Neurobiology of Learning and Memory 136 (2016) 204–209

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Review

Effects of 5-HT-7 receptor ligands on memory and cognition

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ARTICLE INFO

Article history:
Received 8 July 2016
Revised 12 October 2016
Accepted 21 October 2016
Available online 22 October 2016

Keywords:
Serotonin
5-HT7 receptor
Agonist
Antagonist
Learning
Memory

ABSTRACT

The 5-HT7R is the most recently cloned serotonin receptor and thus one the least studied. Many drugs, experimental and in clinical use bind to 5-HT7 with high affinity, though their effects have yet to be clearly elucidated. Its physiological function, though not completely clear, is mostly associated with learning and memory, with both agonists and antagonists possessing subtle procognitive and promnesic properties. We consider it a promising area of research, though still in its infancy, which may one day lead to clinical benefits for patients with various afflictions characterised by cognitive dysfunction, particularly autism spectrum disorder, fragile X syndrome and Alzheimer's disease.

1. Introduction

Among the key neurotransmitters implicated in the modulation of fundamental neurophysiological processes such as memory, mood and sleep, few have been studied as extensively as serotonin. Considering the multitude of psychotropic drugs which exert their effects by directly or indirectly affecting serotonergic neurotransmission, this trend seems quite reasonable (Stahl, Lee-Zimmerman, Cartwright, & Morrissette, 2013). Each psychotropic drug class generally has a primary target, its interaction with which is considered necessary for therapeutic efficacy. Notable examples include the case of antipsychotics, which are dopamine D2 receptor antagonists and certain antiparkinsonian drugs, which are dopamine D2 agonists. However, none of these drugs is truly selective, and they display multiple interactions with other receptors (Stahl, 2010). Some of these may actually contribute to the drug's therapeutic effects, while others are responsible for many undesirable side effects. Serotonin receptors are frequently implicated in these "secondary interactions" and the newest member of their family, the one which has been most recently identified and cloned, 5-HT7, is no exception. A plethora of approved drugs act as potent 5-HT7 antagonists, many of which were marketed before the scientific community was even aware of the receptor's existence. In the case of risperidone and its metabolite paliperidone (Smith et al., 2006), as well as the ergot derived antiparkinsonian agents lisuride and bromocriptine (Toohey, Klein, Knight, Smith, & Teitler, 2009), the interaction is irreversible (Table 1). Specifically, the drugs in question act as irreversible antagonists as they form a covalent bond with the receptor, deactivating it permanently. The pharmacological effect is gradually reversed as new receptors are synthesized during the weeks following initial exposure. The clinical significance of 5-HT7 antagonism however is hotly debated and has yet to be clearly elucidated. The same is true of the receptor's physiological function (Gellynck et al., 2013). It does however seem to exert its most profound effects on memory processes (Meneses, 2013), which we seek to clarify in this review.

1.1. 5-HT7 receptor structure, function and distribution

The 5-HT7 receptor is a typical G-protein coupled receptor, signaling via the Gs α subunit of the G-protein complex, leading to the activation of adenyl cyclase and an increase in the intracellular concentration of cAMP, which is the principle second messenger involved. Thus, 5-HT7 agonists would be expected to enhance memory consolidation by increasing phosphorylation of the CREB transcription factor, though the evidence is contrasting with this hypothesis. It can also be coupled to a G11/12 subunit, in which case its activation increases Rho kinase activity. Rho activates the mitogen activated (MAP) kinase cascade promoting neuronal survival and proliferation. In the hippocampus particularly the aforementioned cascade culminates in the activation of ERK and

Abbreviation: 5-HT7R, 5-HydroxyTyptamine Receptor 7.

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http://dx.doi.org/10.1016/j.nlm.2016.10.011
1074-7427/

Table 1
5-HT7 antagonists currently marketed.

Drug name	Official indication/classification	Year of discovery/ approval	Other targets	Effects attributed to 5-HT7 antagonism
Clomipramine	Tricyclic Antidepressant	1964 (Discovery)	SERT/5-HT2A/NET(metabolite)/D2	Not investigated Generally considered superior to other TCAs for OCD
Amitriptyline	Tricyclic Antidepressant	1960	5-HT2A/5-HT2C/5-HT6/H1/a1/M1-M5/SERT/ NET	Not investigated. Generally considered superior to other TCAs for MDD
Amoxapine	Tricyclic Antidepressant	1992 (FDA approval	5-HT2A/5-HT2C/D2/D3/M1-M5/H1/a1	Contribution to its profile as a mixed antidepressant/antipsychotic
Lisuride (Irreversible)	Dopamine Agonist, Ergot Derived	1975	D2/D3/5-HT2A/5-HT1A (agonist)	None
Bromocriptine (Irreversible)	Dopamine Agonist, Ergot Derived	1967	D2/D3/5-HT1A/a1/5-HT2A (agonist)	None
Risperidone (Irreversible)	Atypical Antipsychotic	1993	D2/D3/5-HT2A/H1/a1/a2	Efficacy as adjunct in MDD, efficacy for negative symptoms, efficacy for autism-official indication
Paliperidone (Irreversible)	Atypical Antipsychotic	2006	D2/D3/D4/5-HT2A/H1/a1/a2	Efficacy as adjunct in MDD, efficacy for negative symptoms, efficacy for autism
Aripiprazole	Atypical Antipsychotic (partial agonist at D2) 39	2002	D2/5-HT1A/5-HT2A/a1	Efficacy as adjunct in MDD, efficacy for negative symptoms, efficacy for autism-official indication
Clozapine	Atypical Antipsychotic	1971 (initial approval)	5-HT2A/5-HT2C/5-HT2B/5-HT3/5-HT4/5-HT6/ 5-HT7/D2/D3/D4/H1/H2/a1/a2/M1-M5/δ opioid	Not applicable/the most promiscuous drug on the market 40
Amisulpride	Atypical Antipsychotic	1986	D2/D3	Efficacy for dysthymia and negative symptoms at low dosage
Lurasidone	Atypical Antipsychotic	2010	D2/D3/5-HT2A	Efficacy for MDD and bipolar depression, as well as cognitive symptoms of schizophrenia
Vortioxetine	Antidepressant	2013	SERT/5-HT1A/5-HT2A/5-HT3	Prolongation of Circadian Rhythms

