Serotonin and interventions in intensive care.

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Abstract

Serotonin (5-hydroxytryptamine, 5-HT) plays two important roles in humans – one central and the other peripheral – depending on the location of the 5-HT pools of on either side of the blood-brain barrier. In the central nervous system, it acts as a neurotransmitter, controlling such brain functions as autonomic neural activity, stress response, body temperature, sleep, mood, and appetite. This role is very important in intensive care, as critically ill patients are usually under medications like opioids, antiemetics, antidepressants and other serotoninergic agents. High serotonin levels lead to altered mental status, deliria, rigidity, and myoclonus – together recognised as serotonin syndrome. In its role as a peripheral hormone, serotonin is unique in controlling the functions of several organs. It also has fundamental effects on haemostasis, vascular tone, heart rate, respiratory drive, cell growth and immunity. Serotonin regulates almost all immune cells in response to inflammation, following the activation of platelets.

Keywords: Neurotransmitter, Peripheral hormone, Energy metabolism, Immunoregulatory functions, Serotonin syndrome, Intensive care.

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Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is produced mainly in the serotoninergic neural network of the central nervous system, in the gastrointestinal (GI) tract, it is stored in platelets. Serotonin acts as both a neurotransmitter and as a peripheral hormone. The gut is the main endocrine organ in human body, where is almost 95 % of all the serotonin produced in enterochromaffin (EC) cells.

Materials and Methods

Peripheral serotonin synthesized by EC cells is taken up and stored in the platelets. Platelets have the capacity to store and release the 5-HT and thus regulate peripheral serotonin level. Under normal conditions the blood serotonin level is maintained at 1-5 ng/ml, but it can increase 1000-fold upon platelet activation in response to inflammation. Serotonin plays a role in hemostasis, thrombosis and in immune functions [1]. The main role of platelets is regulation of hemostasis following injury. The release of serotonin leads and activates the rolling and adhesion of neutrophils. When serotonin is depleted, this innate immune reaction of neutrophils is reduced. In the central nervous system, serotonin is produced by neurons located in the raphe nuclei in the brainstem. Serotonin regulates diverse behavioral manifestations such as mood, perception, memory and stress responses, as well as influencing parameters like circadian rhythms, body temperature and emesis. Nevertheless, most serotonin is located outside the CNS, where it modulates major organ functions such as heart rate, respiratory drive, vasoconstriction, intestinal motility, and secretion. Serotonin also plays a critical role in the endocrine secretion, in the control of energy balance and metabolism, as well as in the regulation of glucose homeostasis and lipid metabolism. 5-HT aids the regeneration of metabolic organs, e.g., liver regeneration following volume loss after resection. Serotonin is synthetized in two steps from tryptophan, an essential amino acid acquired from food. Serotonin cannot cross the blood-brain barrier and therefore central and peripheral serotonin form two distinct pools. Serotonin synthesis depends on the level of circulating tryptophan absorbed from the diet [2]. Tryptophan can cross the blood-brain barrier (Figure 1).

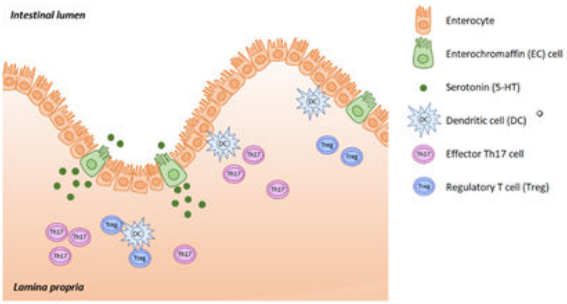

Figure 1. *Serotonin is synthesized in EC cells and the majority of it is released into the lamina propria with smaller amounts being released into the gut lumen.*

Serotonin syndrome

Serotonin syndrome (SS) is a potentially life-threatening condition, which is due to excessive serotonin action on the

central and peripheral nervous system. SS is an adverse drug reaction due to serotoninergic medication overdose, mostly via inadvertent interaction of several serotoninergic drugs. Especially from the point of view of intensive care specialists, this condition is not as rare as previously thought. SS occurs in the ICU most often because critically ill patients are given multiple serotoninergic agents. Many patients receive opioids, prokinetics and antidepressant medications. They are also routinely prescribed antiemetics, antibiotics and other drugs, where many pose a risk of serotonin release [3].

The main challenge is recognizing SS. Many critically ill patients already present an altered mental status – up to 80 % of ICU patients are delirious (confusion assessment method, CAM-ICU positive) and show sympathetic hyperactivity (hyperthermia, hypertension, tachycardia, diaphoresis). Moreover, patients often have nausea or diarrhea or suffer from neuromuscular excitation. But these symptoms may be due to a range of diverse causes including hyperthermia, leucocytosis, or delirium in septic patients, tachycardia or hypertension caused by pain, or withdrawal syndrome. Nausea, vomiting, or diarrhea are also caused by enteral nutrition, paralytic ileus and so on. Several diagnostic criteria for recognizing SS have been published. Among them Hunter's toxicity criteria seem to be the best, showing 84% sensitivity and 97% specificity (Table 1).

