Original Articles

Review of the Role of the Central Serotonergic Neuronal System in Blood Pressure Regulation

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SUMMARY Alterations in the dynamics of brain serotonin biosynthesis can lead to changes in cardiovascular function. It appears that the activation of cerebral serotonin receptors produces a pressor effect in normotensive rats but produces a depressor effect in normotensive cats or dogs. On the other hand, reductions in the levels of serotonin can prevent the onset of hypertension in some experimental hypertensive models and lower the blood pressure of organisms with established hypertension. The ability of brain serotonin to modulate arterial blood pressure may be mediated by the influences of the serotonergic neuronal systems on efferent sympathetic activity. Finally, the reduction in sympathetic outflow produced by increasing brain serotonin levels in dogs protects the heart against ventricular fibrillation and may, therefore, constitute a reasonable adjunct in the management of high-risk, cardiac-arrest patients. (Hypertension 2: 243-255, 1980)

KEY WORDS • serotonin • blood pressure • sympathetic outflow

It seems somewhat paradoxical that so little is known about the cardiovascular function of a substance first referred to by physiologists as vasotonin or thrombotinon (i.e., serotonin). It was not until the chemical structure of serotonin was actually identified as 5-hydroxytryptamine (5-HT) that progress was made in the understanding of the peripheral effects of 5-HT on the cardiovascular system. Unfortunately, much less progress has been made in identifying the central (brain) effects of 5-HT on blood pressure and heart rate. A precedent for studying the central role of 5-HT on heart function was first set early studies on the cardiovascular pharmacology of intracerebrally injected 5-HT and its precursors; however, it was perhaps the pioneering work of Dahlstrom and Fuxe, demonstrating the existence of discrete 5-HT-containing neurons in the brain, and the apparent "coincidence" of these medullary indolamine tracts with previously identified neural pathways controlling cardiovascular regulation that provided the greatest impetus to the study of this neurotransmitter system in regulating blood pressure. Moreover, since the ramifications of the 5-HT neuronal system are still being "mapped" under intense investigation, it is not surprising that an understanding of the contribution of the brain 5-HT system to cardiovascular control is evolving, likewise, at a rather slow pace.

In the few years that have passed since Chalmers last reviewed the literature on central nervous system 5-HT involvement in cardiovascular regulation, numerous papers have appeared in this area of research, with many of them reporting data obtained by taking advantage of unique new pharmacological and neurophysiological methods. We feel that the progress made is substantial enough to warrant still another review. Hopefully, this review will add some understanding to a literature which, upon casual reading, is quite confusing and paradoxical. The emphasis of this paper will necessarily be on the central 5-HT influence upon blood pressure regulation; however, since many experiments involve the systemic injections of 5-HT precursors, the peripheral effects of these substances cannot be ignored. One only has to look to a classic pharmacology text to learn that the peripheral cardiovascular effects of 5-HT are "notoriously variable," and that "responses to 5-HT differ not only between species but also between animals of the same species and even in successive tests in the individual." This complexity and variability, no doubt, extends into the central 5-HT neuronal system. The interested reader is referred to one of several monographs that describe the peripheral cardiovascular effects of 5-HT in great detail.

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Effects of Serotonin on Cardiovascular Function

Cerebral Biosynthesis

Before proceeding to the discussion of specific results, a few introductory comments on the biosynthesis of 5-HT might be helpful. Serotonin does not readily cross the blood-brain barrier; therefore, the brain depends on the de novo synthesis of this neurotransmitter within specific neurons. The biosynthetic pathway for 5-HT is depicted in figure 1.

The essential amino acid L-tryptophan is converted to 5-hydroxytryptophan (5-HTP) via a reaction catalyzed by tryptophan hydroxylase. Tryptophan hydroxylase is the initial and, under all but very extreme cases, rate-limiting enzyme in the synthesis of serotonin. The 5-hydroxytryptophan is rapidly converted to 5-HT by the ubiquitous L-aromatic amino acid decarboxylase. Systemic injections of either tryptophan or 5-HTP produce large increases in cerebral 5-HT, and this is a strategy often used to manipulate brain serotonin levels in cardiovascular research (see below). Brain 5-HT levels can conveniently be lowered by inhibiting tryptophan hydroxylase by various means. For example, parachlorophenylalanine (PCPA) is an irreversible inhibitor of brain tryptophan hydroxylase. The structural analogs of 5-HT, namely, 5,6- and 5,7-dihydroxytryptamine (DHT) are relatively specific, cytotoxic agents within the 5-HT system when injected directly into the cerebral ventricles. Frequently, PCPA and especially 5,6-DHT have been used in the study of 5-HT-cardiovascular relationships (see below). Detailed discussion of 5-HT neurotoxins can be found in a recently published monograph.

Serotonin Precursor Loading

Tryptophan

Almost without exception, tryptophan is notably without effects on blood pressure (BP). Theoretically, tryptophan loading is the best method for elevating brain 5-HT, since it is converted to 5-HT only in those cells containing tryptophan hydroxylase. Tryptophan hydroxylase is a specific marker for the 5-HT neuronal system; however, the i.v. administration of from 25-100 mg/kg of tryptophan in the normotensive rat produces no conspicuous change in BP. More recently, Sved et al. treated spontaneously hypertensive rats with 225 mg/kg of tryptophan and observed a 27 mm Hg drop in blood pressure 2 hours after treatment. These same investigators demonstrated earlier that injections of 25-50 mg/kg of tryptophan produced maximal increases in brain 5-HT so that the changes in BP seen after a dose as large as 225 mg/kg are probably produced by some property of tryptophan apart from its ability to increase brain 5-HT. If decerebrate cats are first treated with tranylcypromine (5 mg/kg), a monoamine oxidase inhibitor (MAOI), 100 mg/kg of tryptophan (i.v.) produces a 40% and 80% reduction in BP at 30 minutes and 2 hours respectively. The effects of tryptophan on BP are summarized in table 1.

