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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.

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

[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.

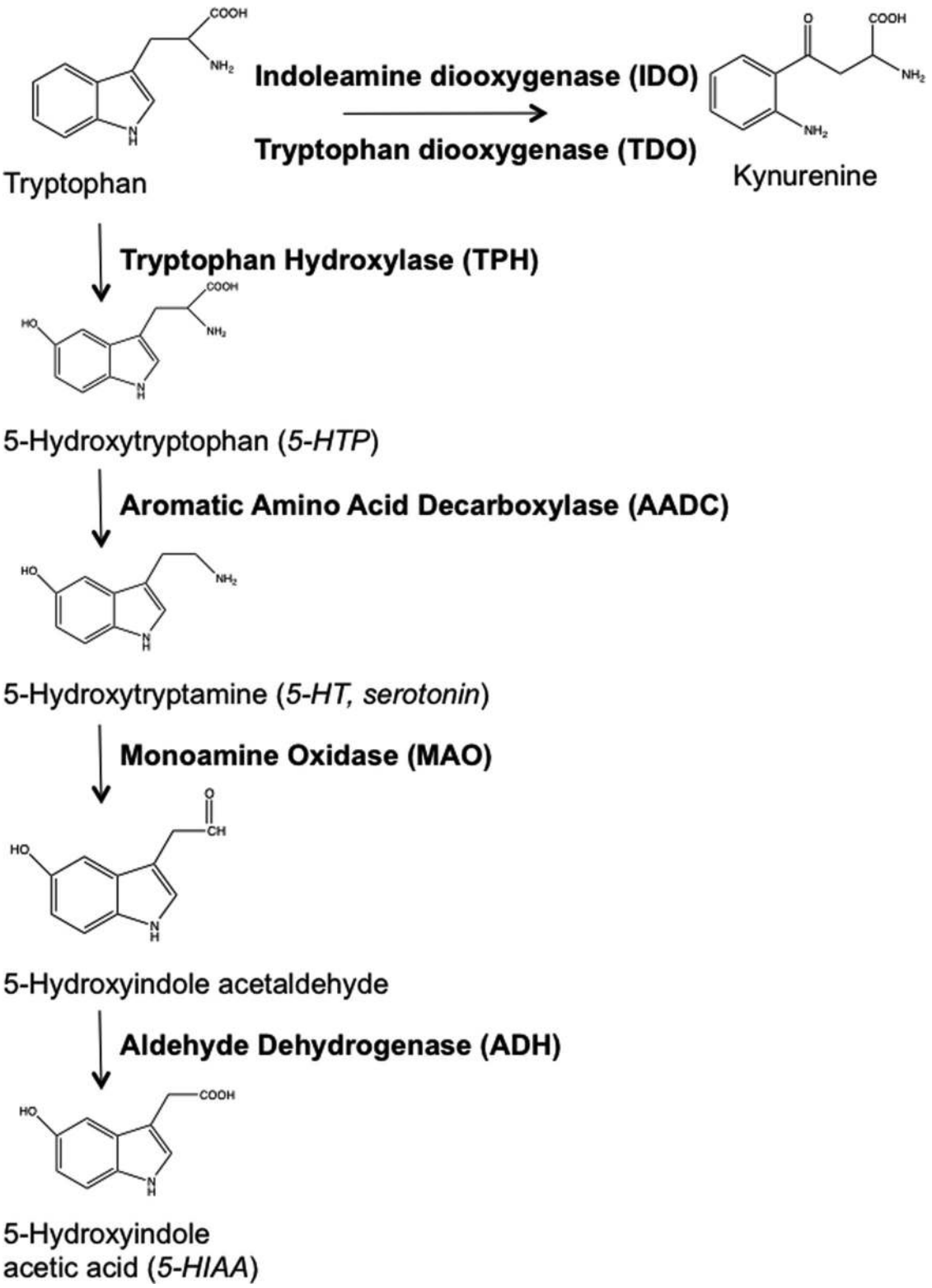

FIG. 1. Chemical schematic of the synthesis and metabolism of 5-HT.

