European Journal of Pharmacology 753 (2015) 2–18

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Serotonin: A never-ending story

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ARTICLE INFO

Article history:
Accepted 16 October 2014
Available online 7 November 2014

Keywords:
Serotonin
Depression
Anxiety
Aggression
SSRI
Fluvoxamine

ABSTRACT

The neurotransmitter serotonin is an evolutionary ancient molecule that has remarkable modulatory effects in almost all central nervous system integrative functions, such as mood, anxiety, stress, aggression, feeding, cognition and sexual behavior. After giving a short outline of the serotonergic system (anatomy, receptors, transporter) the author's contributions over the last 40 years in the role of serotonin in depression, aggression, anxiety, stress and sexual behavior is outlined. Each area delineates the work performed on animal model development, drug discovery and development. Most of the research work described has started from an industrial perspective, aimed at developing animals models for psychiatric diseases and leading to putative new innovative psychotropic drugs, like in the cases of the SSRI fluvoxamine, the serenic eltoprazine and the anxiolytic flesinoxan. Later this research work mainly focused on developing translational animal models for psychiatric diseases and implicating them in the search for mechanisms involved in normal and diseased brains and finding new concepts for appropriate drugs.
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Contents

1. Serotonin, history, drugs

My career in serotonin research started in Groningen at the Biological Psychiatry laboratory of Professor Herman van Praag in 1973 where I contributed to the PhD research of Netty Bouhuys (Bouhuys, 1976). At that time the involvement of serotonin (5-hydroxytryptamine; 5-HT) in mental functions was only emerging after the first suggestions in the 1950s (Gaddum, 1954; Brodie et al., 1955). Initially much research was performed into the synthesis and degradation of this neurotransmitter. In the 1960s serotonin containing neurons were visualized using histochemical fluorescence techniques and via lesion experiments (Dahlström and Fuxe, 1964; 1965). It appeared that the 5-HT containing cell bodies were localized in groups of cells (called B groups) together creating the raphé system in the central nervous system (CNS). The neurons in these systems project both frontally and caudally. The frontally projecting neurons originate in the most rostral localized cell bodies; B5 and B8 (the medial raphé

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http://dx.doi.org/10.1016/j.ejphar.2014.10.031
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nucleus), B6 and B8 (the dorsal raphé nucleus) and B9, more diffusely localized around the lemniscus medialis. The caudally projecting neurons originate from cell bodies in B1-B3. Lesioning of the dorsal (DR) and medial raphé (MR) nuclei reduces the synthesis of 5-HT (Kuhar et al., 1971). There was some evidence at that time (Lorens and Guldberg, 1974) that the medial and dorsal raphé nuclei project to different areas in the forebrain; DR lesions led to decreases in serotonin turnover in the striatum, whereas MR lesions reduced it in the hippocampus. Bouhuys (1976) was interested in the role of the MR and DR in behavior. She found that simultaneous lesioning of the MR and DR in rats led to enhanced locomotor behavior in a new environment. The question of my research in this experiment was whether the enhanced locomotion was due to inactivation of the MR, the DR or both. It appeared that MR lesions led to enhanced locomotion, but not after DR lesions (Olivier, 1976). Both type of lesions led to reduction of 5-HT turnover in the forebrain. Others also found this differential effect of the DR and MR on locomotion (Jacobs et al., 1974). Although a direct correlation between a decrease in 5-HT activity and locomotion is not evident, it appears that different parts of the serotonergic system, projecting to different projection areas contribute differentially to behavior. The experiment described still used quite simple methods to study the relationship between behavior and serotonergic activity, but it already indicated that serotonin contributes in a rather subtle way to various behavioral systems.

Serotonin, a phylogenetically ancient signaling molecule (Hay-Schmidt, 2000), is the most widely distributed neurotransmitter in the brain (Dahlström and Fuxe, 1964; Steinbush, 1981), although its CNS content is less than 5% of the whole bodies content (Jacobs and Azmitia, 1992). In the following decades it has become clear that 5-HT signaling pathways are involved in essential brain functions including sensory processing, cognitive control, emotion regulation, autonomic control and motor activity. At the same time it is a target of many physiological regulatory mechanisms and modulators like gene transcription, neurotrophic peptides, steroids but also psychotropic drugs (Lesch and Waider, 2012). The surprising fact about the 5-HT system in the CNS is that, whereas in the entire mammalian CNS billions of neurons exist, serotonergic cells number only in the ten thousands in rats and cats and in the hundred thousands in man, representing a very tiny amount of all CNS neurons. However, their influence on their target sites goes far beyond these numbers. In the rat brain estimations suggest 6×10^6 serotonergic varicosities/mm^3 of cortical tissue. By extrapolation, this means that each serotonergic neuron projecting to the cortex may be responsible for 5×10^5 serotonergic varicosities, that each of their cortical target neurons receives ~200 varicosities, and that serotonergic terminals may account for as many as 1/500 of all axon terminals in rat cortex (Jacobs and Azmitia, 1992).

