvingedal AM, and Levy FO (2001) The cloned human 5-HT$_7$ receptor splice variants: a comparative characterization of their pharmacology, function and distribution. *Naunyn Schmiedebergs Arch Pharmacol* **363:**620–632.

Krygicz D, Azzadin A, Pawlak R, Małyszko JS, Pawlak D, Myśliwiec M, and Buczko W (1996) Cyclosporine A affects serotonergic mechanisms in uremic rats. *Pol J Pharmacol* **48:**351–354.

Kuhn DM (1999) Tryptophan hydroxylase regulation. Drug-induced modifications that alter serotonin neuronal function. *Adv Exp Med Biol* **467:**19–27.

Kuhn DM, Wolf WA, and Lovenberg W (1980) Review of the role of the central serotonergic neuronal system in blood pressure regulation. *Hypertension* **2:**243–255.

Laguzzi R (2003) Serotonin2 receptors in the nucleus tractus solitarius: characterization and role in the baroreceptor reflex arc. *Cell Mol Neurobiol* **23:**709–726.

Lai FM, Tanikella T, and Cervoni P (1991) Characterization of serotonin receptors in isolated rat intramyocardial coronary artery. *J Pharmacol Exp Ther* **256:**164–168.

Lamping KG and Faraci FM (2001) Role of sex differences and effects of endothelial NO synthase deficiency in responses of carotid arteries to serotonin. *Arterioscler Thromb Vasc Biol* **21:**523–528.

Lazartigues E, Brefel-Courbon C, Bagheri H, Costes S, Gharib C, Tran MA, Senard JM, and Montastruc JL (2000) Fluoxetine-induced pressor response in freely moving rats: a role for vasopressin and sympathetic tone. *Fundam Clin Pharmacol* **14:**443–451.

Le Quan Sang KH, Montenay-Garestier T, and Devynck MA (1991) Alterations of platelet membrane microviscosity in essential hypertension. *Clin Sci* **80:**205–211.

Leff P, Martin GR, and Morse JM (1987) Differential classification of vascular smooth muscle and endothelial cell 5-HT receptors by use of tryptamine analogues. *Br J Pharmacol* **91:**321–331.

Lemberger HF, Mason N, and Cohen ML (1984) 5HT$_2$ receptors in the rat portal vein: desensitization following cumulative serotonin addition. *Life Sci* **35:**71–77.

Lenglet S, Louiset E, Delarue C, Vaudry H, and Contesse V (2002) Activation of 5-HT(7) receptor in rat glomerulus cells is associated with an increase in adenylyl cyclase activity and calcium influx through T-type calcium channels. *Endocrinology* **143:**1748–1760.

Lewis DI and Coote JH (1990) The influence of 5-hydroxytryptamine agonists and antagonists on identified sympathetic preganglionic neurones in the rat, in vivo. *Br J Pharmacol* **99:**667–672.

Li Kam Wa TC, Freestone S, Samson RR, Johnston NR, and Lee MR (1994) The antinatriuretic action of gamma-L-glutamyl-5-hydroxy-L-tryptophan is dependent on its decarboxylation to 5-hydroxytryptamine in normal man. *Br J Clin Pharmacol* **38:**265–269.

Lindbom LO, Malatray J, Hall H, and Ogren SO (1982) Cardiovascular and anticholinergic effects of zimeldine. *Prog Prog Neuropsychopharmacol Biol Psychiatry* **6:**403–406.

Linden A, Desmecht D, Amory H, and Lekeux P (1999) Cardiovascular response to intravenous administration of 5-hydroxytryptamine after type-2 receptor blockade, by metrenperone, in healthy calves. *Vet J* **157:**31–37.

Linder AE, Beggs KM, Burnett RJ, and Watts SW (2009) Body distribution of infused serotonin in rats. *Clin Exp Pharmacol Physiol* **36:**599–601.

Linder AE, Diaz J, Ni W, Szasz T, Burnett R, and Watts SW (2008a) Vascular reactivity, 5-HT uptake, and blood pressure in the serotonin transporter knockout rat. *Am J Physiol Heart Circ Physiol* **294:**H1745–H1752.

Linder AE, Gaskell GL, Szasz T, Thompson JM, and Watts SW (2010) Serotonin receptors in rat jugular vein: presence and involvement in the contraction. *J Pharmacol Exp Ther* **325:**714–722.

Linder AE, Ni W, Szasz T, Burnett R, Diaz J, Geddes TJ, Kuhn DM, and Watts SW (2008b) A serotonergic system in veins: serotonin transporter-independent uptake. *J Pharmacol Exp Ther* **325:**714–722.

Liu GS, Huang DX, Yang XS, Wang SR, Tang XL, Xing JL, Peng SY, and Tong YZ (1991) Ketanserin in the treatment of hypertension: a multicentre dose-finding study in China. *Clin Exp Hypertens A* **13:**541–555.

Louiset E, Cartier D, Contesse V, Duparc C, Lihrmann I, Young J, Bertherat J, Reznik Y, Kuhn JM, Laquerrière A, et al. (2004) Paradoxical inhibitory effect of serotonin on cortisol production from adrenocortical lesions causing Cushing's syndrome. *Endocr Res* **30:**951–954.

MacLean MR and Dempsie Y (2009) Serotonin and pulmonary hypertension–from bench to bedside? *Curr Opin Pharmacol* **9:**281–286.

MacLennan SJ, Bolofo ML, and Martin GR (1993) Amplifying interactions between spasmogens in vascular smooth muscle. *Biochem Soc Trans* **21:**1145–1150.

Madden CJ and Morrison SF (2006) Serotonin potentiates sympathetic responses evoked by spinal NMDA. *J Physiol* **577:**525–537.

Manivet P, Mouillet-Richard S, Callebert J, Nebigil CG, Maroteaux L, Hosoda S, Kellermann O, and Launay JM (2000) PDZ-dependent activation of nitric-oxide synthases by the serotonin 2B receptor. *J Biol Chem* **275:**9324–9331.

Mankad PS, Chester AH, and Yacoub MH (1991) 5-Hydroxytryptamine mediates endothelium dependent coronary vasodilatation in the isolated rat heart by the release of nitric oxide. *Cardiovasc Res* **25:**244–248.