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/FamilyMenuForward?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/FamilyMenuForward?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 depends on the 5-HT receptor expressed by a blood vessel, 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}^{α} (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, (2*S*)-(+)-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-1*H*-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-1*H*-benzimidazole-1-carboxamide; BRL15572, 3-[4-(4-chlorophenyl)piperazin-1-yl]-1,1-diphenyl-2-propanol; BRL54443, 5-hydroxy-3-(1-methylpiperidin-4-yl)-1*H*-indole; BW723C86, α-methyl-5-(2-thienylmethoxy)-1*H*-indole-3-ethanamine; CP-93129, 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl-5*H*-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)-1*H*-indole; GR113808, 1-methyl-1*H*-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-dioxodo-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-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-1*H*-pyrido[3,4-*b*]indole; LY310762, 1-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one; LY334370, 4-fluoro-*N*-(1-methyl-4-piperidinyl)-1*H*-indol-5-yl]-benzamide; LY344864, *N*-[(3*R*)-3-(dimethylamino)-2,3,4,9-tetrahydro-1*H*-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-1*H*-2-benzopyran-6-carboxamide; R-96544, (2*R*,4*R*)-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]-1*H*-indole-1-carboxyamide dihydrochloride; SB258719, 3-methyl-*N*-[(1*R*)-1-methyl-3-(4-methyl-1-piperidinyl)propyl]-*N*-methylbenzenesulfonamide; SB269970, (2*R*)-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]-1*H*-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, [(7b*R*, 10a*R*)-1,2,3,4,8,9,10, 10*a*-octahydro-7b*H*-cyclopenta-[*b*][1,4]diazepino[6,7,1-*hi*]indole]; WAY 181,187, 2-(1-{6-chloroimidazo[2,1-b][1,3]thiazole-5-sulfonyl}-1*H*-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 $5\text{-}HT_{2A}$ 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 $5\text{-}HT_{2B}$ and $5\text{-}HT_7$ 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 $5\text{-}HT_7$ 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 $5\text{-}HT_3$ receptor, a receptor unusual to the vasculature. Because of the inherent difficulty in performing studies in