The inability of tryptophan itself to alter BP while producing large increases in cerebral 5-HT does not necessarily argue against a role for 5-HT in BP regulation and can be explained by two closely related observations: 1) Tryptophan administration in rats leads to a marked inhibition of the firing of at least the ascending and probably the descending midbrain raphe neuronal tracts. This treatment, in effect, "turns off" the presynaptic 5-HT system. In fact, behavioral

\[ \text{tryptophan} \rightarrow \text{L-tryptophan} \rightarrow \text{5-Hydroxytryptophan} \rightarrow \text{5-Hydroxytryptamine} \]

Figure 1. The role of the central serotonergic neuronal system in blood pressure regulation.
evidence for postsynaptic 5-HT receptor supersensitivity after feeding mice a high tryptophan diet was recently presented.⁵⁰ Thus, tryptophan loading can increase synaptic 5-HT in the area of the raphe nuclei but apparently produces a paradoxical decrease in synaptic 5-HT in the forebrain; 2) Tryptophan loading does not ostensibly produce an increase in functional (synaptic) 5-HT since the transmitter is rapidly metabolized intracellularly by monoamine oxidase (MAO). Therefore, pretreatment of animals with a MAO inhibitor allows the newly formed 5-HT to “spill over” into the synapse, producing marked neurological and cardiovascular effects.⁵¹ While treatment of animals with tryptophan + MAOI seems ideally suited from a practical standpoint, this paradigm has several shortcomings. First, inhibition of MAO also leads to the accumulation of catecholamines (CA) in addition to 5-HT since they, too, are catabolized by MAO. Second, MAO inhibitors can have effects on BP by themselves but, more important, they can potentiate the effects of other drugs and amines on BP.³⁸ Third, at least the drastic behavioral/neurological syndrome observed after tryptophan + MAOI, and possibly the BP effect, is mediated almost entirely at the level of the spinal cord.³⁹

5-Hydroxytryptophan

The administration of 5-HTP usually has interesting effects on BP. With the exception of one study, 5-HTP has produced dose- and time-dependent depressor effects in most species examined thus far. For example, after either intraperitoneal (i.p.) administration of 5-HTP in the conscious rat⁴⁴ or subcutaneous (s.c.) administration of 5-HTP (200 mg/kg or 100 mg/kg respectively) in the anesthetized rat,⁴⁵ BP falls 20–30 mm Hg within 20–40 minutes after injection and returns to normal within 1–2 hours.

Similarly, both intracerebroventricular (i.c.v.; 0.5–1.0 mg) and i.v. injections (3.2–32 mg/kg) of 5-HTP in the intact⁴⁶ and decerebrate cat⁴⁷ produce a lowering of BP. Concomitant with the decrease in BP seen in cats after 5-HTP, decreases in heart rate (HR) and sympathetic nerve (splanchnic and renal) activity are also observed.⁴⁸ If cats are pretreated i.c.v. with a decarboxylase inhibitor (Ro4-4602), the depressor effects of 5-HTP are prevented.⁴⁹

Experiments with dogs have been somewhat variable. Whether administered i.v. or i.c.v., 5-HTP usually has a depressor effect. For example, McCubbin et al.,⁵⁰ observed that i.c.v. injection of from 0.25 to 5 mg of 5-HTP into anesthetized or unanesthetized dogs resulted in a drop in BP ranging from 32 to 40 mm Hg. The BP effect persisted for 1–2 hours. The usual pressor response to bilateral carotid occlusion (BCO) was also depressed by these same doses of 5-HTP, and sympathetic activity (SA) was reduced. More recently, Rabinowitz and Lown⁵¹ observed that 25 mg/kg of 5-HTP (i.v.) reduced BP in anesthetized dogs pretreated with both peripheral decarboxylase and MAOI. Maximal reductions of up to 30 mm Hg were seen from 0.5–2 hours after treatment.⁵²

Antonacci and Robson⁵³,⁵⁴ observed that neither tryptophan nor 5-HTP had effects on BP in non-MAO-inhibited dogs. However, an i.v. dose of 5-HTP as low as 5–10 mg/kg injected into MAO inhibited, anesthetized dogs reduced BP by approximately 70 mm Hg. This effect was gradual in onset and of long duration (peak effect at 90 minutes). These investigators also observed that the BCO response was severely depressed in 5-HTP treated dogs.⁵⁵,⁵⁶ If dogs were pretreated with a selective extracerebral decarboxylase inhibitor (25 mg/kg MK-486), 5-HTP still produced a depressor response, but instead of increasing HR, bradycardia was seen; however, inhibition of both cerebral and extracerebral decarboxylase (25 mg/kg i.v., Ro4-4602) prevented the 5-HTP effect on both BP and BCO.⁵⁷,⁵⁸ In contrast to these studies, Dunkley et al.,⁵⁹ observed that 30 mg/kg 5-HTP i.v. in conscious dogs produced a pressor effect of approximately 20–50 mm Hg 30 minutes after injection. If the dogs were pretreated with a decarboxylase inhibitor (Ro4-4602, 10 mg/kg, i.v.) or haloperidol, the pressor response to 5-HTP was blocked.⁶⁰ The data for experiments with 5-HTP are summarized in table 2.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Injection route</th>
<th>Species</th>
<th>Time (min)</th>
<th>BP</th>
<th>HR</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan</td>
<td>100</td>
<td>s.c.</td>
<td>rat (c)</td>
<td>90</td>
<td>NC</td>
<td>20</td>
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<tr>
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<td>100</td>
<td>s.c.</td>
<td>rat (a)</td>
<td>90</td>
<td>NC</td>
<td>21</td>
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<td>225</td>
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<td>hypertens.</td>
<td>120</td>
<td>↓</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>100</td>
<td>i.v.</td>
<td>cat (a, d)</td>
<td>90</td>
<td>NC</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Tryptophan + MAOI</td>
<td>100</td>
<td>i.v.</td>
<td>cat (a, d)</td>
<td>120</td>
<td>↓</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>25</td>
<td>i.v.</td>
<td>dog (a)</td>
<td>0–6 hr</td>
<td>NC</td>
<td>NC</td>
<td>35</td>
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<tr>
<td>Tryptophan</td>
<td>dog (a)</td>
<td></td>
<td></td>
<td></td>
<td>NC</td>
<td>NC</td>
<td>36</td>
</tr>
</tbody>
</table>

