Serotonin and anesthesia

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The author presents a comprehensive look at the autacoid serotonin and its many diverse effects on the body. Special emphasis is placed on those factors which pertain to the administration of anesthesia.

Serotonin is an important monoamine to the anesthetist for many reasons. An increase or decrease of serotonin concentration in the brain changes the minimum alveolar concentration (MAC) of inhalational anesthetics; precipitous release systemically, as in carcinoid syndrome, produces devastating effects on the cardiovascular and pulmonary systems. Serotonin is ubiquitous and has many roles in the body. Those aspects relevant to anesthesia are reviewed in this article.

Pharmacology and physiology

Serotonin (5-hydroxytryptamine or 5-HT) is classified with the autacoids (from the Greek autos "self" and akos "remedy"); it is endogenous and vasoactive (Figure 1). Direct vasoconstriction is the classical effect of 5-HT and hence the synonyms vasotonin and serotonin.

In nature, large amounts of 5-HT are found in pineapples, bananas, plums and various nuts, as well as in some insect stingers and snake venom. In man, about 90% of the body's serotonin is confined to the enterochromaffin cells of the gastrointestinal tract. Another 8-10% is carried by the platelets, with only 1-2% present in the central nervous system. Although serotonin does occur naturally in the brain, a blood-brain barrier exists which allows little crossover between the systemic circulation and the central nervous system (CNS).

Serotonin is formed enzymatically from tryptophan by hydroxylation, followed by decarboxylation (Figure 2). Once synthesized, catabolism is achieved via deamination by monoamine oxidase (MAO).

The substrate tryptophan is an amino acid abundantly available in the normal diet. Elimination of tryptophan from the diet has been found to profoundly decrease the brain levels of serotonin. Excess amounts of 5-HT are metabolized across the intestinal wall and the remainder is destroyed by the liver and lungs. The 5-HT present in the neurons, enterochromaffin cells, and other cells of the body is synthesized in situ from the tryptophan. Platelets, on the other hand, scavenge 5-HT from their environment.

Uptake of serotonin is achieved by high-affinity platelets passing through the serotonin-rich intestinal blood vessels. Also using high-affinity up-
take mechanisms, tryptaminergic nerve endings recapture the released transmitter.\(^1\)

In the cytoplasm, the synthesized 5-HT is taken up into vesicles, awaiting signals for excretion. Serotonin is stored and secreted in a manner similar to the endogenous catecholamines. Drugs that disrupt the storage of these catecholamines such as reserpine likewise impair the storage of 5-HT.\(^1\)

Receptors for serotonin have not yet been visualized. It is known, however, that translation of receptor occupancy into an organic response involves changes in membrane permeability to inorganic ions. This leads to ion fluxation and changes in membrane potential.\(^1\)

The intestinal enterochromaffin cells release 5-HT at a baseline level. This release can be increased by several mechanisms, including mechanical stimulation, hypertonicity, acidity, norepinephrine and also by vagal reflexes.\(^1\)

### Systemic Effects

Pharmacologically, 5-HT has the ability to stimulate or to inhibit smooth muscle and nerves. This dual action has led to conflicting reports from investigators and some confusion among readers. Variability of action can be attributed to two factors:

1. Researchers have found that many 5-HT effects are mediated by reflexes and therefore are subject to several parameters. These include the pattern of innervation, anesthetic depth, preexisting tone, dose, route and speed of injection of 5-HT and/or endogenous release.

2. Tachyphylaxis has been encountered by some researchers when giving 5-HT at frequent intervals.

Serotonin's primary effect on the respiratory system is stimulation of afferent nerves. 5-HT given intravenously yields a temporary increase in minute volume with a variable effect on respiratory rate. With low doses, effects are attributed to stimulation of carotid and aortic chemoreceptors. Bronchoconstriction may occur, primarily in asthmatics, due to direct stimulation of bronchial smooth muscles.\(^1\)

Serotonin is a powerful constrictor of pulmonary vessels. It greatly increases pulmonary artery pressure, right atrial pressure and central venous pressure, and it may increase cardiac output as much as 50%. The change in cardiac output is dependent upon the degree of pulmonary vasoconstriction. A slight increase in pulmonary vascular resistance (PVR) could increase the cardiac output whereas a marked increase in PVR diminishes output.\(^8\)

Serotonin again elicits disparate responses in the cardiovascular system. Depending on vasomotor tone, size of the vascular bed, and the amount of active substance present in the body, serotonin induces either vasoconstriction or dilatation, and activates either pressor or depressor reflexes.

