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Serotonin/5-hydroxytryptamine (5-HT) physiology

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Summary

Serotonin has a pervasive presence within both the central and peripheral nervous systems. Peripherally, serotonin stimulates various functions such as vasoconstriction, uterine contraction, bronchoconstriction, and platelet aggregation. Centrally acting serotonin inhibits excitatory neurotransmission and modulates alertness, concentration, emotions and mood, sexual behaviour, appetite, nociception and aggression. In addition to its extensive physiological role in the body, it is also the cause of certain diseases and the target of several pharmacological therapies. This review summarises the physiology of serotonin in humans and the clinical applications that are of relevance within anaesthesia.

Keywords: serotonin, 5-hydroxytryptamine, physiology

Synthesis

Serotonin (5-hydroxytryptamine) is synthesised from the essential amino acid L-tryptophan, found in dietary proteins.[1] Only 1% of dietary tryptophan is converted to serotonin. Tryptophan is transported into the serotonergic nerve by a sodium-dependent aromatic L-amino acid transporter, and tryptophan is converted to serotonin (5-HT) in a two-step process. Initially enzymatic hydroxylation of tryptophan to 5-hydroxytryptophan (5-HTP) occurs by tryptophan hydroxylase. This is followed by decarboxylation of 5-HTP to form 5-hydroxytryptamine (5-HT).[2]

5-HT is then transported from the cytoplasm into vesicles by the vesicular monoamine transporter (VMAT). An action potential opens voltage gated calcium channels allowing an influx of calcium and the fusion of vesicles with the surface membrane. 5-HT is exocytosed into the nerve terminal to act then on G protein-coupled receptors on the postsynaptic neuron. 5-HT can diffuse out of the cleft or be transported back into the nerve terminal by the 5-HT transporter. 5-HT can also act on presynaptic autoreceptors to inhibit further release.[3]

Tryptophan hydroxylase (TPH1) is found predominately in the enterochromaffin cells of the small intestine and produces 95% of the body's serotonin. The remainder is synthesised in the central nervous system (CNS), in the raphe nuclei located in the brainstem by the isoform of tryptophan hydroxylase (TPH2).[3,4]

Reuptake and metabolism

The synaptic effects of 5-HT are terminated by reuptake and metabolism. Reuptake occurs via the serotonin reuptake transporter (SERT) that is located on presynaptic serotonergic neurons. Reuptake by the SERT controls the amount of serotonin in the synaptic cleft. It is an energy and temperature dependent process, and it is inhibited by drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), and inhibitors of sodium-potassium ATPase activity.[1]

Once serotonin is returned to the nerve terminal, it is either taken back into the vesicles or inactivated by monoamine oxidase (MAO) into isoform A to form 5-hydroxyindoleacetic acid (5-HIAA). This substance is the principal urinary metabolite of serotonin, and urinary output of 5-HIAA is used as an index of the rate of serotonin metabolism in the body. The metabolism process of serotonin is mainly processed in the liver.[1]

Serotonergic receptors

There are seven classes of serotonin receptors (5-HT1 to 5-HT7), and all except 5-HT3 are G protein-coupled receptors and affect adenylyl cyclase or phospholipase C. Some of the serotonin receptors are presynaptic and others are postsynaptic.[5] 5-HT3 receptor is unique in that it belongs to the cys-loop family of ligand-gated ion channels.[6]

Central nervous system effects and clinical applications

Serotonin modulates virtually all behavioural processes. Serotonin regulates mood, appetite, wakefulness, and feelings of wellness or happiness. Serotonin plays a role in cognition, such as memory and learning. Several social behaviours are reported to be regulated by serotonin, e.g. sexual behaviour and violence.[7]

Serotonin does not cross the blood–brain barrier, however 5-hydroxytryptophan enters freely.[3] Serotonin within the CNS is almost exclusively produced in neurons originating in the raphe nuclei within the brainstem. The most caudal raphe innervates the spinal cord, while the more rostral raphe, the dorsal raphe nucleus, and the medial raphe nucleus, innervate the rest of the CNS by diffuse projections.[3]

Pain

Serotonin regulates pain perception and nociception at many levels with the CNS as well as the peripheral nervous system (PNS). Tissue damage releases serotonin activating peripheral nociceptors. This in turn causes the release of substance P and calcitonin gene-related peptide (CGRP).[3]