s.c. = subcutaneous; i.v. = intravenous; c = conscious; a = anesthetized; d = decerebrate; NC = no change; MAOI = monoamine oxidase inhibitor.
## Table 2. Effects of 5-Hydroxytryptophan (5-HTP) on Blood Pressure (BP), Heart Rate (HR), Sympathetic Activity (SA), and Bilateral Carotid Occlusion Response (BCO)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Injection route</th>
<th>Species</th>
<th>Time (min)</th>
<th>BP</th>
<th>HR</th>
<th>SA</th>
<th>BCO</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HTP</td>
<td>100</td>
<td>s.c.</td>
<td>rat (c)</td>
<td>90</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTP</td>
<td>200</td>
<td>i.p.</td>
<td>rat (c)</td>
<td>20</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTP</td>
<td>5-10</td>
<td>i.v.</td>
<td>cat (d)</td>
<td>5</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTP + TCP</td>
<td>5-10</td>
<td>i.v.</td>
<td>cat (d)</td>
<td>5-120</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>5-HTP + Ro4-4602</td>
<td>1-32 mg</td>
<td>i.c.v.</td>
<td>cat (a, p)</td>
<td>10-30</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>5-HTP + MK486</td>
<td>0.75-3 mg</td>
<td>i.c.v.</td>
<td>cat (a, p)</td>
<td>30-120</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTP</td>
<td>0.1-5 mg</td>
<td>i.c.v.</td>
<td>dog (c, a)</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>5-HTP</td>
<td>30</td>
<td>i.v.</td>
<td>dog (c)</td>
<td>30</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTP + SU11739</td>
<td>10</td>
<td>i.v.</td>
<td>dog (a)</td>
<td>90</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
<td>35, 36</td>
</tr>
<tr>
<td>5-HTP + MK486</td>
<td>25</td>
<td>i.v.</td>
<td>dog (a)</td>
<td>10-30</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>35, 36</td>
</tr>
<tr>
<td>5-HTP + Ro4-4602</td>
<td>25</td>
<td>i.v.</td>
<td>dog (a)</td>
<td>10-30</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>35, 36</td>
</tr>
<tr>
<td>5-HTP</td>
<td>25</td>
<td>i.v.</td>
<td>dog (a)</td>
<td>30</td>
<td>↓</td>
<td></td>
<td>NC</td>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

s.c. = subcutaneous; i.p. = intraperitoneal; i.v. = intravenous; c = conscious; a = anesthetized; d = decerebrate; s = paralyzed; NC = no change; ↓ = decrease; ↑ = increase.

It seems clear from the foregoing results with 5-HTP that theconversion of 5-HTP to 5-HT is necessary for BP changes to occur. Pretreatment of animals with a variety of decarboxylase inhibitors prevents both the usual depressor effect and the occasional pressor effect seen after 5-HTP (see table 2). In view of the relative extracerebral versus cerebral specificity of these decarboxylase enzyme inhibitors, it could be concluded that the cerebral conversion of 5-HTP to 5-HT is the essential event mediating BP alterations.

Interpretation of the data with 5-HTP is made somewhat difficult for several reasons, despite the general agreement among the experiments performed thus far. First, when given systemically, 5-HTP is converted to 5-HT peripherally and centrally and, therefore, both peripheral and central 5-HT effects on the cardiovascular system must be considered. Although it has been demonstrated that selective inhibition of the peripheral decarboxylase did not alter the hypotensive effects of 5-HTP in dogs, the administration of an extracerebral decarboxylase inhibitor shunts 5-HTP metabolism into the cerebral compartment, and this extra, central loading could overshadow any changes that might be mediated peripherally. Second, most of the experiments using dogs have also included pretreatment with MAOI. Perhaps a species difference in MAO activity exists such that rats and cats are affected by 5-HTP (i.e., 5-HT alone whereas dogs are not (see table 3); however, experiments that include MAO inhibitors as a treatment are difficult to interpret for the reasons discussed.
Serotonin Agonists and Antagonists

The effects of systematically administered 5-HT on BP and HR will not be discussed presently for reasons listed earlier (see above). Therefore, the following discussion will concentrate on those experiments in which 5-HT was injected directly into the cerebroventricular system or into specific brain areas. The influence of central 5-HT on BP was a subject of great interest as early as 1960. McCubbin et al. determined that the i.c.v. injection of from 1-10 mg of 5-HT in anesthetized dogs produced an average decline of 28 mm Hg in BP and reduced the BCO response by almost 70%. The HR was also reduced. Dhawan et al. obtained essentially the same results.

Several experiments have investigated the effects of central 5-HT injections on BP in cats. Baum and Shropshire observed a depressor response to 0.01-1 mg of 5-HT injected i.c.v. in anesthetized cats. Heart rate was slightly decreased (15%) by the highest dose of 5-HT, and renal nerve activity reduced by 48%.

Far more extensive experimentation has been carried out using rats for studies of 5-HT-BP interactions. For example, Lambert et al. demonstrated that i.c.v. injections of 50 ng to 25 μg of 5-HT produced a dose-related increase in BP in anesthetized rats. The duration of the BP effect was 30 minutes or longer, and within 90 minutes, BP returned to normal. Changes in BP were accompanied by biphasic (decrease, then a slight increase) changes in HR. The pressor response to 5-HT was blocked by transection of the spinal cord at C-1 or by pretreatment (i.c.v.) with the 5-HT antagonist bromo-lysergic acid diethylamide (BOL). Krstic and Djurkovic reported essentially the same results with i.c.v. 5-HT in rats. After a latent period of 10-30 seconds post-injection, 1.5-6.0 μg of 5-HT induced a dose- and time-dependent pressor effect in anesthetized rats that could be prevented by i.c.v. injections of methysergide. More recently, Lambert et al. repeated many of their earlier studies that extended their findings considerably. In particular, the 5-HT-induced BP effect was found to be greatest in magnitude if the amine was injected into the third cerebral ventricle, smaller if injection was into the lateral cerebral ventricles, and smallest if 5-HT was injected into the fourth cerebral ventricle. The pressor response in this study was coincident with a sympathetically mediated reduction in HR and a decrease in ventilation.

Before, the 5-HT (5 μg) pressor effect was abolished by BOL or by C-1 or C-3 transections, but not by transection at C-5 or C-7. Finally, hexamethonium was without an effect, whereas 6-hydroxydopamine and atropine partially reduced the 5-HT pressor response. Nahmod et al. also recently reported that injections of 50 ng of 5-HT into the third cerebral ventricle of rats increased BP. Similarly, i.c.v. injections of 2-200 ng of angiotensin II produced a pressor effect. From this result, the authors have drawn the conclusion that the pressor effect of angiotensin II was mediated, in part, by the peptide-induced release of serotonin in the area of the hypothalamus.