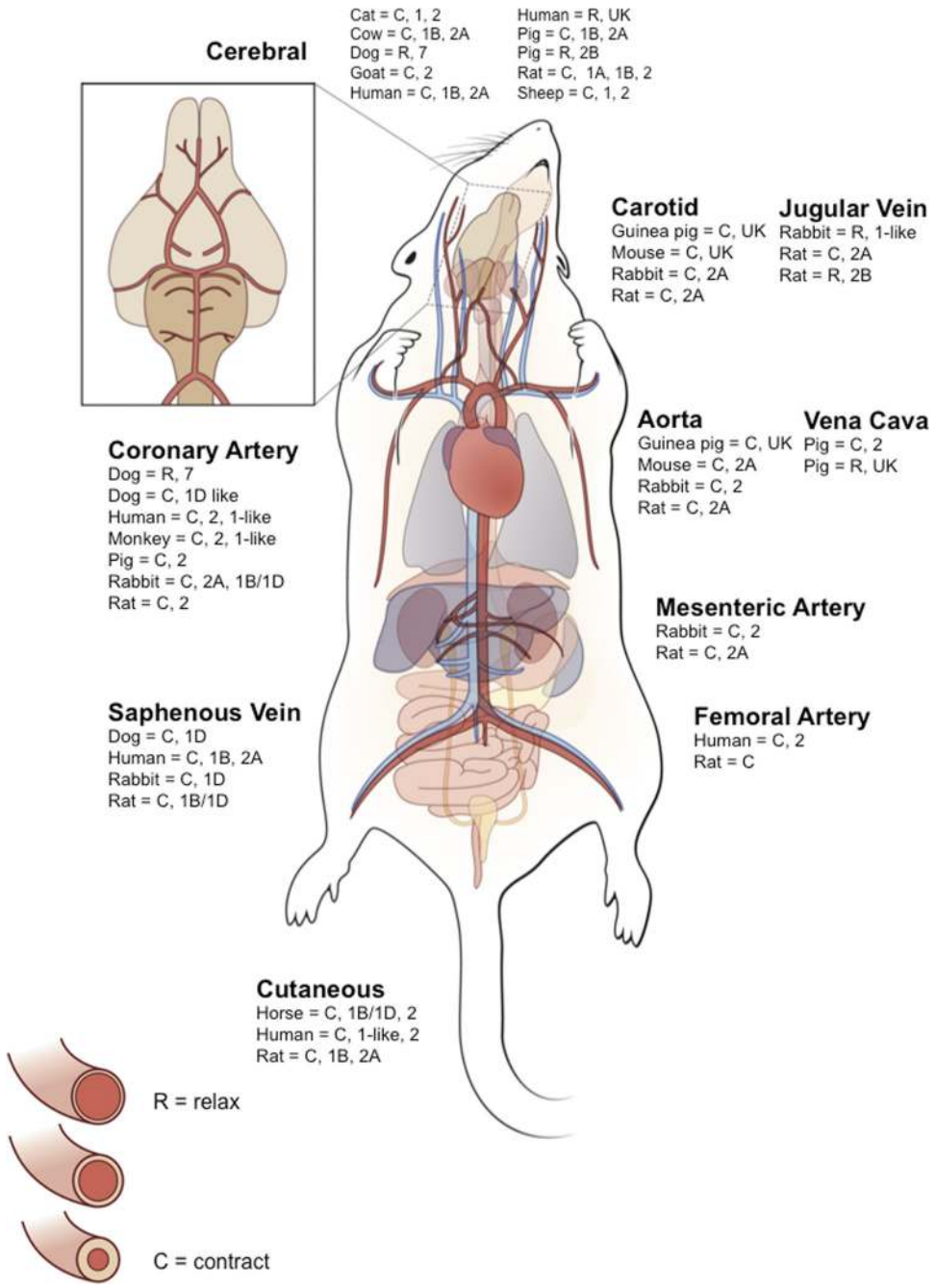

FIG. 2. Response of the vasculature to 5-HT, as depicted by using the rat vasculature as a model. Both constriction (C) and relaxation (R) may be listed for the same species if both responses were observed. Species name is listed, and the subtype of the receptor mediating the response is listed second (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 ($1–10\ \mu g \cdot kg^{-1} \cdot min^{-1}$) 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 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.,

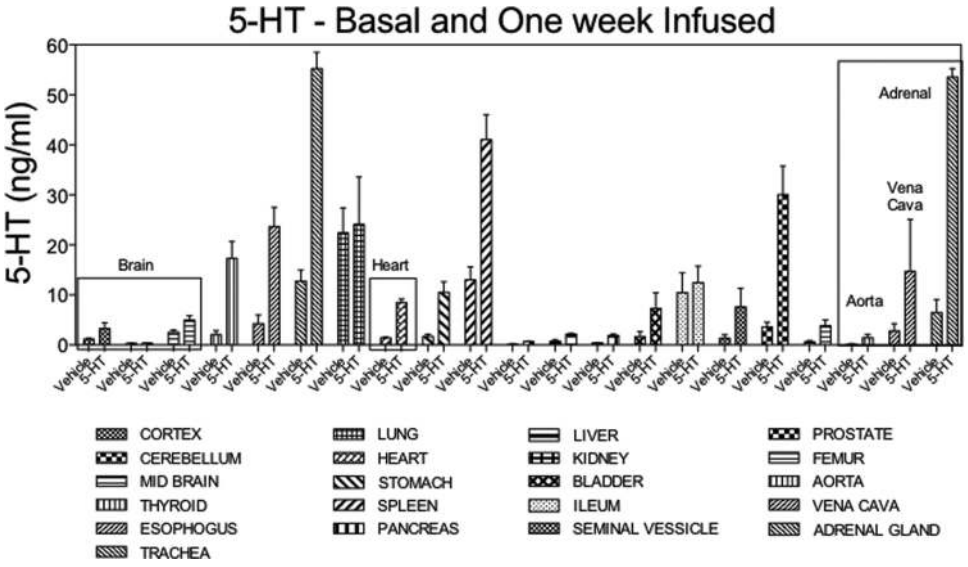

FIG. 3. Distribution of 5-HT in organs when infused with vehicle or 5-HT at a dose of 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the rat for one week. Vehicle animals receive saline. Bars represent means ± S.E.M. for $n = 6$. Boxes highlight organs that are of cardiovascular interest. [Adapted from Linder 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