Serotonergic neurons within the brainstem send projections into the spinal cord which control incoming nociceptive stimuli. These same neurons also send ascending projections to regulate the psychological perception of pain.[8,9]

Neuropathic pain

The usefulness of SSRIs and SNRIs to reduce pain and the need for opioid therapy have been studied extensively. Duloxetine (SNRI) has been shown to decrease pain in peripheral neuropathy, osteoarthritis, and fibromyalgia. For chronic pain management, tricyclic antidepressants are the most used antidepressants.[9]

Migraine

Migraine is a chronic neurovascular disorder, characterised by headache, visual disturbances, and vomiting. Severe migraines benefit from the use of triptan drugs (e.g. sumatriptan) which activate serotonin receptors 1B and 1D. Triptans work by producing selective vasoconstriction and pre-synaptic inhibition of the inflammatory response.[6,10]

Nausea and vomiting

Serotonin released in the small intestine stimulates 5-HT3 receptors that trigger vomiting. 5-HT3 receptor antagonists have become the preferred treatment of postoperative nausea and vomiting.[3]

Ondansetron, a highly selective 5-HT3 receptor antagonist, works both in the CNS and PNS. It has no cardiovascular, respiratory, or sedative effects. Ondansetron blocks sodium channels which may result in QRS widening. Other serotonin antagonists include granisetron, dolasetron and palonosetron.

Due to its effect on the QTc interval, dolasetron has been withdrawn from use in the United States. Palonosetron is a second generation 5-HT3 antagonist which appears to be more effective than either granisetron or ondansetron, with no effect on the QTc interval.[6,11]

Sleep and arousal

The brainstem reticular activating system (RAS) is composed of several groups of neurons that release noradrenaline, serotonin, and acetylcholine. The transitions from sleep to wakefulness involve alternating activity of different groups of RAS neurons. The awake state occurs when the activity of noradrenaline and serotonin containing neurons (locus coeruleus and raphe nuclei) is dominant. There is an associated decrease in the level of activity in acetylcholine-containing neurons in the pontine reticular formation. The reversal of this pattern occurs during REM sleep. Wakefulness also occurs when gamma aminobutyric acid (GABA) release is reduced, and histamine release is increased.[3]

Modafinil is a "wake-promoting agent" licenced for treatment of excessive daytime somnolence associated with narcolepsy, sleep apnoea, shift worker sleep disorder and attention deficit and hyperactivity disorder (ADHD).[12] The mode of action is not fully understood. Modafinil inhibits noradrenaline and dopamine, and increases the release of histamine, glutamate and serotonin. Modafinil has been shown to improve mood, fatigue and cognition in sleep-deprived patients; but the evidence for cognitive improvement in non-sleep-deprived patients is lacking. Modafinil has also been shown to improve recovery following general anaesthesia in patients coming for day-case surgery at a dose of 200 mg.[13]

Central serotonergic drugs

Antidepressants are divided into four main groups: tricyclic antidepressants (TCAs), selective serotonin/noradrenaline reuptake inhibitors (SSRIs/SNRIs), monoamine oxidase inhibitors (MAOIs) and atypical agents.[14]

SSRIs/SNRIs

The mechanism of action involves the selective inhibition of reuptake of serotonin/noradrenaline from the synaptic cleft. The main advantage of SSRIs/SNRIs is an improved side effects profile in comparison with TCAs. They have fewer anticholinergic effects and are less sedating with minimal cardiovascular side effects. They are also safer in overdose compared to TCAs. Side effects include gastrointestinal upset and central effects, such as altered sleep, tremor, and headache.[2]

They inhibit cytochrome p450 enzymes resulting in increased levels of drugs such as warfarin, theophylline, phenytoin, benzodiazepines. Anaesthesia in patients taking SSRIs can, rarely, precipitate hypotension, arrhythmias, altered thermoregulation/postoperative shivering, and postoperative confusion. SSRIs may decrease platelet aggregation, but there is no clinical evidence of increased bleeding in the perioperative period.[6]