The hallucinogenic agent 2,5-dimethoxy-4-methylamphetamine (DOM), which has 5-HT agonist properties, produces a rise in BP and HR in anesthetized rats that is similar to the effects of 5-HT. Doses (i.c.v.) ranging from 0.001 to 10 μg produce increases in BP ranging from 10-20 mm Hg in magnitude. The effect of DOM on HR was variable. Transections at C-1 or i.c.v. injections of BOL (10 μg) reduced the pressor effect of 4 μg of DOM, whereas hexamethonium altered neither the BP nor the HR response to DOM.

It is difficult to determine if the 5-HT pressor effect in rats is site-specific, since the amine would be widely distributed throughout the brain after i.c.v. injection. Recently, however, Smits and Struyker-Boudier injected 5-HT directly into various areas of the diencephalon of anesthetized rats and observed that as little as 20 ng of 5-HT injected into the anterior hypothalamus/preoptic area (AH/PO) produced a small but statistically significant increase in blood pressure (8 mm Hg). Doses higher than 10 μg produced larger increases in BP (+ 33 mm Hg) within 5 minutes, and BP remained elevated for 20-40 minutes. Changes in HR were negligible. Finally, i.c.v., but not intra-AH/PO pretreatment of rats with methysergide (2 × 5 μg), significantly reduced the pressor effect of intrahypothalamic 5-HT.

The effects of 5-HT on BP are summarized in table 3.

Despite the general agreement among the experiments just discussed (table 3), the effects of 5-HT on BP, at least in rats, are in the opposite direction of those produced by 5-HTP. This discrepancy between the effects of 5-HT and 5-HTP is made even more perplexing by the observation that the effects of 5-HTP are apparently mediated by the cerebral conversion of the amino acid to 5-HT (see above). Thus, the effect of 5-HT on BP appears to be dependent on the manner in which the transmitter is introduced into the brain: direct application into the ventricles, or even at specific sites, produces a pressor effect, whereas precursor (5-HTP) loading results in a depressor effect. Although far fewer experiments have been done using dogs and cats as subjects, the effects of 5-HT and 5-HTP on BP are generally consistent in these species (see tables 2 and 3).

Based on the results with 5-HT, it appears that the stimulation of cerebral 5-HT receptors, at least in rats, initiates a chain of events that culminates with an increase in BP. In cats and dogs, the response to 5-HT...
is a depressor response (see table 3). One might expect, therefore, that antagonists of 5-HT would have the opposite effect of 5-HT on BP; however, this is not always true. For example, Dunkley et al. reported that doses of methysergide (0.2-0.6 mg/kg, i.v.) sufficient to block the cardiovascular effects (pressor) of 5-HT in conscious dogs, had no effect on BP by itself. On the other hand, Antonaccio et al. reported that i.v. injections of 1 and 3 mg/kg of methysergide in anesthetized dogs reduced BP, HR, left ventricular pressure, and peripheral resistance. Furthermore, the BCO response was markedly inhibited by methysergide. Hypotension and bradycardia were also seen after i.c.v. injections of 0.2 mg/kg of methysergide. On the other hand, Saxena did not observe hypotension in dogs after 20-640 μg/kg of methysergide i.v., although the depressant effect of methysergide on the BCP response was confirmed. The effects of methysergide in cats are similar to those seen in dogs (above). Doses of 1 and 3 mg/kg (i.v.) decrease BP, HR, and SA. Recall that injections of both 5-HTP and 5-HT produce depressor effects, bradycardia, and decreases in SA in anesthetized dogs and cats (see tables 2 and 3).

Experiments with 5-HT antagonists in rats have probably been equally as confusing as comparable experiments in cats and dogs. The i.v. administration of 25 μg of methysergide in anesthetized rats leads to a long-lasting (90-120 min) fall in BP. This dose of methysergide attenuates the pressor response to AH/PO injections of 5-HT. Methysergide also produces a dose-related reduction in BP and HR in conscious, spontaneously hypertensive rats (SHR), while cyproheptadine, another 5-HT antagonist, is without effects in SHR. The nonhallucinogenic analog of LSD, bromo-lysergic acid diethylamide (BOL), has central 5-HT antagonist properties, but the i.c.v. administration of this drug produces only small and variable changes in the BP and HR of anesthetized rats at doses (20 μg) that markedly attenuate the pressor effects of 5-HT. The effects of 5-HT antagonists on cardiovascular function are presented in table 4.

Antonaccio and his colleagues have studied the mechanisms underlying the effects of methysergide on BP and HR quite extensively in dogs and cats, and perhaps their findings with methysergide apply, in general, to other putative 5-HT antagonists. Specifically, these investigators have been careful to point out that the hemodynamic effects of methysergide are mediated by a centrally initiated reduction in sympathetic outflow. Furthermore, at effective doses, methysergide has no α-receptor, ganglionic, or adrenergic neuronal blocking properties, nor does it have a pronounced, direct vasodilator effect. Since methysergide and cyproheptadine are equally effective in blocking 5-HT pressor responses in SHR, but only methysergide lowers BP, it appears that the cardiovascular effects of methysergide in cats and dogs, as well as the antihypertensive effect of methysergide in SHR, are not entirely dependent on the blockade of central serotonin receptors. In normotensive rats, the situation is not quite as confusing. The 5-HT antagonists methysergide and BOL have slight effects or no effect at all on resting BP and HR but each sharply attenuates the pressor effects of i.c.v. 5-HT.

The apparent lack of effect of 5-HT antagonists on resting BP in rats can be more easily understood when considered in light of the role of the 5-HT system in cardiovascular regulation (see below); however, one must also realize that the putative 5-HT antagonists may be nontoxic as such or lack specificity of action within the central nervous system.