facilitation of hippocampal neurogenesis (Guseva, Wirth, & Ponimaskin, 2014). Also, Rho activation can, via the RhoBTB3 molecule, prevent the degradation of 5-HT7 receptors (Matthys, Van Craenenbroeck, Lintermans, Haegeman, & Vanhoenacker, 2012). In the hippocampal CA3 area 5-HT7 receptor activation also results in enhancement of the hyperpolarization induced cation current (Ohmura et al., 2015) (Ih, mediated by non-selective cation channels similar to the cardiac pacemaker current, If), which diminishes excitatory post synaptic potentials and thus reduces neuronal excitability. The inhibition of such inhibitory 5-HT7 mediated effects may explain the beneficial effects of 5-HT7 antagonists on cognition and memory (Ciranna & Catania, 2014). In the limbic system 5-HT7 receptors coupled to G11/12 also interact with RhoBTB3, which prevents receptor degradation and may potentiate 5-HT7 mediated effects such as enhancement of working memory, self-control and reduction of impulsivity, effects doubtlessly relevant to the treatment of autism (Costa et al., 2012).

As with most GPCRs, chronic agonist exposure results in down-regulation. Thus prolonged use of agonists may theoretically produce effects similar to acute antagonist exposure, as in both cases the receptor's effect on intracellular signaling cascades is diminished, due to reduced receptor density in the former case and because of reduced endogenous ligand binding in the latter (Srinivas, Subhash, & Vinod, 2001; Thomas et al., 1998). Furthermore, acute exposure to high agonist concentrations may produce immediate desensitization via phosphorylation and arrestin binding (Carton et al., 2015; El Mansari, Lecours, & Blier, 2015; Tokarski et al., 2012). Other researchers have also observed that the palmitoylation of the receptor increases its constitutive activity, conferring resistance to the effects of silent antagonists and necessitating the use of inverse agonists to restore baseline 5-HT7 mediated neurotransmission (Guseva et al., 2014). Selective 5-HT7 ligands have been developed for research purposes, though their affinity is low and their selectivity also leaves much to be desired. Thus radioligand labelling studies of 5-HT7 receptors are not currently feasible, which may explain the relative paucity of literature regarding its utilization in animal studies (Zimmer & Billard, 2014). Typically, molecules with a dissociation constant from 5-HT7 in the nanomolar range are promiscuous and highly potent serotonergic drugs. However, since these findings novel radioligand compounds have been developed, and may accelerate research into the 5-HT7 receptors (Zimmer & Billard, 2014).

It is the most scarcely expressed among the serotonin receptors, and its affinity for the endogenous ligand is higher than other, more ubiquitous subtypes. It is expressed mainly in the hippocampus (with higher density in the CA-1 area than in the CA-3), the prefrontal cortex (Aubert et al., 2013) and the thalamus, where it is located postsynaptically and commonly forms heterodimers with 5-HT1A (Nativio et al., 2015). The aforementioned GPCR is Gi coupled and its activation may increase hyperpolarizing K+ currents, a mechanism of action for all intents and purposes opposite to that of 5-HT7. Since serotonin binds to 5-HT1A more avidly than to 5-HT7, we could assume that the latter's role is to counteract the inhibitory effects of the former when synaptic serotonin concentration is markedly increased.

1.2. 5-HT7 receptors, memory and cognition

Several reviews (Meneses, 2015), have been relatively recently published on the role of 5-HT7 receptors, with great emphasis placed on its modulatory role regarding memory and other higher cognitive functions. They accurately summarize relevant animal studies, noting the inconclusive and often conflicting results, while also addressing the paradox that both 5-HT7 agonists and antagonists have promnesic and pro-cognitive effects (Meneses, 2014).

The same researchers (Meneses et al., 2015) have shown in well-designed rat studies that the selective 5-HT7 agonist LP-211 significantly enhances instrumental learning, increased the efficiency of Pavlovian autoshaping sessions and attenuated the detrimental effects of scopolamine (a non-selective antimuscarinic agent with profound amnestic properties) during coadministration. Afterwards the animals were sacrificed and it was found that LP-211 administration greatly increased cAMP concentrations in the prefrontal cortex but not in the hippocampus or raphe nuclei, where it prevented the increase in cAMP associated with scopo-