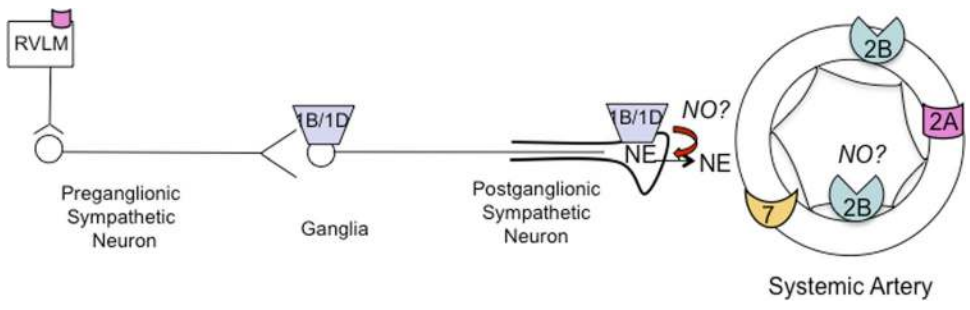

FIG. 4. Schematic of the potential sites at which 5-HT could interact to lower blood pressure within the context of the sympathetic nervous system. Small geometric shapes represent individual classes of 5-HT receptors; semicircular red arrow indicates inhibition.

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.