**Drugs that Deplete Brain Serotonin**

**Parachlorophenylalanine (PCPA)**

A great deal of interest has centered around the use of relatively specific depletors of cerebral 5-HT in cardiovascular research. One drug frequently used is PCPA, an irreversible inhibitor of tryptophan hydroxylase. Ito and Schanberg first demonstrated that PCPA injected either i.p. (100-200 mg/kg) or i.c.v. (1-10 mg/kg) produced an increase in BP of conscious rats without changing HR. After i.c.v. injection

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**Table 4. Effects of 5-Hydroxytryptophan (5-HT) Antagonists on Blood Pressure (BP), Heart Rate (HR), Sympathetic Activity (SA), and Bilateral Carotid Occlusion Response (BCO)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
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<th>BP</th>
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<th>BCO</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOL</td>
<td>20 μg</td>
<td>i.c.v. (L)</td>
<td>rat (a)</td>
<td></td>
<td>NC</td>
<td></td>
<td></td>
<td></td>
<td>40,42,46</td>
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<tr>
<td>Methysergide</td>
<td>25 μg</td>
<td>i.c.v. (L)</td>
<td>rat (a)</td>
<td>90-120</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Methysergide</td>
<td>10-100</td>
<td>p.o.</td>
<td>SHR (c)</td>
<td>1-4 hr</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>100</td>
<td>p.o.</td>
<td>SHR (c)</td>
<td>1-4 hr</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Methysergide</td>
<td>1-3</td>
<td>i.v.</td>
<td>cat (a)</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Methysergide</td>
<td>1-3</td>
<td>i.v.</td>
<td>dog (a)</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Methysergide</td>
<td>0.1</td>
<td>i.c.v. (L)</td>
<td>dog (a)</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Methysergide</td>
<td>0.02-0.64</td>
<td>i.v.</td>
<td>dog (a)</td>
<td></td>
<td>NC</td>
<td></td>
<td></td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>Methysergide</td>
<td>3.0</td>
<td>i.v.</td>
<td>cat (a)</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
</tbody>
</table>

BOL = bromo-lysergic acid diethylamide; i.e.v. = intracerebroventricular; L = lateral ventrical; p.o. = by mouth; i.v. = intravenous; a = anesthetized; SHR = spontaneously hypertensive rat; c = conscious; NC = no change; ↓ = decrease.
of 10 mg/kg of PCPA, BP increased as much as 40 mm Hg and remained elevated for 4-5 days. The pressor responses to i.p. PCPA are much smaller than those seen after i.c.v. injections. The PCPA-induced hypertension could be reversed by injections of 5-HTP (150 mg/kg/day, s.c.) for 4 days and was blocked by transections of the brain stem at the level of the posterior fovea.\(^5\) If rats were treated with PCPA for 3 weeks, BP increased to a maximum at Day 2 of treatment, but gradually declined to control BP levels despite continued PCPA injections and extensive 5-HT depletion.\(^4\) Using a similar, chronic-treatment regimen, Ogawa\(^5\) recently reported that the BP of rats can remain elevated if PCPA injections (100 mg/kg) are given at 3-day intervals for 12 to 14 days.

De Jong et al.\(^6\) found that treatment of conscious normotensive or spontaneously hypertensive rats with single (200 mg/kg, i.p.) or multiple (40 to 250 mg/kg/day for 3 days) doses of PCPA significantly increased BP by 20 hours after treatment. The BP remained elevated (approximately 20 mm Hg) for at least 4 days, at a time when 5-HT was still significantly depleted from brain.\(^4\) Similarly, Yamori et al.\(^6\) injected (i.p.) SHR with 100 mg/kg/day of PCPA for 3 days and observed a slight (+11 mm Hg) increase in BP. The levels of 5-HT in brain at this time were undetectable.\(^4\)

Contrary results with PCPA were obtained by Jarrott et al.\(^6\) These investigators found that daily, oral administration of 300 mg/kg of PCPA to SHR produced a mean decrease in BP of approximately 30 mm Hg. To confuse matters further, Browning et al.\(^8\) reported that an i.p. injection of 500 mg/kg of PCPA did not deplete 5-HT in rabbits. Cats are also apparently resistant to cardiovascular alterations by PCPA. Helke et al.\(^9\) administered 300 mg/kg of PCPA i.p. for 3 days in cats and observed no changes in HR or BP. Similarly, Coote et al.\(^1\) reported that an i.p. injection of 500 mg/kg of PCPA did not significantly alter the BP of anesthetized cats. The effects of PCPA on BP are presented in table 5.

**Neurotoxic Indolethylamines 5,6- and 5,7-DHT**

The neurotoxic indolethylamines 5,6-DHT and 5,7-DHT are frequently used to destroy serotoninergic neurons in studies concerned with the role of the 5-HT neuronal system in BP regulation. When 450 µg/kg of 5,6-DHT was injected i.c.v. in conscious rats, BP did not change from control.\(^52\) Furthermore, 5,6-DHT alters neither the development nor the maintenance of DOCA-salt hypertension.\(^5\) Helke et al.\(^9\) also observed that 100-200 µg/kg of 5,7-DHT (i.c.v.) was without effects on HR or BP in anesthetized, normotensive cats, and Coote et al.\(^4\) found that intraspinal injections of a 0.2% solution of 5,6-DHT in cats did not change BP. Contrary to these results, Finch\(^9\) reported that 50 µg of 5,6-DHT i.c.v. produced a rapid reduction in the BP of conscious DOCA-salt hypertensive rats. The hypotension (-40 mm Hg) was observed by 30-60 minutes after injection and persisted for up to 4 hours. The depressor response was accompanied by a marked bradycardia.

### Table 5. Effects of Parachlorophenylamine (PCPA) on Blood Pressure (BP) and Heart Rate (HR)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Injection route</th>
<th>Species</th>
<th>Time</th>
<th>BP</th>
<th>HR</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPA</td>
<td>100-200</td>
<td>i.p.</td>
<td>rat (c)</td>
<td>1-4 days</td>
<td>↑</td>
<td>NC</td>
<td>52</td>
</tr>
<tr>
<td>PCPA</td>
<td>1-10</td>
<td>i.c.v.</td>
<td>rat (c)</td>
<td>1-2 days</td>
<td>↑</td>
<td>NC</td>
<td>52</td>
</tr>
<tr>
<td>PCPA</td>
<td>100 (×3)</td>
<td>i.p.</td>
<td>SHR (c)</td>
<td>↑</td>
<td>NC</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>PCPA</td>
<td>250 (×3)</td>
<td>i.p.</td>
<td>rat (c)</td>
<td>20 hr</td>
<td>↑</td>
<td>↑</td>
<td>54</td>
</tr>
<tr>
<td>PCPA</td>
<td>200</td>
<td>i.p.</td>
<td>SHR (c)</td>
<td>20 hr</td>
<td>↑</td>
<td>↑</td>
<td>54</td>
</tr>
<tr>
<td>PCPA</td>
<td>300 (×3)</td>
<td>p.o.</td>
<td>SHR (c)</td>
<td>11 days</td>
<td>↓</td>
<td>NC</td>
<td>56</td>
</tr>
<tr>
<td>PCPA</td>
<td>100 (×3)</td>
<td>i.p.</td>
<td>rat (c)</td>
<td>2 days</td>
<td>↑</td>
<td>NC</td>
<td>53</td>
</tr>
<tr>
<td>PCPA</td>
<td>100 (×3)</td>
<td>i.p.</td>
<td>SHR (c)</td>
<td>↑</td>
<td>NC</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>PCPA</td>
<td>300 (×3)</td>
<td>i.p.</td>
<td>cat (a)</td>
<td>↑</td>
<td>NC</td>
<td>59, 60</td>
<td></td>
</tr>
<tr>
<td>PCPA</td>
<td>500</td>
<td>i.p.</td>
<td>cat (a)</td>
<td>3 days</td>
<td>↓</td>
<td>NC</td>
<td>61</td>
</tr>
<tr>
<td>PCPA</td>
<td>100 (×5)</td>
<td>i.p.</td>
<td>dog (c)</td>
<td>↑</td>
<td>NC</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>PCPA</td>
<td>400</td>
<td>i.p.</td>
<td>rabbit (c)</td>
<td>1-14 days</td>
<td>↓</td>
<td>NC</td>
<td>58</td>
</tr>
<tr>
<td>PCPA</td>
<td>100</td>
<td>i.p.</td>
<td>rabbit (c)</td>
<td>1-14 days</td>
<td>↓</td>
<td>NC</td>
<td>58</td>
</tr>
<tr>
<td>PCPA</td>
<td>1-5</td>
<td>i.c.v.</td>
<td>rabbit (c)</td>
<td>↑</td>
<td>NC</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