Table 1: *Hunter's toxicity criteria.*

The condition is exposure to a serotonin agent plus one of the following:
Spontaneous clonus
Inducible or ocular clonus and agitation or diaphoresis
Inducible or ocular clonus and increased muscle tone and temperature >38°C
Tremor and hyperreflexia

The activation of 5-HTR1A causes myoclonus, hyperreflexia, and changes to the mental status. But 5-HTR2A activation is dangerous, is responsible for tachycardia, hypertension, and can lead to renal failure, followed by fever and neuromuscular excitation.

The onset of SS ranges from several hours to several weeks following administration of serotoninergic drugs. It typically occurs soon (within 12 - 24 hours) after exposure to medication and resolves within 24 hours following discontinuation. This rapid onset and rapid resolution can help in differential diagnosis. Symptoms can be mild to life-threatening; if SS is recognized early and causative drugs are stopped immediately, the symptoms usually subside. Almost all patients improve with supportive therapy, but it is critical to take SS into account while making a diagnosis. Severe forms can end in death, mainly through rigidity, extreme hyperthermia, seizures and rhabdomyolysis. Fever is not centrally (hypothalamus) mediated, so antipyretics will not work physical cooling and non-depolarizing paralysis and intubation are necessary. The basic principle of treatment is to stop causative medications and follow up with high-quality supportive therapy. Only early diagnosis and treatment can prevent complications such as multiple organ dysfunction and death [4].

Results and Discussion

Differential diagnosis can discriminate SS from other toxidromes such as neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic syndrome, and sympathomimetic syndrome. More and more patients take antidepressants before hospitalization. Polypharmacy for chronic pain, common in more than 60% patients with depression, poses a risk of adverse drug interactions. Added to this is the serotoninergic medication in the ICU. Twenty- two different drugs with serotoninergic activity have been identified. When ICU patients develop changes in mental status accompanied by signs of neuromuscular excitation, it is crucial to promptly check the list of medications and stop all serotoninergic drugs without delay. When in doubt, drug interaction programs may help.

Table 2: *Drug potentially causing serotonin syndrome (SS).*

	Result from intrasynaptic serotonin excess	**Drug1**
1	Increased synthesis	L-tryptophan
2	Increased release	Amphetamines, Cocaine, Ecstasy, Opioids
3	Decreased reuptake	TCA: Amitriptyline, Imipramine etc.,
		SSRI: Sertraline, Fluoxetine, Citalopram etc.,
		SNRI: Venlaflaxine, Duoxetine
		Other antidepressants: Trazodone
		Opioids: Fentanyl, Tramadol etc.,

4	Decreased metabolism	MAOI: Moclobemide, Selegiline, Methylene blue
	CYP inhibitors (CYP3A4, CYP2C19)	Antibiotics/antimycotics: Linezolid, Ciprofloxacin, Fluconazole
5	5-HT receptors agonists	LSD, Triptans, Mirtazapine, Buspirone
6	Increased 5-HT receptor sensitivity	Lithium
7	Others	Antiemetics: Metoclopramide, Ondasetron etc.,
		Antimigraines: Carbamazepine, Triptanes
		Antiepileptics: Valproate

SSRI Selective serotonin reuptake inhibitors, SNRI Serotonin noradrenalin reuptake inhibitors, TCA tricyclic antidepressants, MAOI Monoamine oxidase inhibitors. LSD Lysergic acid diethylamide. It is highly challenging for clinicians to identify drug combinations that may increase the risk of SS. Avoiding these drug combinations is often not entirely possible – selecting the least distressing combinations is therefore crucial. SSRI are the most common agents associated with SS. Their concurrent use with other serotoninergic drugs increases the risk of SS. Early recognition of SS and discontinuation of the responsible drugs are vital for successful management of this serious adverse reaction. Once serotoninergic agents are removed, supportive care is the mainstay of treatment. Anxiety, agitation and seizure can be managed with benzodiazepines. Serotonin symptoms can be managed with the 5-HT1A/2A receptor antagonist cyproheptadine, a first-generation antihistamine with a sedative effect and anti-serotonin activity. But this agent is available only in the oral form; its intravenous alternative is chlorpromazine. Pain sources in the patient should be treated with appropriate analgesia. The aim is to avoid opioids with serotoninergic potential (fentanyl, oxycodone etc.). Benzodiazepines cause anxiolysis, amnesia, sedation and have an anticonvulsant effect. Dexmedetomidine, a centrally acting α2 agonist with sympatholytic, sedative, amnestic, anxiolytic, and analgesic properties, seems to be advantageous for sedation. There are two mechanisms by which dexmedetomidine may efficiently mitigate SS [5].

Conclusion

Serotonin regulates a wide range of physiological and pathophysiological processes in most human organs and plays an important role in immunity and in inflammation. New serotoninergic drugs have opened up the possibility of effectively managing a number of diseases. Intensive care specialists must take SS into account as early diagnosis has the potential to significantly improve a patient's prognosis.

Author Contribution

Writing review and editing, P.K., M.K; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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