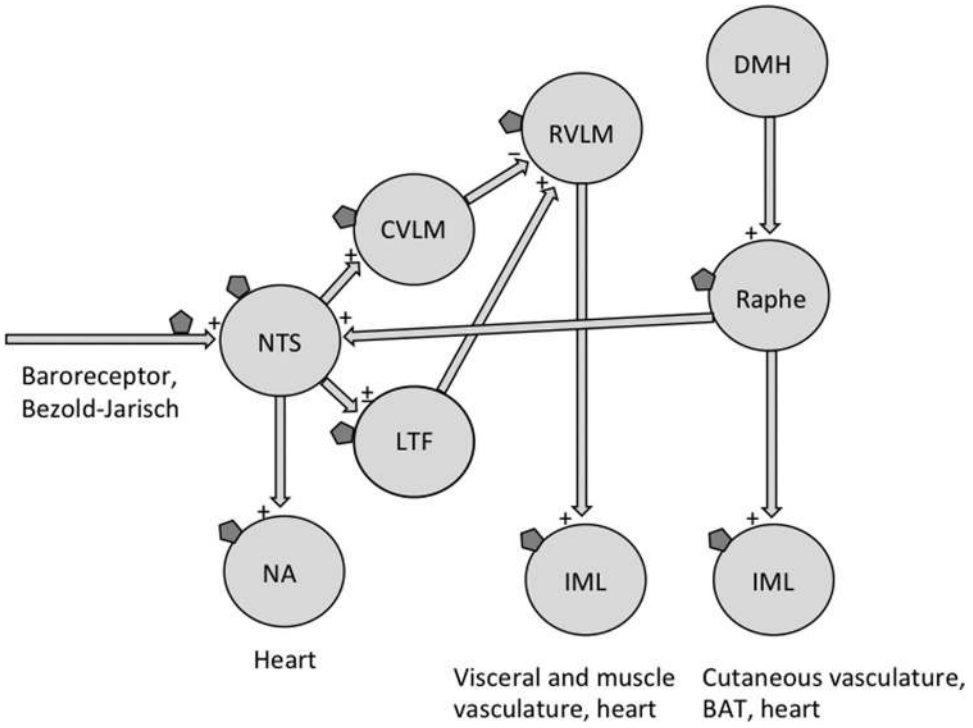

FIG. 5. Central autonomic circuits and potential central sites of action of systemically administered serotonin. The excitatory (+), inhibitory (−), or mixed (±) connections shown between the various autonomic nuclei are based on data described by Barman and Gebber (2000), Guyenet (2006), and Morrison (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 μg/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 μg	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, vagosympathectomized, ketanserin	IV	1–30 μg/kg	Decrease		Minutes	Centurión et al., 2004
Rat, pithed	IV	5–20 μg/kg	Increase		Minutes	Cavero et al., 1981
Rat, syrosingopine and mianserin	IV	20 μg/kg	Decrease		Minutes	Cavero et al., 1981
Rat, anesthetized	IR, IMes	1–3 μg/min	Increase	Increase	Minutes	Janssen et al., 1989
Rat, anesthetized	ICV	20 μg	Increase	Decrease	5 min	Montes and Johnson, 1990
Rat, anesthetized	ICV	20 μg	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 μg/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 μg/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 μg/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 μg/kg	Decrease	No change	Minutes	Dabiré et al., 1990
Dog	VA	0–3 μg/kg	Decrease	Decrease	Minutes	Dabiré et al., 1990
Dog	VLPA	0.2 μg/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–*Contiuned*

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	≤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 · kg^{-1} · 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 · kg^{-1} · h^{-1}	No change		24 h	Echizen and Freed, 1982

5-HTP, 5-hydroxytryptophan; DOB, 2,5-dimethoxy-4-bromoamphetamine hydrochloride; DOI, (±)-2,5-dimethoxy-4-iodoamphetamine; DP-5-CT, dipropyl-5-carboxamidotryptamine; 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., 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).

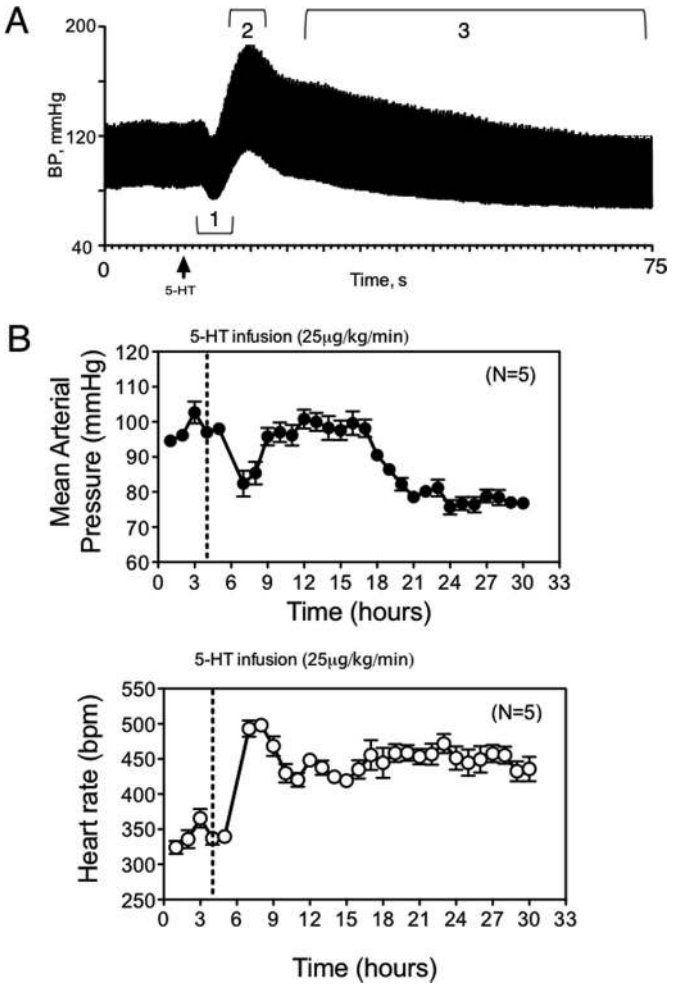

FIG. 6. A, classic triphasic (1, 2, 3) effect of 5-HT (75 μg/kg bolus) on blood pressure in the anesthetized rat. Time base below traces is 1 s/division. Total time base is 75 s. B, effect of 5-HT (25 $\mu g \cdot kg^{-1} \cdot min^{-1}$, subcutaneous pump) on blood pressure (top) and heart rate (bottom) 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.