Extra-CNS effects and clinical applications

Cardiovascular system

Serotonin plays several roles, from the control of vascular resistance and blood pressure to the control of haemostasis and platelet function.[8] Evidence that serotonin modulates heart function is seen in patients with serotonin-producing carcinoid tumours. High serotonin levels can cause atrial fibrillation, mediated by cardiac 5-HT4 receptors. Ventricular remodelling in cardiac failure may also be mediated by these same cardiac receptors.[9] Piboserod is a 5-HT4 receptor antagonist currently under investigation as a treatment for atrial fibrillation and cardiac failure. New serotonin antagonists may also have potential anti-anginal benefits.[6]

Serotonin plays a pathological role in the cardiac valvulopathy due to appetite suppressants fenfluramine via 5-HT2B receptor activation. It has been suggested that the valvulopathy seen in carcinoid syndrome may have a similar aetiology.[8]

Haemostasis

Platelets have substantial vesicular serotonin stores but lack the enzymes to synthesise serotonin. They take up serotonin from the plasma via the serotonin transporter. Serotonin is secreted by the platelet dense granules during platelet activation and plays a role in promoting platelet aggregation and vasoconstriction of surrounding blood vessels facilitating haemostasis.[8]

Pulmonary

Serotonin is almost completely removed from the circulation in the lung, and pulmonary clearance prevents recirculation.[3] Serotonin helps with the control of the breathing and respiratory drive through its action on the brainstem and on the pulmonary vasculature. In pulmonary artery hypertension, hypoxia elevates plasma serotonin levels and likely increases 5-HT2B receptor expression on pulmonary artery endothelium. Increased 5-HT2B receptor signalling results in increased pulmonary vascular resistance. Serotonin may be implicated in the transient pulmonary vasoconstriction which occurs after a pulmonary thromboembolic event. Serotonergic abnormalities have also been found in nearly 50% of infants who have died from sudden infant death syndrome (SIDS).[8]

Endocrine

Serotonin mediates various aspects of endocrine function. It is responsible for central control of energy balance and central modulation of the hypothalamic-pituitary-adrenal (HPA) axis, as well as direct regulation of mammary gland development.[3,8]

Hypothalamic 5-HT2C receptors play a role in controlling energy balance and regulating glucose homeostasis. 5-HT2C and 5-HT1B receptors act by modulating melanocortin pathways, and serotonin release stimulates sympathetic nerves that innervate brown adipose tissue. 5-HT2C receptor agonists may be useful for treating obesity and diabetes. Serotonin also plays a role in setting metabolic rate and temperature control. In the adult mammary gland, serotonin regulates epithelial tight junctions and milk release.[3]

Gastrointestinal tract (GIT)

Serotonin regulates digestion at multiple levels within the GIT. Activation of taste-bud cells on the tongue causes serotonin release that transmit taste information to the CNS. Once food enters the GIT, peristaltic waves and intestinal secretion are modulated by serotonin.[3,6] Intestinal serotonin also regulates pancreatic enzyme release. Altered serotonin signalling has been linked to functional bowel disorders, such as irritable bowel syndrome (IBS). Drugs targeting both the 5-HT3 and 5-HT4 receptors have been used to treat IBS. In addition, excessive GIT serotonin release can activate 5-HT3 receptors on afferent vagal nerves that innervate brainstem vomiting centers.[8]

Genitourinary and reproductive systems

Serotonin increases ejaculatory latency and delays orgasm through 5-HT2C and 5-HT1B receptors, as a result SSRIs are prescribed off-label to treat premature ejaculation.[8] Serotonin modulates micturition in a similar fashion as it does ejaculation. It controls urinary function via actions in the brain and spinal cord, and it regulates parasympathetic input to the bladder and somatic input to the external urinary sphincter. SSRIs are used clinically to treat stress incontinence.[3]

Pregnancy

Increased serotonin levels are found in pregnancy and may play a role in the altered vascular physiology of pregnancy. Approximately tenfold increases in serotonin have been observed in the serum of preeclamptic women, and levels correlate with the severity of preeclampsia. Increased platelet activation and aggregation and decreased metabolism by monoamine oxidase is the proposed reason for this increase.

Ketanserin, a selective 5-HT2 antagonist, has been used in Europe as an antihypertensive. Its antihypertensive effect is like that of hydralazine, but with a lower incidence of side effects.[6] Serotonin also regulates uterine contraction through 5-HT2A receptors and has been shown promote uterine involution.[8]

Conflict of interest

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