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The serotonergic 5-HT4 receptor: A unique modulator of hippocampal synaptic information processing and cognition

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ABSTRACT

Serotonin (5-hydroxytryptamine, 5-HT) contributes in multifarious ways to the regulation of brain function, spanning key aspects such as the sleep-wake cycle, appetite, mood and mental health. The 5-HT receptors comprise seven receptor families (5-HT_{1-7}) that are further subdivided into 14 receptor subtypes. The role of the 5-HT receptor in the modulation of neuronal excitability has been well documented. Recently, however, it has become apparent that the 5-HT_4 receptor may contribute significantly to cognition and regulates less ostensible aspects of brain function: it engages in metaplastic regulation of synaptic responsiveness in key brain structures such as the hippocampus, thereby specifically promoting persistent forms of synaptic plasticity, and influences the direction of change in synaptic strength in selected hippocampal subfields. This highly specific neuromodulatory control by the 5-HT_4 receptor may in turn explain the reported role for this receptor in hippocampus-dependent cognition.

In this review article, we describe the role of the 5-HT_4 receptor in hippocampal function, and describe how this receptor plays a unique and highly specialised role in synaptic information storage and cognition.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is one of the most studied neurotransmitters, due to its involvement in general physiological functions such as sleep and pain, but also because serotonin is connected to human diseases such as depression, schizophrenia and obsessive compulsive disorders (Filip & Bader, 2009; Martinowich & Lu, 2008; Nordquist & Oreland, 2010). Furthermore, 5-HT_4 receptors may also play a role in Alzheimer's disease (AD) as it has been shown that 5-HT_4 receptor expression is reduced in patients that suffer from AD and activation of these receptors inhibits biochemical cascades that lead to AD (Nirogi et al., 2015; Ramirez, Lai, Tordera, & Francis, 2014; Tesseur et al., 2013; Wong, Reynolds, Bonhaus, Hsu, & Eglen, 1996).

All 5-HT receptors are expressed within the hippocampus (Berumen, Rodríguez, Miledi, & García-Alcocer, 2012). The limbic system and thereby, also the hippocampus are major targets of serotonergic projections (Hensler, 2006). Of the eighteen 5-HT receptors currently identified, it has emerged that particularly the 5-HT_4 receptor plays an important and differentiated role in processes related to learning and memory (Bockaert, Claeysen, Compan, & Dumuis, 2004; Buhot, Martin, & Segu, 2000; Kemp & Manahan-Vaughan, 2005; Lamirault & Simon, 2001; Twarkowski, Hagena, & Manahan-Vaughan, 2016) that in turn critically depend on information processing at the level of the hippocampus.

5-HT_4 receptors are localized post-synaptically within the hippocampus (Vilaró, Cortés, & Mengod, 2005; Vilaró et al., 1996; Waeber, Sebben, Nieoullon, Bockaert, & Dumuis, 1994). Activation of 5-HT_4-receptors results in increased neuronal excitability that is mediated by activation of adenylate cyclase (Eglen, Wong, Dumuis, & Bockaert, 1995). This leads to an increase of protein kinase A (PKA) and cyclic adenosine monophosphate (cAMP) levels and the inhibition of K^+-channels (Ansanay, Dumuis, Sebben, Bockaert, & Fagni, 1995; Bockaert et al., 1998; Torres, Chaput, & Andrade, 1995). Activation of 5-HT_4 receptors also reduces afterhyperpolarization currents in CA1 pyramidal cells (Torres, Arfken, & Andrade, 1996) that contributes to increased excitability of neurons (Nicoll, 1988). Interestingly, besides the known activation of G-protein coupled signalling cascades, 5-HT_4 receptor activation also initiates pathways that are G-protein independent (Bockaert, Claeysen, Compan, & Dumuis, 2011) such as phosphorylation of the 5-HT_4 receptor-associated non-receptor tyrosine kinase Src

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(Src: sarcoma), that leads to the activation of extracellular signal-regulated kinase (ERK) (Barthet et al., 2007). ERK in turn is critically involved in hippocampal synaptic plasticity, most specifically in long-term depression (LTD) of synaptic efficacy (Norman, Thiels, Barrionuevo, & Klann, 2000; Thiels & Klann, 2001). 5-HT_4 receptor activation also stimulates hippocampal expression of plasticity/learning-related proteins such as BDNF, AKT, CREB expression, as well as neurogenesis in the dentate gyrus (Pascual-Brazo et al., 2011).

In addition to direct effects on neuronal function, 5-HT_4 receptors indirectly influence neuronal activity through modulation of the release of different neurotransmitters, such as γ-aminobutyric acid (GABA) (Bijak & Misgeld, 1997), acetylcholine (ACh) (Consolo, Arnaboldi, Giorgi, Russi, & Ladinsky, 1994; Matsumoto et al., 2001; Mohler et al., 2007; Siniscalchi, Badini, Beani, & Bianchi, 1999; Yamaguchi, Suzuki, & Yamamoto, 1997) or dopamine (DA) (Steward et al., 2012; Bockaert, Claeysen, Compan, & Dumuis, 2008; Bockaert et al., 2004).

This high degree of neurotransmitter regulation and action on diverse signalling cascades, as well as on plasticity/learning-related proteins is likely to confer the 5-HT_4 receptor with its particular capacity to regulate cognition and learning. In this review we will examine this possibility from the perspective of the hippocampus, and most particularly with regard to synaptic plasticity.