Direct vasoconstriction of blood vessels is the usual response. This is illustrated most vividly by the pithed animal where indirect effects are obliterated. 5-HT then causes an immediate increase in blood pressure. Vasodilatation occurs in superficial vessels of the skin (accounting for the typical flushed appearance) as well as in skeletal muscle. No change in capillary permeability has been demonstrated.\(^1,8\)

5-HT causes positive inotropy and chronotrophy to varying degrees. These responses may be obscured or blunted by autonomic reflexes or by the direct effect of 5-HT on baroreceptors, chemoreceptors, or vagal endings in the coronary bed. Serotonin, via the vagus, can initiate the Bezold-Jarisch reflex, i.e., inhibition of sympathetic outflow and increased vagal tone which results in profound bradycardia and hypotension. This perilous reflex can induce cardio-vascular collapse.\(^1\)

Both the intact experimental animal and the human subject demonstrate variable changes in blood pressure after intravenous administration of 5-HT. There are three phases to this response: (1) brief depressor phase upon injection of 5-HT;
(2) brief pressor phase; and (3) prolonged depressor phase.

The combined duration of the first two phases is only one to two minutes. The early depressor phase results from the coronary chemoreflex. It can be abolished by cutting the vagi or by administering a combination of parasympathetic and sympathetic blocking agents. The all too brief pressor phase is due primarily to direct effects of 5-HT: increased total peripheral resistance and increased cardiac output. The late depressor phase is mainly due to the direct vasodilatory effects of 5-HT in skeletal muscle; it persists after block of sympathetic outflow.1

Serotonin has several other systemic effects. It causes strong venoconstriction. It promotes platelet aggregation, but this effect is minor and self-limited. Intravenously administered 5-HT stimulates the motility of the small intestines and reduces the volume and acidity of gastric juices. High doses of serotonin cause a release of catecholamines from the adrenals by depolarizing the chromaffin cells.2

Central nervous system effects

Almost all serotonin-containing cells of the brain are located in the raphe nuclei, groups of neurons lying in the pons and upper brain stem. Uptake is similar to that of catecholamines. This uptake is energy dependent; it requires glucose and oxygen and is more active at 37°C than at 0°C. Ouabain, dinitrophenol and iodoacetate all inhibit serotonin uptake. The same drugs which inhibit uptake of catecholamines into nerve endings (desmethylimipramine, chlorpromazine, and cocaine) also partially inhibit uptake of serotonin.2

The tissue oxygen level influences the rate of serotonin formation. Rats given 100% inspired O2 greatly increase their synthesis of 5-HT.2 Conversely, rats rendered hypoxic by the administration of 5.6% O2 show decreased synthesis of central norepinephrine, dopamine, and serotonin.4

Animals depleted of 5-HT exhibit decreased motor activity, decreased emotional reactivity, and increased sensitivity to painful stimuli. There is a marked decrease in the amount of slow wave sleep time proportional to the extent of serotonin loss.2

The serotonergic system exerts an inhibitory influence over the general arousal system of the brain. When 5-HT transmission is disrupted, the locomotor stimulant effects of amphetamine are enhanced.

Amphetamine exerts a primary effect on the dopaminergic neuronal system. This system, however, is under inhibitory control by the serotoninergic neurons. A reduction in transmission in the serotonergic system therefore permits amphetamines to exert a greater effect on behavior.5

Increased central serotonin levels were found to have an effect on the myocardium. A recent study showed that serotonergic agents in dogs inhibit arrhythmogenic sympathetic outflow from the brain to the heart. It is therefore postulated that increased concentrations of central 5-HT raise the extrasystolic threshold of the myocardium.6

Drugs which increase the concentration of brain amines elevate depressed mood. Conversely, lithium, which is used to treat manic-depressive illness, has the opposite effect on these amines. Lithium inhibits release of both norepinephrine and 5-HT from stimulated neurons.7

Drugs that alter serotonin metabolism also change the discharge pattern of the raphe neurons. Monoamine oxidase (MAO) inhibitors and tryptophan, which increase serotonin levels, slow raphe discharge. Tricyclic anti-depressant drugs (imipramine, chlorimipramine, and amitriptyline) also slow the discharge of serotonin from raphe neurons and locally increase 5-HT levels by inhibition of re-uptake.2 Reserpine interferes with uptake-storage mechanisms of the amine granules causing a drastic depletion of 5-HT. Use of MAO inhibitors such as iproniazid increases concentrations of 5-HT by preventing its degradation.2

Serotonin may be important in the mechanisms of analgesia. Electrical stimulation of the raphe nuclei produces analgesia. This effect can be antagonized by depletion of brain 5-HT or by high spinal cord transection. Rat studies indicate that injection of serotonin into the lumbar subarachnoid space produces analgesia in animals that are not serotonin depleted. It is assumed that intrathecal 5-HT molecules penetrate spinal cord tissue and inhibit nociceptive transmission, possibly by affecting the specific serotonin receptors. The hypothesis that serotonin neurons may be related to pain has been further substantiated by decreased electro-shock response thresholds in rats on long-term tryptophan-poor diets. The hyperalgesia thus appears to be directly related to decreased brain concentrations of 5-HT.8

Anesthetic considerations

Mueller and colleagues studied the effect of 5-HT on the halothane MAC in rats. When the serotonin level was reduced by 38%, the MAC of halothane was significantly decreased. No change was found in the MAC of cyclopropane after serotonin depletion.4

In a more recent study with rats, Roizen and
associates postulated that general anesthesia results from interruption of neural transmission in discrete areas of the brain rather than from a global depression of transmission. By ablating the raphe nuclei, they found a 25% decrease in halothane MAC and a 16% decrease in cyclopropane MAC. The raphe lesions had decreased the hypothalamic serotonin content by 40% and cortical serotonin content by 80%.