i.p. = intraperitoneal; i.c.v. = intracerebroventricular; c = conscious; a = anesthetized; ↑ = increase; ↓ = decrease; NC = no change.

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Pretreatment of rats with phenolamine, methysergide, or BOL did not modify the cardiovascular effects of 5,6-DHT.

Buckingham et al. treated prehypertensive SHR (6 weeks old) i.c.v. with 25 μg of 5,6-DHT and reported that the onset of hypertension was retarded for at least 6 weeks. If SHR with established hypertension (14–15 weeks old) are treated i.c.v. with 50 μg of 5,6-DHT, BP is slightly reduced for at least 4 hours and returns to control levels by 24 hours. The HR was significantly increased by 5,6-DHT 2 to 4 hours after injection. Goertt and Klupp improved the specificity of the 5-HT neurotoxic effects of 5,7-DHT by pretreating rats with the norepinephrine (NE) uptake inhibitor desipramine. Injections of 120 μg of 5,7-DHT i.c.v. significantly reduced BP of conscious SHR by 1 day after treatment. The BP remained below control (approximately 20 mm Hg) for up to 6–8 days. The depressor response to 5,7-DHT was accompanied by an increase in HR that was maximal 2 days after treatment and returned to control values by 3 days.

Wing and Chalmers studied the effects of 5,6-DHT on BP in normal and hypertensive rabbits. After i.c. injection of 300 μg/kg of 5,6-DHT in rabbits, a significant decrease in BP (11%) and HR (9%) was observed 7 days after drug treatment. The BP was still slightly reduced as long as 14 days after 5,6-DHT injections, while HR had returned to control values. Rabbits made hypertensive by sinoaortic denervation responded to i.c. injections of 300 μg/kg 5,6-DHT with an immediate and persistent reduction in arterial BP. If rabbits are treated with 5,6-DHT before sinoaortic denervation, the usual denervation-induced increase in BP and HR is markedly attenuated and is of short duration. It is interesting to note that sinoaortic denervation also leads to a significant increase in the levels of 5-HT and 5-HIAA in the medulla-pons as well as PCPA. Therefore, it is possible that the serotonin, recent behavioral studies have demonstrated that PCPA can have central 5-HT agonist properties when injected along with MAOI. It appears that a decarboxylation product of PCPA, namely p-chlorophenylethylamine (PCPEA), and not PCPA itself, produces the behavioral responses observed, apparently by releasing stored 5-HT.

In another interesting experiment, Theron et al. administered PCPA to rats and observed that cardiac tissue was resistant to the 5-HT depleting effects of PCPA. A dose of 250 mg/kg i.p. led to a large increase in the number of atrial-specific granules, and evidence was also presented that indicated that after PCPA treatment, these atrial granules retain 5-HT as well as PCPEA. Thus, it is possible that the resiliency of cardiac tissue to the 5-HT depleting effects of PCPA as well as the 5-HT agonist properties of PCPEA could contribute, at least in part, to the

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**Table 6. Effects of 5,6- and 5,7-Dihydroxytryptamine (DHT) on Blood Pressure (BP) and Heart Rate (HR)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Injection route</th>
<th>Species</th>
<th>Time</th>
<th>BP</th>
<th>HR</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,6-DHT</td>
<td>450 μg/kg</td>
<td>i.c.v.</td>
<td>rat (c)</td>
<td>6 wk</td>
<td>NC</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>5,7-DHT + protriptyline</td>
<td>150 μg</td>
<td>i.c.v.</td>
<td>rat (c) or</td>
<td>4 wk</td>
<td>NC</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>20 mg/kg</td>
<td>i.p.</td>
<td>SHR (e)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,6-DHT</td>
<td>50 μg</td>
<td>i.c.v.</td>
<td>rat (he)</td>
<td>4 days</td>
<td>↓</td>
<td>↓</td>
<td>62</td>
</tr>
<tr>
<td>5,7-DHT + protriptyline</td>
<td>50 μg</td>
<td>i.c.v.</td>
<td>SHR (e)</td>
<td>4 hr</td>
<td>↑</td>
<td>↑</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>120 μg</td>
<td>i.c.v.</td>
<td>SHR (e)</td>
<td>1-6 days</td>
<td>↓</td>
<td>↑</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg</td>
<td>i.p.</td>
<td>SHR (e)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,7-DHT</td>
<td>100-200 μg/kg</td>
<td>i.c.v.</td>
<td>cat (a)</td>
<td>8 days</td>
<td>NC</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>5,6-DHT</td>
<td>4 μg</td>
<td>i.s.</td>
<td>cat</td>
<td></td>
<td>NC</td>
<td>↓</td>
<td>61</td>
</tr>
<tr>
<td>5,6-DHT</td>
<td>300 μg/kg</td>
<td>i.c.v.</td>
<td>rabbit (c)</td>
<td></td>
<td>↓</td>
<td>↑</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.c.v.</td>
<td>s-a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DMI = desmethyliimipramine; i.c.v. = intracerebroventricular; i.p. = intraperitoneal; c = conscious; SHR = spontaneously hypertensive rat; h = DOCA-salt hypertensive; s-a = sino-aortic denervation; NC = no change; ↓ = decrease; ↑ = increase; i.s. = intraspinal.
variability in the BP changes seen after injections of the large doses of PCPA that are typically used. Finally, PCPA is not entirely specific in its depleting actions on monoaminergic neurons. Substantial reductions in brain CA levels have been observed relatively soon after PCPA treatment.