Martin GR (1994) Vascular receptors for 5-hydroxytryptamine: distribution, function and classification. *Pharmacol Ther* **62:**283–324.

Martinez AA and Lokhandwala MF (1980) Evidence for a presynaptic inhibitory action of 5-hydroxytryptamine on sympathetic neurotransmission to the myocardium. *Eur J Pharmacol* **63:**303–311.

Marwood JF, Huston V, and Wall KT (1985) Some cardiovascular effects of monoamine oxidase inhibitors in unanaesthetized rats. *Clin Exp Pharmacol Physiol* **12:**161–168.

Marwood JF and Stokes GS (1984) Serotonin (5HT) and its antagonists: involvement in the cardiovascular system. *Clin Exp Pharmacol Physiol* **11:**439–455.

Mason PJ, Morris VA, and Balcezak TJ (2000) Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine* **79:**201–209.

Masu K, Saino T, Kuroda T, Matsuura M, Russa AD, Ishikita N, and Satoh Y (2008) Regional differences in 5-HT receptors in cerebral and testicular arterioles of the rat as revealed by Ca^{2+} imaging of real-time confocal microscopy: variances by artery size and organ specificity. *Arch Histol Cytol* **71:**291–302.

Maurer-Spurej E (2005) Serotonin reuptake inhibitors and cardiovascular diseases: a platelet connection. *Cell Mol Life Sci* **62:**159–170.

Mbaya P, Alam F, Ashim S, and Bennett D (2007) Cardiovascular effects of high dose venlafaxine XL in patients with major depressive disorder. *Hum Psychopharmacol* **22:**129–133.

McCall RB and Clement ME (1994) Role of serotonin$_{1A}$ and serotonin$_2$ receptors in the central regulation of the cardiovascular system. *Pharmacol Rev* **46:**231–243.

McGregor DD and Smirk FH (1970) Vascular responses to 5-hydroxytryptamine in genetic and renal hypertensive rats. *Am J Physiol* **219:**687–690.

McKune CM and Watts SW (2001) Characterization of the serotonin receptor mediating contraction in the mouse thoracic aorta and signal pathway coupling. *J Pharmacol Exp Ther* **297:**88–95.

McLennan PL and Taylor DA (1984) Antagonism by ketanserin of 5-HT-induced vasoconstriction unmasks a 5-HT-induced vasodilation. *Eur J Pharmacol* **104:**313–318.

McMahon FG, Fujioka K, Singh BN, Mendel CM, Rowe E, Rolston K, Johnson F, and Mooradian AD (2000) Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* **160:**2185–2191.

Medow MS, Stewart JM, Sanyal S, Mumtaz A, Sica D, and Frishman WH (2008) Pathophysiology, diagnosis, and treatment of orthostatic hypotension and vasovagal syncope. *Cardiol Rev* **16:**4–20.

Meehan AG and Kreulen DL (1991) Electrophysiological studies on the interaction of 5-hydroxytryptamine with sympathetic transmission in the guinea pig inferior mesenteric artery and ganglion. *J Pharmacol Exp Ther* **256:**82–87.

Merahi N and Laguzzi R (1995) Cardiovascular effects of 5HT2 and 5HT3 receptor stimulation in the nucleus tractus solitarius of spontaneously hypertensive rats. *Brain Res* **669:**130–134.

Mercado CP, Ziu E, and Kilic F (2011) Communication between 5-HT and small GTPases. *Curr Opin Pharmacol* **11:**23–28.

Meyer T and Brinck U (1999) Differential distribution of serotonin and tryptophan hydroxylase in the human gastrointestinal tract. *Digestion* **60:**63–68.

Miller M, Hasson R, Morgane PJ, and Resnick O (1980) Adrenalectomy: its effects on systemic tryptophan metabolism in normal and protein malnourished rats. *Brain Res Bull* **5:**451–459.

Miller RC, Cornish EJ, and Goldie RG (1984) Responses of sheep and kitten isolated coronary arteries to some vasoactive agents. *Pharmacol Res Commun* **16:**667–677.

Miranda FJ, Torregrosa G, Salom JB, Alabadí JA, Jover T, Barberá MD, and Alborch E (1995) Characterization of 5-hydroxytryptamine receptors in goat cerebral arteries. *Gen Pharmacol* **26:**1267–1272.

Molderings GJ, Werner K, Likungu J, and Göthert M (1990) Inhibition of noradrenaline release from the sympathetic nerves of the human saphenous vein via presynaptic 5-HT receptors similar to the 5-HT 1D subtype. *Naunyn Schmiedebergs Arch Pharmacol* **342:**371–377.

Monaghan PJ, Brown HA, Houghton LA, and Keevil BG (2009) Measurement of serotonin in platelet depleted plasma by liquid chromatography tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* **877:**2163–2167.

Monassier L, Laplante MA, Ayadi T, Doly S, and Maroteaux L (2010) Contribution

of gene-modified mice and rats to our understanding of the cardiovascular pharmacology of serotonin. *Pharmacol Ther* **128:**559–567.

Montes R and Johnson AK (1990) Efferent mechanisms mediating renal sodium and water excretion induced by centrally administered serotonin. *Am J Physiol* **259:** R1267–R1273.

Morán A, Restrepo B, de Urbina AV, García M, Martín ML, and Román LS (2010) Pharmacological profile of 5-hydroxytryptamine-induced inhibition on the pressor effect elicited by sympathetic stimulation in long-term diabetic pithed rats. *Eur J Pharmacol* **643:**70–77.

Morecroft I, Dempsie Y, Bader M, Walther DJ, Kotnik K, Loughlin L, Nilsen M, and MacLean MR (2007) Effect of tryptophan hydroxylase 1 deficiency on the development of hypoxia-induced pulmonary hypertension. *Hypertension* **49:**232–236.

Moreira TS, Takakura AC, Colombari E, and Guyenet PG (2007) Activation of 5-hydroxytryptamine type 3 receptor-expressing C-fiber vagal afferents inhibits retrotrapezoid nucleus chemoreceptors in rats. *J Neurophysiol* **98:**3627–3637.

Moreno L, Martínez-Cuesta MA, Piqué JM, Bosch J, and Esplugues JV (1996) Anatomical differences in responsiveness to vasoconstrictors in the mesenteric veins from normal and portal hypertensive rats. *Naunyn Schmiedebergs Arch Pharmacol* **354:**474–480.