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 $\mu g \cdot kg^{-1} \cdot min^{-1}$)] 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

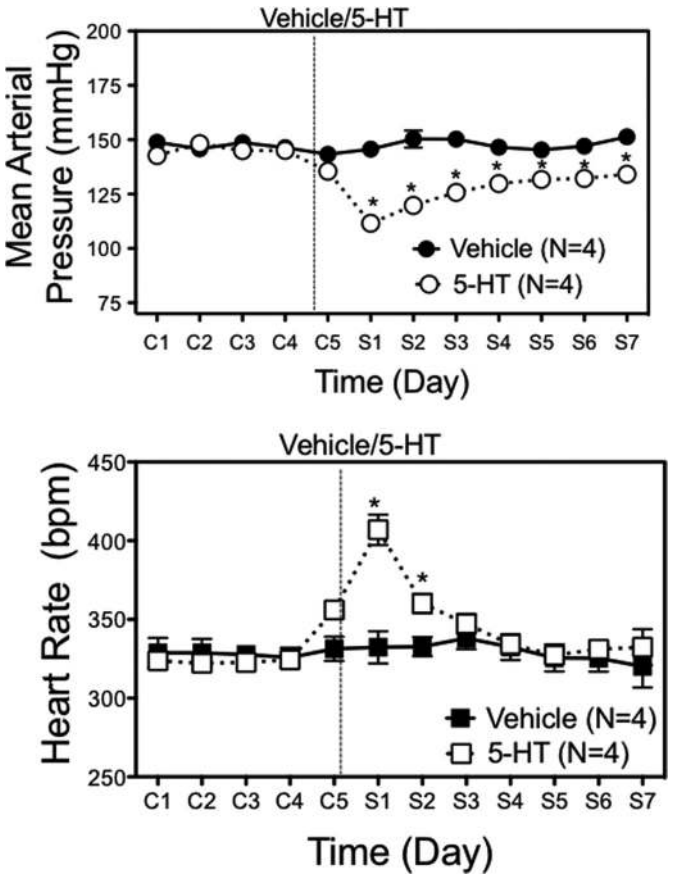

FIG. 7. Top, ability of 5-HT (25 $\mu g \cdot kg^{-1} \cdot min^{-1}$, subcutaneous pump) to lower blood pressure of a male SHR. Bottom, concomitant heart rate measures. Dashed vertical line indicates implantation of the pump. Points are means ± S.E.M. for the number of animals in parentheses. *, $p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

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 mg · kg^{-1} · 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 $\geq$20 mm Hg decrease of systolic blood pressure or $\geq$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

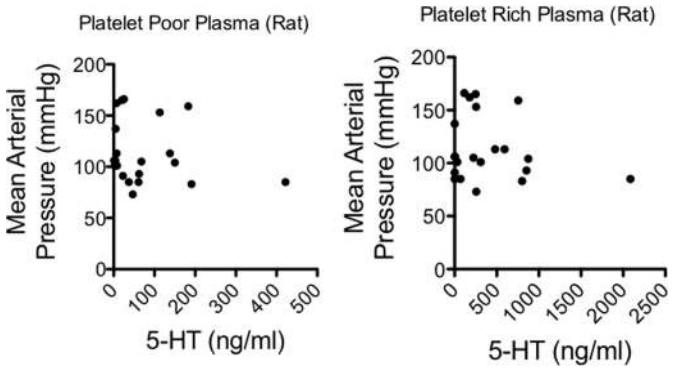

FIG. 8. Correlation between platelet poor plasma (*x*-axis, left) and rich plasma (right) with mean arterial blood pressure (telemetric) taken from conscious rats at the end of a 1-week infusion of 5-HT.

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.

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

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