2. 5-HT_4 receptors are involved in cognitive diseases

5-HT_4 receptors are implicated in diseases that involve impairments of cognitive functions, such as depression-related disorders (Porter, Gallagher, Thompson, & Young, 2003) or AD (Madsen et al., 2011; Morris et al., 2001), whereby cognitive impairments in these diseases are accompanied by a downregulation of 5-HT_4 receptors (Reynolds et al., 1995; Tsang et al., 2010; Wong et al., 1996). Furthermore, treatment with 5-HT_4 receptor agonists alleviates symptoms associated with depression (Mendez-David et al., 2014; Samuels et al., 2016) and at the same time improves cognitive deficits in AD (Claeysen, Bockaert, & Giannoni, 2015; Giannoni et al., 2013; Werner & Coveñas, 2016; Wilkinson, Windfeld, & Colding-Jørgensen, 2014).

But how might 5-HT_4 receptor activation counteract the negative symptoms that occur in diseases such as AD? Amyloid-beta (Aβ) peptides accumulate in the brain of AD patients and are believed to contribute importantly to the pathophysiology of the disease (Selkoe & Hardy, 2016). Aβ is generated by the cleavage of amyloid precursor protein (APP) by β- and γ-secretases (De Strooper, Vassar, & Golde, 2010; Turner, O'Connor, Tate, & Abraham, 2003; Wolfe, De Los Angeles, Miller, Xia, & Selkoe, 1999). Another pathway emanating from APP, termed the non-amyloidogenic pathway, leads to the creation of the extracellular soluble fragment of APP (sAPPα) and impedes the generation of Aβ through activation of α- and γ-secretases (Postina et al., 2004). Whereas Aβ has been associated with the negative effects of AD, sAPPα has been shown to have neurotrophic and neuroprotective, as well as positive cognitive, effects. Interestingly, activation of 5-HT_4 receptors is important in promoting the necessary steps resulting in the cleavage of APP and the subsequent release of sAPPα (Cachard-Chastel et al., 2007; Cho & Hu, 2007; Lezoualc'h, 2007). This may thus comprise the means whereby 5-HT_4 receptor activation ameliorates AD symptoms. Furthermore, in AD, a reduction in cholinergic function is a major cause of cognitive deficits (Pákáski & Kálmán, 2008). Thus, activation of 5-HT_4 receptors may improve cognitive symptoms through their known ability to boost ACh release (Bijak & Misgeld, 1997), and thus compensate, to some extent, for deficits in cholinergic transmission in AD.

3. The role of 5-HT_4 receptors in hippocampus-dependent cognition and learning behavior

At the level of cognition, numerous studies on 5-HT_4 receptors have revealed an intrinsic role for this receptor in a large variety of behavioral learning tasks. Tables 1 and 2 show the very distinctive effects of either activation or inhibition of 5-HT_4 receptors on hippocampus-dependent tasks, respectively (Bockaert et al., 2004; King, Marsden, & Fone, 2008). Most strikingly, 5-HT_4 receptors play an important role in hippocampus-dependent learning and memory (Buhot, 1997; Buhot, Malleret, & Segu, 1999; Kemp & Manahan-Vaughan, 2004; King et al., 2008; Kulla & Manahan-Vaughan, 2002) such that activation of 5-HT_4 receptors supports enhancing effects in cognitive functions (Kemp & Manahan-Vaughan, 2005; Lamirault & Simon, 2001; Lelong, Dauphin, & Boulouard, 2001; Marchetti et al., 2004). Moreover, 5-HT_4 receptors have been proposed as neuronal markers for learning and memory: active cognitive processing results in increased expression of 5-HT_4 receptors in the corresponding brain regions (Manuel-Apolinar et al., 2005; Meneses, 2015). Furthermore, hip-

Table 1
Effect of 5-HT_4 receptor antagonism on hippocampus-dependent learning tasks.

Hippocampus-dependent learning task	Antagonist	Effect on plasticity	Reference
Olfactory association learning	RS67532	Facilitates procedural memory if applied at onset of training	Marchetti et al. (2004)
	GR125487	Impairs enhanced short-term memory induced by the 5-HT_4 receptor agonist BIMU 1	Letty et al. (1997)
	RS67532	When injected before 3rd training session, impairment in performance in subsequent sessions	Marchetti, Dumuis, Bockaert, Soumireu-Mourat, and Roman (2000)
Morris water maze	RS67532	Impairs positive effects of the 5-HT_4 receptor agonist, RS 67333, on cognitive dysfunction induced by the muscarinic antagonist atropine	Fontana et al. (1997)
Object recognition	SDZ 205557	Impairment of improved performance induced by a 5-HT_4 receptor agonist	Moser et al. (2002)
	GR 125487	Impairment of improved place and object recognition in young and old adult rats induced by the 5-HT_4 receptor agonist, RS 67333	Lamirault and Simon (2001)
Passive/inhibitory Avoidance	SDZ 205557, GR 125487	Application immediately after training results in amnesic effect	Galeotti, Ghelardini, and Bartolini (1998)
Autoshaping task	SDZ 205557, GR 125487D	Prevents impairment of conditioned response caused by post-training injection of 5-HT_4 agonists	Meneses and Hong (1997)
Spatial alternation task	GR 125487	Reverses effects of improved memory in a delayed alternation task induced by a 5-HT_4 receptor agonist	Mohler et al. (2007)
Five-choice serial reaction time task	SL65.0155	Increased latency and reduced recurring responses as well as reduction of incorrect trials on 2nd day of treatment.	Hille, Bate, Davis, and Gonzalez (2008)