Morrison SF (2004) Central pathways controlling brown adipose tissue thermogenesis. *News Physiol Sci* **19:**67–74.

Murphy DL, Lipper S, Slater S, and Shiling D (1979) Selectivity of clorgyline and pargyline as inhibitors of monoamine oxidases A and B in vivo in man. *Psychopharmacology* **62:**129–132.

Mylecharane EJ (1990) Mechanisms involved in serotonin-induced vasodilatation. *Blood Vessels* **27:**116–126.

Nagai S, Tsurumaki T, Abe H, and Higuchi H (2007) Functional serotonin and histamine receptor subtypes in porcine ciliary artery in comparison with middle cerebral artery. *Eur J Pharmacol* **570:**159–166.

Nagatsu I, Ichinose H, Sakai M, Titani K, Suzuki M, and Nagatsu T (1995) Immunocytochemical localization of GTP cyclohydrolase I in the brain, adrenal gland, and liver of mice. *J Neural Transm Gen Sect* **102:**175–188.

Nakatani Y, Sato-Suzuki I, Tsujino N, Nakasato A, Seki Y, Fumoto M, and Arita H (2008) Augmented brain 5-HT crosses the blood-brain barrier through the 5-HT transporter in rat. *Eur J Neurosci* **27:**2466–2472.

Nalivaiko E and Sgoifo A (2009) Central 5-HT receptors in cardiovascular control during stress. *Neurosci Biobehav Rev* **33:**95–106.

Nebigil CG, Etienne N, Messaddeq N, and Maroteaux L (2003a) Serotonin is a novel survival factor of cardiomyocytes: mitochondria as a target of 5-HT$_{2B}$ receptor signaling. *FASEB J* **17:**1373–1375.

Nebigil CG, Jaffré F, Messaddeq N, Hickel P, Monassier L, Launay JM, and Maroteaux L (2003b) Overexpression of the serotonin 5-HT2B receptor in heart leads to abnormal mitochondrial function and cardiac hypertrophy. *Circulation* **107:**3223–3229.

Nebigil CG and Maroteaux L (2001) A novel role for serotonin in heart. *Trends Cardiovasc Med* **11:**329–335.

Nelson M, Coghlan JP, Denton DA, Tresham JJ, Whitworth JA, and Scoggins BA (1987) Ritanserin and serotonergic mechanisms in blood pressure and fluid regulation in sheep. *Clin Exp Pharmacol Physiol* **14:**555–563.

Newberry NR, Watkins CJ, Volenec A, and Flanigan TP (1996) 5-HT$_{2B}$ receptor mRNA in guinea pig superior cervical ganglion. *Neuroreport* **7:**2909–2911.

Ni W, Geddes TJ, Priestley JR, Szasz T, Kuhn DM, and Watts SW (2008) The existence of a local 5-hydroxytryptaminergic system in peripheral arteries. *Br J Pharmacol* **154:**663–674.

Ni W, Thompson JM, Northcott CA, Lookingland K, and Watts SW (2004) The serotonin transporter is present and functional in peripheral arterial smooth muscle. *J Cardiovasc Pharmacol* **43:**770–781.

Nichols CD (2009) Serotonin 5-HT$_{2A}$ receptor function as a contributing factor to both neuropsychiatric and cardiovascular diseases. *Cardiovasc Psychiatry Neurol* **2009:**475108.

Nigmatullina RR, Kirillova VV, Jourjikiya RK, Mukhamedyarov MA, Kudrin VS, Klodt PM, and Palotás A (2009) Disrupted serotonergic and sympathoadrenal systems in patients with chronic heart failure may serve as new therapeutic targets and novel biomarkers to assess severity, progression and response to treatment. *Cardiology* **113:**277–286.

Nilsson T, Longmore J, Shaw D, Olesen IJ, and Edvinsson L (1999) Contractile 5-HT$_{1B}$ receptors in human cerebral arteries: pharmacological characterization and localization with immunocytochemistry. *Br J Pharmacol* **128:**1133–1140.

Nishimura M, Sato K, Shimada S, and Tohyama M (1999) Expression of norepinephrine and serotonin transporter mRNAs in the rat superior cervical ganglion. *Brain Res Mol Brain Res* **67:**82–86.

Nishimura Y (1996) Characterization of 5-hydroxytryptamine receptors mediating contractions in basilar arteries from stroke-prone spontaneously hypertensive rats. *Br J Pharmacol* **117:**1325–1333.

Nishimura Y and Suzuki A (1995) Enhanced contractile responses mediated by different 5-HT receptor subtypes in basilar arteries, superior mesenteric arteries and thoracic aortas from stroke-prone spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol Suppl* **22:**S99–S101.

Nolen WA, Haffmans PM, Bouvy PF, and Duivenvoorden HJ (1993) Monoamine oxidase inhibitors in resistant major depression. A double-blind comparison of brofaromine and tranylcypromine in patients resistant to tricyclic antidepressants. *J Affect Disord* **28:**189–197.

Nosjean A, Compoint C, Buisseret-Delmas C, Orer HS, Merahi N, Puizillout JJ, and Laguzzi R (1990) Serotonergic projections from the nodose ganglia to the nucleus tractus solitarius: an immunohistochemical and double labeling study in the rat. *Neurosci Lett* **114:**22–26.

Nosjean A, Franc B, and Laguzzi R (1995) Increased sympathetic nerve discharge without alteration in the sympathetic baroreflex response by serotonin$_3$ receptor stimulation in the nucleus tractus solitarius of the rat. *Neurosci Lett* **186:**41–44.

Nosjean A and Guyenet PG (1991) Role of ventrolateral medulla in sympatholytic effect of 8-OHDPAT in rats. *Am J Physiol* **260:**R600–R609.

Nyborg NC and Mikkelsen EO (1985) In vitro studies on responses to noradrenaline, serotonin, and potassium of intramyocardial and mesenteric resistance vessels from Wistar rats. *J Cardiovasc Pharmacol* **7:**417–423.

Obi T, Kabeyama A, and Nishio A (1994) Equine coronary artery responds to 5-hydroxytryptamine with relaxation in vitro. *J Vet Pharmacol Ther* **17:**218–225.

