What is the role of serotonin during hemorrhage in conscious animals?

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AT THE END OF WORLD WAR II, groups on both sides of the Atlantic (2, 22) demonstrated that loss of central blood volume in human volunteers resulted in a sudden decrease in arterial pressure due to an equally sudden fall in vascular resistance. Subsequent studies have shown that the response observed in humans is common to a variety of conscious mammals and involves two phases (17). In phase 1, arterial pressure is maintained by regional sympathetic vasoconstriction. Phase 2 occurs as blood loss approaches 25–30% of blood volume and involves a rapid fall in arterial pressure due to global vasodilation accompanied by profound sympathoinhibition. In contrast to the effects on sympathetic nerves, adrenal catecholamine release, while at baseline levels during phase 1, increases dramatically in phase 2 (14, 15). Phase 2 is sometimes referred to as the decompensatory phase. This is an unfortunate choice, because the term implies an inability to compensate further for the loss of blood volume. There are at least three reasons this is not the case. First, the events associated with phase 2 are readily reversed by a variety of centrally acting drugs such as methysergide (18) and opiate antagonists (8, 11). Second, exposure to a sensory stressor delays the onset of phase 2 (16). Finally, recovery of sympathetic nerve activity after hypotensive hemorrhage is slower than recovery of arterial pressure with (8) or without (Fig. 3 of Ref. 18) reinfusion of removed blood.

Thus the current view is that the fall in arterial pressure during acute blood loss is actively mediated by a central sympathoinhibitory mechanism. Although the teleological question of why this happens is very interesting, any answer would be based on conjecture rather than facts. On the other hand, the question of how this happens is also interesting and more amenable to experimental studies. Thus, in the context of defining central mechanisms involved in the sympathoinhibition associated with acute hemorrhage, many studies have focused on pharmacological modification of the cardiovascular and sympathetic response. The role of serotonin in this response has been addressed in this way. One of the earliest studies showed that the nonspecific serotonin receptor ligand methysergide aided recovery from hypotension in anesthetized rats (5). Subsequently, Morgan et al. (9) showed that intravenous pretreatment with methysergide abolished the decrease in sympathetic activity seen during hypotensive hemorrhage in conscious rats. Roger Evans, John Ludbrook, and colleagues investigated the central nervous system site of methysergide’s effects during simulated hemorrhage in conscious rabbits. The first of their studies (7) confirmed earlier work showing that systemic methysergide delayed the onset of phase 2. They also showed that methysergide was effective at a lower dose if it was injected into the fourth cerebral ventricle. Thus it seemed that a central, endogenous, serotonergic system must mediate phase 2. However, later work from the same laboratory (6), employing additional serotonergic agonists and antagonists, suggested that methysergide’s effects might actually be due to its agonist activity at 5-HT1A receptors rather than to antagonism of ongoing serotonergic activity.

The report by Dr. Scrogin (18) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology deals specifically with the site of methysergide’s 5-HT1A effects in reversal of acute hemorrhagic hypotension and sympathoinhibition. The author’s first studies in this area (20) showed that central pretreatment with methysergide delayed or abolished the sympathoinhibition associated with hypotensive blood loss. They also showed that the serotonergic pathway in hemorrhage was different from that mediating the sympathoinhibition after activation of peripheral, cardiopulmonary 5-HT3 receptors. Subsequent studies (19) picked up where the Evans et al. study (6) left off and addressed the assumption that methysergide’s effects indicated serotonergic mediation of phase 2. Dr. Scrogin and colleagues (19) demonstrated that the effects of methysergide were likely mediated by its 5-HT1A agonist properties rather than its antagonist actions at another receptor subtype. The present work (18) measured the latency and effectiveness of the response to a specific

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5-HT₁A agonist, 8-OH-DPAT, administered at different central nervous system sites. Although the results did not identify a specific site, it does appear that the effects of 5-HT₁A receptor activation during hemorrhage in conscious rats are mediated in the hindbrain.

A role of serotonin in the response to blood loss is supported by other recent studies. Pelaez et al. (13) demonstrated that hypotensive blood loss in conscious rats activates a medullary serotonergic cell group. This same cell group was not activated by hypotension induced by the vasodilator hydralazine. In addition, Bago and Dean (1) demonstrated in anesthetized rats that ventrolateral periaqueductal gray (VLPAG) stimulation results in sympathoinhibition mediated by activation of 5-HT₁A receptors in the rostroventromedial medulla (RVLM). They also subsequently demonstrated that the renal sympathoinhibition associated with hypotensive hemorrhage in anesthetized rats was mediated by activation of 5-HT₁A receptors in the RVLM (4). Cavun and Millington (3) showed that reversible chemical lesion of the VLPAG of conscious rats delays and reduces the fall in arterial pressure during blood loss. A complicating feature here is that Morgan and Carriere (10) recently reported that although stimulation of the VLPAG produces hypotension in anesthetized rats, it does not in conscious rats. A further complication is introduced by the failure of a specific 5-HT₁A antagonist to modify the response to blood loss in conscious rats (19) and the failure of partial depletion of central serotonin to alter the response to simulated hemorrhage in conscious rabbits (7). There can be no doubt that anesthesia alters the response to hemorrhage (17). Perhaps, as Dr. Scroggin (18) suggests, some of this alteration is due to the effects of anesthesia on the actions of serotonin.

The importance of differential control of regional sympathetic nerve activity has recently been reviewed in this journal (12). One of the best examples of differential control is the qualitative separation of activation of sympathetic nerves and the adrenal medulla during hemorrhage (14, 15, 21). Could central serotonergic mechanisms be involved? If 5-HT₁A receptor activation in the RVLM influences activity in renal sympathetic nerves, does it also affect the adrenal medulla? Although regional vascular responses are quite variable during hemorrhage, it is not known if these end-organ responses involve differential sympathetic effects. Most, if not all, studies of hemorrhage have relied on measurements of renal sympathetic nerve activity. It is clear that many questions remain about the role of the central nervous system in the response to acute hypotensive hemorrhage. Perhaps the present findings (18) will lead to future studies that identify the trigger for sympathoinhibition and better define the central nervous system pathways contributing to the fall in blood pressure during blood loss.

REFERENCES