The present paper will particularly deal with the rostral serotonergic system (B5-B9) because these serotonergic systems seem to be involved in the modulatory role in higher mental functions, including mood, anxiety and fear, cognition and other functions, whereas the caudal system (B1-B3) mainly projects to the spinal cord and cerebellum and is involved in motor activity, pain control and regulation of autonomic processes (Jacobs and Azmitia, 1992).

Rostral serotonergic projections project to the forebrain innervating virtually all regions (Calizo et al., 2011). Two classes of fine and beaded fibers (D and M fibers, resp.) exist, originating from the dorsal and median raphé nuclei, resp. (Törk, 1990). The M fibers, also called the basket axon system, contain thick fibers without varicosities and originate in the MR. These M fibers form extensive (classic) synaptic connections and project heavily e.g. to cortical areas, and hippocampus. The other system, the varicose axon system (D fibers) originates in the DR, has thin fibers with lots of spindle-like varicosities. These fibers ramify extensively and are extremely diffuse. The small spindle-like boutons are present along the fibers and it is still doubtful whether real synaptic

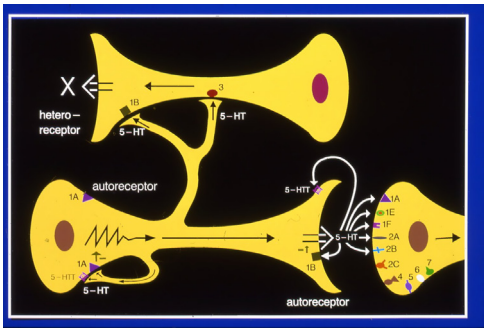

Fig. 1. Cartoon of a serotonergic neuron with a schematic depiction of the localization of 14 serotonergic receptors and the serotonergic transporter.

contacts are present. They mainly innervate the dorsal striatum, amygdala and prefrontal cortex. Although the functional role of both serotonergic systems is badly understood, there is evidence that they display a differential sensitivity for certain substituted amphetamines (including e.g. methylenedioxymethamphetamine (MDMA-ecstacy). The latter has been suggested to induce degeneration of the fine, varicose system, leaving the thick M system unaffected (Biezonski and Meyer, 2011; Parrott, 2013).

Although the raphé nuclei are generally described as 'serotonergic', large quantities of non-serotonergic cells emerge in these structures, including neurons transmitting glutamate, GABA, dopamine, nitric oxide and various neuropeptides (Adell et al., 2002). Numerous projections from different brain regions reach the raphé nuclei including glutamatergic, cholinergic, GABA-ergic, noradrenergic and various neuropeptidergic transmitters (Adell et al., 2002; Artigas, 2013a,b).

The serotonergic system contains at least 14 different serotonin classes of receptors (5-HT$_{1A, 1B, 1D, 1E, 1F; 2A, 2B, 2C, 3, 4, 5A, 5B, 6 \text{ and } 7}$) and a serotonin transporter (SERT)(Fig. 1). Except the 5-HT$_3$ receptor, gating a cation-permeable ion channel, all 5-HT receptors are G-protein coupled. The signaling via G-protein-coupled serotonin receptors is extremely diverse and we are still in the dark how these brain 5-HT receptors operate in real life (for an extensive review Millan et al. (2008)), but they generate many possibilities to modulate other systems in the brain, like the glutamatergic and GABA-ergic ones (Artigas, 2013b; Fink and Göthert, 2007). This diversity coupled to a complex and differential distribution of the various 5-HT receptor classes in the CNS brings 5-HT into a position where it may modulate various core functions in the brain. It can also easily be assumed that disruption of various aspects of serotonergic neurotransmission may lead to vulnerability or even pathology, including depression, anxiety disorders, schizophrenia, food disorders, chronic pain and others.

Some 5-HT receptors function as autoreceptors, some as heteroreceptors and some as both (5-HT$_{1A,1B}$). Although it is unclear whether every single 5-HT neuron in the brain is equipped with similar autoreceptors, for the DR and MR it is known that they have somatodendritically localized 5-HT$_{1A}$ autoreceptors, presynaptically localized 5-HT$_{1B}$ autoreceptors and 5-HT transporters, both localized at the cell body and the synapse (see Fig. 1). All 5-HT receptors are also localized postsynaptically as heteroreceptors, e.g. on glutaminergic and GABA-ergic cells (Adell et al., 2002; Artigas, 2013a,b).

If a serotonergic neuron fires, 5-HT is released into the synaptic cleft where it exerts its action on nearby pre- and postsynaptic serotonergic receptors. In order to terminate its action, 5-HT activity has to be terminated which is effectuated via reuptake of 5-HT by the serotonin transporter molecule (SERT), a complex molecule with 13 transmembrane loops located at the presynaptic and somatodendritic membranes of most (if not all) serotonergic neurons. After this uptake over the cell membrane via the SERT from the synapse, 5-HT is subsequently taken up by the vesicular

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