Ogura C, Kishimoto A, Mizukawa R, Hazama H, Honma H, and Kawahara K (1983) Age differences in effects on blood pressure, flicker fusion frequency, salivation and pharmacokinetics of single oral doses of dothiepin and amitriptyline. *Eur J Clin Pharmacol* **25:**811–814.

Ohtsuki S (2004) New aspects of the blood-brain barrier transporters; its physiological roles in the central nervous system. *Biol Pharm Bull* **27:**1489–1496.

Ootsuka Y and Blessing WW (2005) Activation of slowly conducting medullary raphe-spinal neurons, including serotonergic neurons, increases cutaneous sympathetic vasomotor discharge in rabbit. *Am J Physiol Regul Integr Comp Physiol* **288:**R909–R918.

Ootsuka Y and Blessing WW (2006) Activation of 5-HT$_{1A}$ receptors in rostral medullary raphe inhibits cutaneous vasoconstriction elicited by cold exposure in rabbits. *Brain Res* **1073–1074:**252–261.

Orer HS, Merahi N, Nosjean A, Fattaccini CM, and Laguzzi R (1991) Cardiovascular effects of the local injection of 5,7-dihydroxytryptamine into the nodose ganglia and nucleus tractus solitarius in awake freely moving rats. *Brain Res* **553:**123–128.

Page IH and McCubbin JW (1953a) The variable arterial pressure response to serotonin in laboratory animals and man. *Circ Res* **1:**354–362.

Page IH and McCubbin JW (1953b) Modification of vascular responses to serotonin by drugs. *Am J Physiol* **174:**436–444.

Pagniez F, Valentin JP, Vieu S, Colpaert FC, and John GW (1998) Pharmacological analysis of the haemodynamic effects of 5-HT1B/D receptor agonists in the normotensive rat. *Br J Pharmacol* **123:**205–214.

Päivärinta H, Park DH, Towle AC, and Joh TH (1989) Tryptophan hydroxylase activity and 5-hydroxytryptamine-immunoreactive cells in the superior cervical ganglion of hydrocortisone-treated neonatal rats. *Neurosci Res* **6:**276–281.

Park CS, Chu CS, Park YS, and Hong SK (1968) Effect of 5-hydroxytryptamine on renal function of the anesthetized dog. *Am J Physiol* **214:**383–388.

Parsons AA (1991) 5-HT receptors in human and animal cerebrovasculature. *Trends Pharmacol Sci* **12:**310–315.

Parsons AA, Raval P, Smith S, Tilford N, King FD, Kaumann AJ, and Hunter J (1998) Effects of the novel high-affinity 5-HT$_{(1B/1D)}$receptor ligand frovatriptan in human isolated basilar and coronary arteries. *J Cardiovasc Pharmacol* **32:**220–224.

Parsons AA, Stutchbury C, Raval P, and Kaumann AJ (1992) Sumatriptan contracts large coronary arteries of beagle dogs through 5-HT1-like receptors. *Naunyn Schmiedebergs Arch Pharmacol* **346:**592–596.

Parsons AA, Whalley ET, Feniuk W, Connor HE, and Humphrey PP (1989) 5-HT1-like receptors mediate 5-hydroxytryptamine-induced contraction of human isolated basilar artery. *Br J Pharmacol* **96:**434–440.

Paulmann N, Grohmann M, Voigt JP, Bert B, Vowinckel J, Bader M, Skelin M, Jevsek M, Fink H, Rupnik M, et al. (2009) Intracellular serotonin modulates insulin secretion from pancreatic β-cells by protein serotonylation. *PLoS Biol* **7:**e1000229.

Pavone LM, Spina A, Lo Muto R, Santoro D, Mastellone V, and Avallone L (2008) Heart valve cardiomyocytes of mouse embryos express the serotonin transporter SERT. *Biochem Biophys Res Commun* **377:**419–422.

Pavone LM, Spina A, Rea S, Santoro D, Mastellone V, Lombardi P, and Avallone L (2009) Serotonin transporter gene deficiency is associated with sudden death of newborn mice through activation of TGF-beta1 signalling. *J Mol Cell Cardiol* **47:**691–697.

PDSP Ki Database; http://pdsp.med.unc.edu/indexR.html.

Pedersen OL, Kragh-Sørensen P, Bjerre M, Overø KF, and Gram LF (1982) Citalopram, a selective serotonin reuptake inhibitor: clinical antidepressive and long-term effect—a phase II study. *Psychopharmacology* **77:**199–204.

Penttilä J, Syvälahti E, Hinkka S, Kuusela T, and Scheinin H (2001) The effects of amitriptyline, citalopram and reboxetine on autonomic nervous system. A randomised placebo-controlled study on healthy volunteers. *Psychopharmacology* **154:** 343–349.

Perahia DG, Quail D, Gandhi P, Walker DJ, and Peveler RC (2008) A randomized, controlled trial of duloxetine alone vs. duloxetine plus a telephone intervention in the treatment of depression. *J Affect Disord* **108:**33–41.

Persson B, Gradin K, Pettersson A, and Hedner T (1988) Antihypertensive effects of ketanserin and ritanserin in the spontaneously hypertensive rat. *J Cardiovasc Pharmacol* **11(S1):**S22–S24.

Phillips CA, Mylecharane EJ, and Shaw J (1985) Mechanisms involved in the vasodilator action of 5-hydroxytryptamine in the dog femoral arterial circulation in vivo. *Eur J Pharmacol* **113:**325–334.

Pickering AE, Spanswick D, and Logan SD (1994) 5-Hydroxytryptamine evokes depolarizations and membrane potential oscillations in rat sympathetic preganglionic neurones. *J Physiol* **480:**109–121.

Pierce PA, Xie GX, Levine JD, and Peroutka SJ (1996) 5-Hydroxytryptamine receptor subtype messenger RNAs in rat peripheral sensory and sympathetic ganglia: a polymerase chain reaction study. *Neuroscience* **70:**553–559.

Pozdzik M, Zajac D, Zasada I, Czarnocki Z, Matysiak Z, Mazzatenta A, and Pokorski M (2010) Absence of bioactivity of lipid derivatives of serotonin. *Eur J Med Res* **15:**128–134.

Radenkoviä M, Stojanoviä M, and Topaloviä M (2010) Contribution of thromboxane A2 in rat common carotid artery response to serotonin. *Sci Pharm* **78:**435–443.