The lack of agreement among experiments where 5,6- or 5,7-DHT were used is disconcerting, since these drugs are injected directly into the brain, avoiding peripheral contamination; however, the non-specific but avoidable90 depleting effects of DHT may explain these discrepancies (see table 6). In fact, Wing and Chalmers91 reported that 5,6-DHT reduced NE concentration in the pons-medulla to 67% of control and thoracolumbar NE was reduced to 74% of control. This amount of NE depletion, although small, may have important consequences on BP regulation especially when viewed in light of where in the brain the nonspecific depletion of NE occurs.

Electrical Stimulation of the Raphe Nuclei

Electrical stimulation in and around various midbrain structures often collectively referred to as medullary raphe areas, produces both pressor and depressor responses in a variety of species.1,3,5,7 Using more stringent neuroanatomical criteria than previous studies to identify the raphe nuclei in cats, Adair et al.72 observed that stimulation of the nucleus raphe pallidus (B1) yields both pressor and depressor responses, with depressor responses predominating. In the anterior region of nucleus raphe obscurus (B2), stimulation yields primarily depressor responses, whereas stimulation of the posterior region of B2 results in pressor responses. The nucleus raphe magnus (B3) is subdivided into anterior pressor and posterior depressor areas.73 The B1–B3 raphe nuclei are the primary cells of origin of descending serotonin axons.3 Stimulation of the dorsal raphe in cats consistently produces increases in HR and BP and can induce ventricular arrhythmias,74 whereas stimulation of the medullary raphe in pigeons causes bradycardia and a lowering of BP.75

More recently, Smits et al.76 demonstrated that electrical stimulation of either the dorsal (B7) or median (B8) raphe — nuclei of the major ascending 5-HT systems — leads to pressor effects in anesthetized rats. Increases as large as 50 mm Hg were observed. The pressor effect seen after stimulation of B8 was largely abolished if the rats were first treated with PCPA to deplete 5-HT, whereas stimulation of the dorsal nucleus still had pressor effects.77 Preliminary experiments in our laboratory have been successful in replicating these exciting results with stimulation of the B7 and B8 nuclei (Kuhn, Wolf, and Lovenberg, unpublished observations). Despite the problems inherent in electrical stimulation of the brain,78 this procedure is perhaps the best method for selectively activating the 5-HT system. Presumably, raphe stimulation leads to the release of 5-HT, which activates postsynaptic 5-HT receptors, leading to the pressor effect seen. The results of experiments with 5-HT are consistent with this hypothesis (see table 3). Obviously, additional studies are necessary to determine which 5-HT pathway mediates this pressor effect, and which area or areas contain the critical 5-HT receptors.

Sites of Action of 5-HT in Blood Pressure Regulation

Serotonergic neurons are strategically located near neural cardiovascular control sites. For example, the 5-HT input into sympathetic preganglionic neurons arises from the raphe nuclei,4 and the nucleus solitary tract has been recently identified as a specific afferent area to the dorsal raphe.79 It was pointed out earlier that the precise neuroanatomical pathways mediating the effects of 5-HT on BP are not known; however, the results of many of the presently discussed experiments suggest certain critical sites of action for 5-HT apart from the unspecific bulbospinal depressor and pressor areas often referred to. For example, as early as 1960, McCubbin et al.80 ruled out the possibility that 5-HTP or 5-HT was acting directly on the carotid sinus baroreceptors to reduce BP in dogs.

The mediation of the 5-HTP effect in cats has been attributed to neural structures located at or below the midcollicular level, since restriction of 5-HTP to structures rostral to these areas (by cannula drainage in the cerebral aqueduct after injection into the third or lateral cerebral ventricles) prevents the 5-HTP-induced decrease in BP, HR, and sympathetic outflow.81 Tadepalli et al.82 concluded further that the primary effect of 5-HTP (or 5-HT) responsible for its depressor influence is the stimulation of caudal brainstem or spinal cord centers that in turn depresses tonic sympathetic outflow.

Since the spectrum of effects of i.c.v. 5-HT in rats included a decrease in ventilation accompanying the pressor effect, Lambert et al.42 concluded that the rise in BP may result from a direct effect of hypoxia or hypercapnia. These effects of 5-HT were further confined to structures lining the third cerebral ventricle. On the other hand, Smitts and Struyker-Boudier83 concluded that the primary site of action of 5-HT for producing a pressor effect in rats is the AH/PO region, although relatively large doses of 5-HT were given. The anterior hypothalamus does contain rather high concentrations of 5-HT84 and it also receives projections from the raphe nuclei.1,8,9 Thus it is conceivable that electrical stimulation of the B7 and B8 nuclei produces a pressor effect77 as a result of 5-HT release in the AH/PO region.

Functional Implications of 5-HT Regulation of Cardiovascular Function

Table 7 presents a somewhat oversimplified summary of the effects of 5-HT agents on BP. It is clear that changes in the central 5-HT system can modulate arterial blood pressure. It is also obvious from table 7 that many critical experiments remain to be done. Based on the methodologies and animal preparations used to collect the results summarized, it is virtually impossible to conclude that 5-HT is a pressor or...
depressor amine across species. It appears, for example, that the effects of 5-HT on BP in rats are generally in the opposite direction from the effects of 5-HT on BP in cats and dogs. Furthermore, numerous other variables including anesthetic agents used and method of recording BP, as well as the method, dose, and site of drugs injected, have undoubtedly contributed to the variety of results obtained. The importance of all of these variables needs no further discussion.

While most studies have been concerned with determining the role of 5-HT in maintaining normal, resting BP, some attempts have been made to examine the role of 5-HT in the development and maintenance of hypertension. For example, treatment of prehypertensive SHR with 5,6-DHT delays the onset of hypertension, and either 5,6-DHT or PCPA can reduce the BP of rats with established hypertension. Similarly, prior treatment of rabbits with 5,6-DHT prevents the rise in BP observed after sino-aortic denervation and sharply reduces the BP of rabbits with established neurogenic hypertension. More recently, Smith et al. discovered that the in vivo rate of tryptophan hydroxylation was higher in prehypertensive SHR than in control rats. This difference was no longer evident in SHR with established hypertension. It is not clear from this study whether BP increases in response to changes in 5-HT synthesis rate or vice versa. Thus it appears that 5-HT can contribute to the development and maintenance of hypertension.