In dogs, depletion of central and peripheral catecholamines and 5-HT by giving reserpine or alphamethyldopa potentiates the effect of anesthetics. Use of MAO inhibitors, thereby interfering with normal breakdown of amines, increases MAC for halothane and cyclopropane.

The many and varied systemic effects of serotonin and its anesthetic importance are well illustrated by the patient with a serotonin secreting carcinoid tumor. However, detailed anesthetic management of the carcinoid patient is beyond the intent and scope of this paper as it is a subject in itself.

Carcinoid tumors arise from Kulchitsky's cells of the gastrointestinal tract. Involvement of the liver seems to be essential for the development of the true carcinoid syndrome and these liver metastases enlarge slowly and may become massive. Twenty-five per cent of all malignant carcinoid tumors produce and secrete serotonin. In a healthy person, only 1% of dietary tryptophan is utilized in serotonin synthesis. In patients with a secreting carcinoid tumor, as much as 60% of the daily intake of tryptophan may be so utilized.

Release of this serotonin is precipitated by a variety of stimuli, including palpation of the enlarged liver or abdominal mass, hypotension, fear, anxiety, anger, alcoholic or hot beverages, eating, and defecation. Barring direct palpation, hypotension is the most important stimulus triggering serotonin release. The important factor is not the degree of hypotension, but rather, the rate at which the pressure falls.

Excessive amounts of serotonin are released from the tumor mass into the hepatic vein. This accounts for the right heart and pulmonary changes associated with direct exposure to high titres of serotonin. By its direct effect and with repeated exposures, serotonin may cause permanent tissue changes. These include a rheumatoid-type arthritis, scleroderma changes in skin (especially in areas of flushing), facial telangiectasias, chronic elevation of the central venous pressure, engorgement of the external jugular veins, dependent edema, and fibrosis of the tricuspid and pulmonic valves.

Nausea and vomiting with abdominal cramping are the symptoms that usually bring the patient to the doctor. Bronchoconstriction is also a frequent symptom. There is little correlation between the blood titre of 5-HT and the severity of an attack or degree of pathology.

Serotonin alone cannot account for all the symptoms of carcinoid syndrome. Bradykinin appears to be the main flush mediator and contributes to the hypotensive episodes with its potent vasodilatative properties. Bradykinins also increase capillary permeability. This could account for the edema sometimes present in the carcinoid patient.

Five groups of drugs have been used in an attempt to mitigate the symptoms of carcinoid syndrome. Antiserotonin drugs, inhibitors of the kallikrein-bradykinin system, corticosteroids, adrenergic blockers and cytotoxic agents have all met with limited success to varying degrees.

The current treatment of choice remains surgical. Hence, the anesthetist will be seeing more carcinoid patients present for excision of the primary tumor, removal or inactivation of hepatic or other metastases, or replacement of fibrotic cardiac valves.

The serotonin secreting patient presents the anesthetist with quite a challenge. Agents with the greatest potential for hypotension should be avoided. A slow incremental induction may circumvent a precipitous drop in blood pressure that could trigger a release of serotonin. If a severe carcinoid attack does occur, the decrease in left heart filling pressure, reduced cardiac output, and profound hypotension are refractory to treatment. Fluid resuscitation may be hazardous since right-sided pressures are already increased. Spinal or epidural anesthesia may compound the hypotension with sympathetic blockade. Whatever anesthetic technique is employed, an endotracheal tube is indicated in the carcinoid patient since bronchostenosis is extremely common and is not significantly reduced by conventional bronchodilators.

The complications which occur most often under anesthesia are hypotension, bronchospasm, flushing, hypertension with tachycardia, and edema. When bronchospasm does occur, it is usually associated with severe hypotension and flushing. If complications occur the first time the patient is anesthetized, subsequent anesthetics are more than likely to be complicated as well.

*An article on "Anesthesia and malignant carcinoid syndrome" by Mary Patchak, CRNA, and Ronald M. Jones, MD, was published in the June, 1981 issue of the AANA Journal.
Conclusion
From the above, it is obvious that serotonin has diverse effects on the body. Many of these are relevant factors in the administration of anesthesia, especially the change in MAC produced and the systemic vasoactivity. Ideally, serotonin (as well as the other autacoids) should be specifically augmented, blocked, or otherwise manipulated during anesthesia to achieve the greatest therapeutic effect. Although much has been discovered about serotonin, research is far from complete.

REFERENCES

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