Rajapakse S, Abeynaike L, and Wickramarathne T (2010) Venlafaxine-associated serotonin syndrome causing severe rhabdomyolysis and acute renal failure in a patient with idiopathic Parkinson disease. *J Clin Psychopharmacol* **30:**620–622.

Ramage AG (2001) Central cardiovascular regulation and 5-hydroxytryptamine receptors. *Brain Res Bull* **56:**425–439.

Ramage AG and Daly MB (1998) The central action of the 5-HT$_2$ receptor agonist

1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on cardiac inotropy and vascular resistance in the anaesthetized cat. *Br J Pharmacol* **125:**1172–1179.

Ramage AG and Fozard JR (1987) Evidence that the putative 5-HT1A receptor agonists, 8-OH-DPAT and ipsapirone, have a central hypotensive action that differs from that of clonidine in anaesthetised cats. *Eur J Pharmacol* **138:**179–191.

Ramage AG and Villalón CM (2008) 5-Hydroxytryptamine and cardiovascular regulation. *Trends Pharmacol Sci* **29:**472–481.

Rapport MM, Green AA, and Page IH (1948) Serum vasoconstrictor, serotonin; isolation and characterization. *J Biol Chem* **176:**1243–1251.

Razzaque Z, Pickard JD, Ma QP, Shaw D, Morrison K, Wang T, and Longmore J (2002) 5-HT1B-receptors and vascular reactivity in human isolated blood vessels: assessment of the potential craniovascular selectivity of sumatriptan. *Br J Clin Pharmacol* **53:**266–274.

Roon KI, Maassen Van Den Brink A, Ferrari MD, and Saxena PR (1999) Bovine isolated middle cerebral artery contractions to antimigraine drugs. *Naunyn Schmiedebergs Arch Pharmacol* **360:**591–596.

Rosón MI, Maquieira MK, and de la Riva IJ (1990) Contrasting effects of norepinephrine and 5-hydroxytryptamine on contractility of abdominal aorta of two kidney-two clip hypertensive rats. Effects of inhibitors of arachidonic acid metabolic enzymes. *Clin Exp Hypertens A* **12:**285–306.

Ross RJ, Zavadil AP 3rd, Calil HM, Linnoila M, Kitanaka I, Blombery P, Kopin IJ, and Potter WZ (1983) Effects of desmethylimipramine on plasma norepinephrine, pulse, and blood pressure. *Clin Pharmacol Ther* **33:**429–437.

Roth BL (2007) Drugs and valvular heart disease. *N Engl J Med* **356:**6–9.

Roux F and Couraud PO (2005) Rat brain endothelial cell lines for the study of blood-brain barrier permeability and transport functions. *Cell Mol Neurobiol* **25:**41–58.

Russell A, Banes A, Berlin H, Fink GD, and Watts SW (2002) 5-Hydroxytryptamine(2B) receptor function is enhanced in the N(omega)-nitro-L-arginine hypertensive rat. *J Pharmacol Exp Ther* **303:**179–187.

Saletu B, Grünberger J, and Linzmayer L (1986) On central effects of serotonin re-uptake inhibitors: quantitative EEG and psychometric studies with sertraline and zimelidine. *J Neural Transm* **67:**241–266.

Salter M, Hazelwood R, Pogson CI, Iyer R, and Madge DJ (1995) The effects of a novel and selective inhibitor of tryptophan 2,3-dioxygenase on tryptophan and serotonin metabolism in the rat. *Biochem Pharmacol* **49:**1435–1442.

Sari Y and Zhou FC (2003) Serotonin and its transporter on proliferation of fetal heart cells. *Int J Dev Neurosci* **21:**417–424.

Saveleva KV, Zhao S, Pogorelov VM, Rajan I, Yang Q, Cullinan E, and Lanthorn TH (2008) Genetic disruption of both tryptophan hydroxylase genes dramatically reduces serotonin and affects behavior in models sensitive to antidepressants. *PLoS ONE* **3:**e3301.

Saxena PR and Verdouw PD (1982) Redistribution by 5-hydroxytryptamine of carotid arterial blood at the expense of arteriovenous anastomotic blood flow. *J Physiol* **332:**501–520.

Saxena PR and Villalón CM (1991) 5-Hydroxytryptamine: a chameleon in the heart. *Trends Pharmacol Sci* **12:**223–227.

Saydoff JA, Rittenhouse PA, Carnes M, Armstrong J, Van De Kar LD, and Brownfield MS (1996) Neuroendocrine and cardiovascular effects of serotonin: selective role of brain angiotensin on vasopressin. *Am J Physiol* **270:**E513–E521.

Schmuck K, Ullmer C, Kalkman HO, Probst A, and Lubbert H (1996) Activation of meningeal 5-HT2B receptors: an early step in the generation of migraine headache? *Eur J Neurosci* **8:**959–967.

Schöning C, Flieger M, and Pertz HH (2001) Complex interaction of ergovaline with 5-HT2A, 5-HT1B/1D, and alpha1 receptors in isolated arteries of rat and guinea pig. *J Anim Sci* **79:**2202–2209.

Scrogin KE (2003) 5-HT1A receptor agonist 8-OH-DPAT acts in the hindbrain to reverse the sympatholytic response to severe hemorrhage. *Am J Physiol Regul Integr Comp Physiol* **284:**R782–R791.

Sharma AM, Caterson ID, Coutinho W, Finer N, Van Gaal L, Maggioni AP, Torp-Pedersen C, Bacher HP, Shepherd GM, James WP, et al. (2009) Blood pressure changes associated with sibutramine and weight management - an analysis from the 6-week lead-in period of the sibutramine cardiovascular outcomes trial (SCOUT). *Diabetes Obes Metab* **11:**239–250.

Sharma HS and Dey PK (1984) Role of 5-HT on increased permeability of blood-brain barrier under heat stress. *Indian J Physiol Pharmacol* **28:**259–267.

Shepheard SL, Jordan D, and Ramage AG (1994) Comparison of the effects of IVth ventricular administration of some tryptamine analogues with those of 8-OH-DPAT on autonomic outflow in the anaesthetized rat. *Br J Pharmacol* **111:**616–624.