Although it is difficult to conclude whether 5-HT actually plays a primary, tonic role in maintaining normal BP in rats, it appears that it does not. The strongest evidence for this conclusion comes from the studies of Ito and Schanberg, which demonstrated that the slight, initial pressor response to daily injections of 100 mg/kg of PCPA in rats returned to normal despite continued PCPA injections and almost total depletion of brain 5-HT. Similarly, depletion of 5-HT with 5,6-DHT or 5,7-DHT does not alter the BP of normotensive rats, and PCPA can depress BP in normotensive rabbits without changing the levels of 5-HT.

The various hypertensive states discussed above may share a common factor: increased sympathetic outflow. It is clear that sino-aortic denervation results in an immediate increase in sympathetic activity, and evidence has been presented that suggests that efferent sympathetic nervous traffic is increased in SHR. In light of evidence just discussed, it appears that 5-HT participates as a phasic modulator of SA in rats at the level of the brain stem, spinal cord, or both. Specifically, 5-HT can play a "permissive," excitatory role along the midbrain raphe-hypothalamic axis under conditions involving increased efferent sympathetic outflow, perhaps by overriding more tonic inhibitory centers that predominate under normal conditions. Alternatively, the modulatory influences of 5-HT on BP may be mediated at the level of the spinal cord. There is ample evidence demonstrating that the systemic injection of 5-HT precursors facilitates the spinal monosynaptic reflex and leads to increases in motoneuron activity. More recently, McCall and Aghajanian have demonstrated that 5-HT itself does not directly affect rat facial motoneuron activity but acts, instead, to facilitate excitatory afferent input into the motoneuron. This 5-HT facilitatory influence on motoneurons is blocked by methysergide. Regardless of which (or both) alternative is operational, depletion of 5-HT or blockade of 5-HT receptors in normal rats need not change BP, but 5-HT agonists (drugs or electrical stimulation) can have direct (brain) and/or indirect (spinal motoneuron) pressor effects. Likewise, under conditions where increased sympathetic activity is required to initiate or maintain hypertension (spontaneous or neurogenic), extensive depletion of 5-HT or blockade of 5-HT receptors would prevent the expression of hypertension by disallowing increased sympathetic outflow.

Experiments with cats and dogs have provided results with respect to 5-HT-BP interactions that are often at conflict with similar studies in rats (see table 5). Based on the variety of experiments performed, it may not be incorrect to tentatively conclude that 5-HT has an altogether different physiological role in cats and dogs than in rats, at least with respect to BP modulation. Table 5 indicates that increases in
cerebral 5-HT usually lead to decreases in BP. 5-HT is also quite effective in attenuating the pressor response to BCO. The well-known ability of 5-HT to depress sympathetic outflow in cats and dogs51, 52, 53, 54, 55, 56, 57 can explain the depressor effects of 5-HT as well as its attenuation of the BCO response. Obviously, much additional work is necessary to delineate the role of 5-HT in BP regulation in cats and dogs.

The ability of 5-HT to depress efferent sympathetic nerve flow may have potential clinical applications. It was recently demonstrated by Rabinowitz and Lown58 and Blatt et al.59 that agents that increase cerebral levels of 5-HT appear to protect the heart against ventricular fibrillation. These investigators noted a significant increase in the repetitive extrasystole threshold (electrical current necessary to cause ventricular fibrillation) after pharmacologically inducing increases in brain 5-HT levels of anesthetized dogs. A serotonin defect in the platelets of humans with established hypertension was also reported recently.60

The platelets of hypertensive individuals apparently take up and store less 5-HT than the platelets of normotensive individuals.61

Throughout most of the foregoing discussion, the effects of 5-HT on cardiovascular function have been emphasized; however, a growing number of studies have demonstrated that changes in the cardiovascular system can effect the 5-HT neuronal system. For example, sino-aortic denervation in rabbits increases 5-HT and 5-HIAA in the medulla,62 and stimulation of the carotid sinus nerve evokes activity in the medullary raphe of cats.63, 64 Similarly, Sole et al.65 concluded that left coronary artery ligation in the rat leads to a reflex inhibition of bulbar and hypothalamic 5-HT nerves. These latter conclusions were based on the observation that 5-HT accumulation (in MAOI-pretreated rats) was significantly lower in rats with acute left coronary artery occlusion.66 In corroboration of the hypothesis that 5-HT neurons are altered by peripheral nervous input, Aghajanian et al.67 demonstrated that low-frequency stimulation of the sciatic nerve in rats results in poststimulus periods of suppressed firing of identified 5-HT neurons in the dorsal raphe. Aghajanian et al.68 also identified, by electrophysiological means, two other types of cells within the dorsal raphe nucleus that are apparently not 5-HT containing cells. Interestingly, these non-5-HT raphe cells do not disappear after 5,7-DHT injections, and they retain their characteristic responsiveness to sciatic nerve stimulation despite extensive 5-HT depletion.69 Despite the impact that these interesting results have on the understanding of raphe physiology, they are of primary importance to experiments involved in the study of the effects of raphe stimulation on the cardiovascular system.

Conclusions

Alterations in the dynamics of the cerebral 5-HT system can alter BP but unfortunately, statements concerning the role of 5-HT in BP regulation can only be made with caution at this time. For example, it appears that 5-HT is a pressor agent in rats and rabbits by virtue of its ability to participate in increased sympathetic outflow. On the other hand, it appears that 5-HT is a depressor agent in cats, dogs, and perhaps in humans, by virtue of its ability to depress sympathetic outflow. The HR changes are often variable and probably reflect sympathetic reflex action in response to BP changes. The control of BP is obviously a very complex process, and any understanding of the role that a single factor such as 5-HT may play in BP regulation is complicated by the adaptability of the organism under study and by the extent to which the control of BP is buffered. It is clear that an understanding of the role of the brain 5-HT system in BP regulation will increase in proportion to advances made in the understanding of the pharmacology and electrophysiology of the raphe neuronal systems. There is little doubt that the 5-HT system is just one of many regulatory neuronal networks whose role in BP regulation can best be understood when viewed in concert with other dynamic integrating central and peripheral control systems.

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