Shepherd JT and Vanhoutte PM (1985) Local modulation of adrenergic neurotransmission in blood vessels. *J Cardiovasc Pharmacol* **7 (Suppl 3):**S167–S178.

Shoji T, Tamaki T, Fukui K, Iwao H, and Abe Y (1989) Renal hemodynamic responses to 5-hydroxytryptamine (5-HT): involvement of the 5-HT receptor subtypes in the canine kidney. *Eur J Pharmacol* **171:**219–228.

Skop BP, Finkelstein JA, Mareth TR, Magoon MR, and Brown TM (1994) The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* **12:**642–644.

Soares-da-Silva P, Vieira-Coelho MA, and Pestana M (1996) Antagonistic actions of renal dopamine and 5-hydroxytryptamine: endogenous 5-hydroxytryptamine, 5-HT1A receptors and antinatriuresis during high sodium intake. *Br J Pharmacol* **117:**1193–1198.

Sole MJ, Madapallimattam A, and Baines AD (1986) An active pathway for serotonin synthesis by renal proximal tubules. *Kidney Int* **29:**689–694.

Sole MJ, Shum A, and Van Loon GR (1979) Serotonin metabolism in the normal and failing hamster heart. *Circ Res* **45:**629–634.

Sprouse J, Reynolds L, Li X, Braselton J, and Schmidt A (2004) 8-OH-DPAT as a 5-HT7 agonist: phase shifts of the circadian biological clock through increases in cAMP production. *Neuropharmacology* **46:**52–62.

Stahl SM and Felker A (2008) Monoamine oxidase inhibitors: a modern guide to an unrequited class of antidepressants. *CNS Spectr* **13:**855–870.

Stevens H, Knollema S, De Jong G, Korf J, and Luiten PG (1998) Long-term food restriction, deprenyl, and nimodipine treatment on life expectancy and blood pressure of stroke-prone rats. *Neurobiol Aging* **19:**273–276.

Stier CT Jr and Itskovitz HD (1985) Formation of serotonin by rat kidneys in vivo. *Proc Soc Exp Biol. Med* **180:**550–557.

Stier CT Jr, Brewer TF, Dick LB, Wynn N, and Itskovitz HD (1986) Formation of biogenic amines by isolated kidneys of spontaneously hypertensive rats. *Life Sci* **38:**7–14.

Stone TW and Darlington LG (2002) Endogenous kynurenines as targets for drug discovery and development. *Nat Rev Drug Discov* **1:**609–620.

Stott DJ, Saniabadi AR, Hosie J, Lowe GD, and Ball SG (1988) The effects of the 5 HT2 antagonist ritanserin on blood pressure and serotonin-induced platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* **35:**123–129.

Subramanian S and Vollmer RR (2004) Fenfluramine-induced hypothermia is associated with cutaneous dilation in conscious rats. *Pharmacol Biochem Behav* **77:**351–359.

Sugimoto Y, Yamada J, Yoshikawa T, Nishikawa F, Noma T, and Horisaka K (1996) The involvement of serotonin in the catecholamine release from the adrenal medulla. *Adv Exp Med Biol* **398:**561–563.

Sumner MJ (1991) Characterization of the 5-HT receptor mediating endothelium-dependent relaxation in porcine vena cava. *Br J Pharmacol* **102:**938–942.

Sved AF, Van Itallie CM, and Fernstrom JD (1982) Studies on the antihypertensive action of L-tryptophan. *J Pharmacol Exp Ther* **221:**329–333.

Takeuchi Y and Sano Y (1983) Serotonin distribution in the circumventricular organs of the rat. An immunohistochemical study. *Anat Embryol* **167:**311–319.

Tan T, Watts SW, and Davis RP (2011) Drug delivery: enabling technology for drug discovery and development. iPRECIO micro infusion pump: programmable, refillable, and implantable. *Front Pharmacol* **2:**44.

Teng GQ, Nauli SM, Brayden JE, and Pearce WJ (2002) Maturation alters the contribution of potassium channels to resting and 5HT-induced tone in small cerebral arteries of the sheep. *Brain Res Dev Brain Res* **133:**81–91.

Terrón JA (1996) The relaxant 5-HT receptor in the dog coronary artery smooth muscle: pharmacological resemblance to the cloned 5-ht7 receptor subtype. *Br J Pharmacol* **118:**1421–1428.

Terrón JA (1997) Role of 5-ht7 receptors in the long-lasting hypotensive response induced by 5-hydroxytryptamine in the rat. *Br J Pharmacol* **121:**563–571.

Terrón JA and Falcón-Neri A (1999) Pharmacological evidence for the 5-HT7 receptor mediating smooth muscle relaxation in canine cerebral arteries. *Br J Pharmacol* **127:**609–616.

Terrón JA, Sánchez-Maldonado C, and Martínez-García E (2007) Pharmacological evidence that 5-HT(1B/1D) receptors mediate hypotension in anesthetized rats. *Eur J Pharmacol* **576:**132–135.

Thase ME (1998) Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry* **59:**502–508.

Thayssen P, Bjerre M, Kragh-Sørensen P, Møller M, Petersen OL, Kristensen CB, and Gram LF (1981) Cardiovascular effect of imipramine and nortriptyline in elderly patients. *Psychopharmacology* **74:**360–364.

Thompson LP and Webb RC (1987) Vascular responsiveness to serotonin metabolites in mineralocorticoid hypertension. *Hypertension* **9:**277–281.

Thor KB and Helke CJ (1987) Serotonin- and substance P-containing projections to the nucleus tractus solitarii of the rat. *J Comp Neurol* **265:**275–293.

Tiniakov R, Osei-Owusu P, and Scrogin KE (2007) The 5-hydroxytryptamine1A receptor agonist, (+)-8-hydroxy-2-(di-n-propylamino)-tetralin, increases cardiac output and renal perfusion in rats subjected to hypovolemic shock. *J Pharmacol Exp Ther* **320:**811–818.

Toda N and Okamura T (1990) Comparison of the response to 5-carboxamidot-ryptamine and serotonin in isolated human, monkey and dog coronary arteries. *J Pharmacol Exp Ther* **253:**676–682.

Topsakal R, Kalay N, Gunturk EE, Dogan A, Inanc MT, Kaya MG, Ergin A, and Yarlioglues M (2009) The relation between serotonin levels and insufficient blood pressure decrease during night-time in hypertensive patients. *Blood Press* **18:**367–371.

Tsai ML and Lin MT (1986) Hypertension and tachycardia produced by inhibition of reuptake of 5-hydroxytryptamine by fluoxetine in the rat. *Neuropharmacology* **25:**799–802.

Turkka J, Suominen K, Tolonen U, Sotaniemi K, and Myllylä VV (1997) Selegiline diminishes cardiovascular autonomic responses in Parkinson's disease. *Neurology* **48:**662–667.

Turner EH, Loftis JM, and Blackwell AD (2006) Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. *Pharmacol Ther* **109:**325–338.

Tytgat J, Maertens C, and Daenens P (1997) Effect of fluoxetine on a neuronal, voltage-dependent potassium channel (Kv1.1). *Br J Pharmacol* **122:**1417–1424.

Ueno M (2009) Mechanisms of the penetration of blood-borne substances into the brain. *Curr Neuropharmacol* **7:**142–149.

Umegaki K, Nakamura K, Ikeda M, Inoue Y, and Tomita T (1989) Changes in platelet function due to hypertension: comparison of experimental hypertension with spontaneous hypertension in rats. *J Hypertens* **7:**13–19.

Valenta B and Singer EA (1990) Hypotensive effects of 8-hydroxy-2-(di-n-propylamino)tetralin and 5-methylurapidil following stereotaxic microinjection into the ventral medulla of the rat. *Br J Pharmacol* **99:**713–716.

Valentin JP, Bonnafous R, and John GW (1996) Influence of the endothelium and nitric oxide on the contractile responses evoked by 5-HT1D receptor agonists in the rabbit isolated saphenous vein. *Br J Pharmacol* **119:**35–42.

van den Broek RW, Bhalla P, VanDenBrink AM, de Vries R, Sharma HS, and Saxena PR (2002) Characterization of sumatriptan-induced contractions in human isolated blood vessels using selective 5-HT(1B) and 5-HT(1D) receptor antagonists and in situ hybridization. *Cephalalgia* **22:**83–93.

van den Buuse M and Wegener N (2005) Involvement of serotonin1A receptors in

cardiovascular responses to stress: a radio-telemetry study in four rat strains. *Eur J Pharmacol* **507:**187–198.

van Heuven-Nolsen D, Tysse Klasen TH, Luo QF, and Saxena PR (1990) 5-HT1-like receptors mediate contractions of the rabbit saphenous vein. *Eur J Pharmacol* **191:**375–382.

van Schie DL, de Jeu RM, Steyn DW, Odendaal HJ, and van Geijn HP (2002) The optimal dosage of ketanserin for patients with severe hypertension in pregnancy. *Eur J Obstet Gynecol Reprod Biol* **102:**161–166.

van Zwieten PA, Blauw GJ, and van Brummelen P (1992) Serotonergic receptors and drugs in hypertension. *Pharmacol Toxicol* **70:**s17–s22.

Vanhoutte P, Amery A, Birkenhäger W, Breckenridge A, Bühler F, Distler A, Dormandy J, Doyle A, Frohlich E, and Hansson L (1988) Serotoninergic mechanisms in hypertension. Focus on the effects of ketanserin. *Hypertension* **11:**111–133.

Vanhoutte PM (1991) Serotonin, hypertension and vascular disease. *Neth J Med* **38:**35–42.

Verheggen R, Freudenthaler S, Meyer-Dulheuer F, and Kaumann AJ (1996) Participation of 5-HT1-like and 5-HT2A receptors in the contraction of human temporal artery by 5-hydroxytryptamine and related drugs. *Br J Pharmacol* **117:**283–292.

Verheggen R, Hundeshagen AG, Brown AM, Schindler M, and Kaumann AJ (1998) 5-HT$_{1B}$ receptor-mediated contractions in human temporal artery: evidence from selective antagonists and 5-HT receptor mRNA expression. *Br J Pharmacol* **124:** 1345–1354.

Verheggen R, Meier A, Werner I, Wienekamp A, Kruschat T, Brattelid T, Levy FO, and Kaumann A (2004) Functional 5-HT receptors in human occipital artery. *Naunyn Schmiedebergs Arch Pharmacol* **369:**391–401.

Verheggen R, Werner I, Lücker A, Brüss M, Göthert M, and Kaumann AJ (2006) 5-Hydroxytryptamine-induced contraction of human temporal arteries coexpressing 5-HT2A receptors and wild-type or variant (Phe124Cys) 5-HT1B receptors: increased contribution of 5-HT1B receptors to the total contractile amplitude in arteries from Phe124Cys heterozygous individuals. *Pharmacogenet Genomics* **16:** 601–607.

Verhofstad AA and Jonsson G (1983) Immunohistochemical and neurochemical evidence for the presence of serotonin in the adrenal medulla of the rat. *Neuroscience* **10:**1443–1453.

Vidrio H, Medina M, Fernandez G, Lorenzana-Jimenez M, and Campos AE (2000) Enhancement of hydralazine hypotension by low doses of isoniazid. Possible role of semicarbazide-sensitive amine oxidase inhibition. *Gen Pharmacol* **35:**195–204.

Villalón CM and Centurión D (2007) Cardiovascular responses produced by 5-hydroxytryptamine: a pharmacological update on the receptors/mechanisms involved and therapeutic implications. *Naunyn Schmiedebergs Arch Pharmacol* **376:**45–63.

Villalón CM, Heiligers JP, Centurión D, De Vries P, and Saxena PR (1997) Characterization of putative 5-HT$_7$ receptors mediating tachycardia in the cat. *Br J Pharmacol* **121:**1187–1195.

Villalón CM, Terrón JA, and Hong E (1993) Role of 5-HT1-like receptors in the increase in external carotid blood flow induced by 5-hydroxytryptamine in the dog. *Eur J Pharmacol* **240:**9–20.

Waeber C and Moskowitz MA (1995) Autoradiographic visualisation of [^{3}H]5-carboxamidotryptamine binding sites in the guinea pig and rat brain. *Eur J Pharmacol* **283:**31–46.

Wakayama K, Ohtsuki S, Takanaga H, Hosoya K, and Terasaki T (2002) Localization of norepinephrine and serotonin transporter in mouse brain capillary endothelial cells. *Neurosci Res* **44:**173–180.

Wallis DI and Dun NJ (1987) Fast and slow depolarizing responses of guinea-pig coeliac ganglion cells to 5-hydroxytryptamine. *J Auton Nerv Syst* **21:**185–194.

Walther DJ and Bader M (2003) A unique central tryptophan hydroxylase isoform. *Biochem Pharmacol* **66:**1673–1680.

Walther DJ, Peter JU, Bashammakh S, Hörtnagl H, Voits M, Fink H, and Bader M (2003) Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* **299:**76.

Wan S and Browning KN (2008) Glucose increases synaptic transmission from vagal afferent central nerve terminals via modulation of 5-HT$_3$ receptors. *Am J Physiol Gastrointest Liver Physiol* **295:**G1050–G1057.

Watkins CJ and Newberry NR (1996) Multiple 5-HT receptors in the guinea-pig superior cervical ganglion. *Br J Pharmacol* **117:**21–28.

Watts SW (1997) The 5-HT$_{2B}$ receptor antagonist LY272015 inhibits 5-HT-induced contraction in the aorta of mineralocorticoid-salt hypertensive rats. *J Serotonin Res* **4:**197–206.

Watts SW (2002) Serotonin-induced contraction in mesenteric resistance arteries: signaling and changes in deoxycorticosterone acetate-salt hypertension. *Hypertension* **39:**825–829.

Watts SW (2005) 5-HT in systemic hypertension: foe, friend or fantasy? *Clin Sci* **108:**399–412.

Watts SW (2009) The love of a lifetime: 5-HT in the cardiovascular system. *Am J Physiol Regul Integr Comp Physiol* **296:**R252–R256.

Watts SW, Baez M, and Webb RC (1996) The 5-hydroxytryptamine2B receptor and 5-HT receptor signal transduction in mesenteric arteries from deoxycorticosterone acetate-salt hypertensive rats. *J Pharmacol Exp Ther* **277:**1103–1113.

Watts SW and Fink GD (1999) 5-HT2B-receptor antagonist LY-272015 is antihypertensive in DOCA-salt-hypertensive rats. *Am J Physiol* **276:**H944–H952.

Watts SW, Gilbert L, and Webb RC (1995) 5-Hydroxytryptamine$_{2B}$ receptor mediates contraction in the mesenteric artery of mineralocorticoid hypertensive rats. *Hypertension* **26:**1056–1059.

Watts SW and Thompson JM (2004) Characterization of the contractile 5-hydroxytryptamine receptor in the renal artery of the normotensive rat. *J Pharmacol Exp Ther* **309:**165–172.

Webb RC, Schreur KD, and Papadopoulos SM (1992) Oscillatory contractions in vertebral arteries from hypertensive subjects. *Clin Physiol* **12:**69–77.

Weiner CP, Thompson LP, Liu KZ, and Herrig JE (1992) Pregnancy reduces serotonin-induced contraction of guinea pig uterine and carotid arteries. *Am J Physiol* **263:**H1764–H1769.

Wenting GJ, Man in 't Veld AJ, Woittiez AJ, Boomsma F, and Schalekamp MA (1982) Treatment of hypertension with ketanserin, a new selective 5-HT$_2$ receptor antagonist. *BMJ* **284:**537–539.

Westergaard E (1975) Enhanced vesicular transport of exogenous peroxidase across cerebral vessels, induced by serotonin. *Acta Neuropath* **32:**27–42.

Westergaard E (1978) The effect of serotonin on the blood-brain barrier to proteins. *J Neural Transm Suppl* **14:**9–15.

Wilens TE, Biederman J, March JS, Wolkow R, Fine CS, Millstein RB, Faraone SV, Geller D, and Spencer TJ (1999) Absence of cardiovascular adverse effects of sertraline in children and adolescents. *J Am Acad Child Adolesc Psychiatry* **38:** 573–577.

Wood M, Chaubey M, Atkinson P, and Thomas DR (2000) Antagonist activity of meta-chlorophenylpiperazine and partial agonist activity of 8-OH-DPAT at the 5-HT(7) receptor. *Eur J Pharmacol* **396:**1–8.

Woodman OL and Dusting GJ (1994) Involvement of nitric oxide in coronary vascular responses to 5-hydroxytryptamine in the anaesthetized greyhound. *Clin Exp Pharmacol Physiol* **21:**377–381.

Ye P, Mariniello B, Mantero F, Shibata H, and Rainey WE (2007) G-protein-coupled receptors in aldosterone-producing adenomas: a potential cause of hyperaldosteronism. *J Endocrinol* **195:**39–48.

Yildiz O, Ciçek S, Ay I, Demirkiliç U, and Tuncer M (1996) Hypertension increases the contractions to sumatriptan in the human internal mammary artery. *Ann Thorac Surg* **62:**1392–1396.

Yildiz O, Smith JR, and Purdy RE (1998) Serotonin and vasoconstrictor synergism. *Life Sci* **62:**1723–1732.

Yildiz O and Tuncer M (1994) Comparison of the effect of endothelium on the responses to sumatriptan in rabbit isolated iliac, mesenteric and carotid arteries. *Arch Int Pharmacodyn Ther* **328:**200–212.

Yokota S, Ishikura Y, and Ono H (1987) Cardiovascular effects of paroxetine, a newly developed antidepressant, in anesthetized dogs in comparison with those of imipramine, amitriptyline and clomipramine. *Jpn J Pharmacol* **45:**335–342.

Zellers TM, Shimokawa H, Yunginger J, and Vanhoutte PM (1991) Heterogeneity of endothelium-dependent and endothelium-independent responses to aggregating platelets in porcine pulmonary arteries. *Circ Res* **68:**1437–1445.

Zerpa H, Berhane Y, Elliott J, and Bailey SR (2007) Cooling augments vasoconstriction mediated by 5-HT1 and alpha2-adrenoceptors in the isolated equine digital vein: involvement of Rho kinase. *Eur J Pharmacol* **569:**212–221.

Zwaveling J, Prins EA, Maas MA, Pfaffendorf M, and Van Zwieten PA (1996) The influence of hyperthyroidism on pharmacologically induced contractions of isolated resistance arteries. *Eur J Pharmacol* **300:**91–97.