Involvement of 5-HT_{2A/2B/2C} Receptors on Memory Formation: Simple Agonism, Antagonism, or Inverse Agonism?

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SUMMARY

1. The 5-HT$_2$ receptors subdivision into the 5-HT$_{2A/2B/2C}$ subtypes along with the advent of the selective antagonists has allowed a more detailed investigation on the role and therapeutic significance of these subtypes in cognitive functions. The present study further analyzed the 5-HT$_2$ receptors role on memory consolidation.

2. The SB-200646 (a selective 5-HT$_{2B/2C}$ receptor antagonist) and LY215840 (a nonselective 5-HT$_2$ receptor antagonist) posttraining administration had no effect on an autoshaped memory consolidation. However, both drugs significantly and differentially antagonized the memory impairments induced by 1-(3-chlorophenyl)piperazine (mCPP), 1-naphtyl-piperazine (1-NP), mesulergine, or N-(3-trifluoromethylphenyl) piperazine (TFMPP).

3. In contrast, SB-200646 failed to modify the facilitatory procognitive effect produced by (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) or ketanserin, which were sensitive to MDL100907 (a selective 5-HT$_{2A}$ receptor antagonist) and to a LY215840 high dose.

4. Finally, SB-200646 reversed the learning deficit induced by dizocilpine, but not that by scopolamine; while SB-200646 and MDL100907 coadministration reversed memory deficits induced by both drugs.

5. It is suggested that 5-HT$_{2B/2C}$ receptors might be involved on memory formation probably mediating a suppressive or constraining action. Whether the drug-induced memory impairments in this study are explained by simple agonism, antagonism, or inverse agonism at 5-HT$_2$ receptors remains unclear at this time.

6. Notably, the 5-HT$_2$ receptor subtypes blockade may provide some benefit to reverse poor memory consolidation conditions associated with decreased cholinergic, glutamatergic, and/or serotonergic neurotransmission.

KEY WORDS: autoshaping; 5-HT$_{2B/2C}$ receptors; 5-HT$_{2A}$; learning consolidation; serotonin; rats.

INTRODUCTION

Evidence from aplysia to human studies indicates that serotonin (5-hydroxytryptamine; 5-HT) system mediate learning and memory processes (Barbas et al., 2002). Even though the precise receptors and mechanisms have not
been elucidated yet. 5-HT receptors characterized so far in mammals, i.e., 5-HT\textsubscript{1} through 5-HT\textsubscript{7} subfamilies (Barnes and Sharp, 1999; Hoyer \textit{et al.}, 1994, 2002), show a regional distribution in brain areas implicated in learning and memory, such as hippocampus, amygdala, and cortex (see Meneses, 1999, 2001, for reviews). 5-HT receptors involvement in different learning and memory tasks, using different schedules for drug administration, doses (Meneses, 1999), and inverse agonists (Harvey, 1996), has documented, raising the possibility that inverse agonism may actually have physiological implications and even a possible impact in drug development (De Ligt \textit{et al.}, 2000). Certainly, whether or not different stages of the learning process have a link with changes in constitutive activity of 5-HT receptors remains open for investigation and speculative in the light of the available evidence, particularly in the case of 5-HT\textsubscript{2A/2B/2C} receptors. Interestingly, the 5-HT\textsubscript{3} receptor subdivision into the 5-HT\textsubscript{2A/2B/2C} categories (Hoyer \textit{et al.}, 1994; Martin \textit{et al.}, 1998), along with the advent of the selective antagonists MDL100907 (5-HT\textsubscript{2A}) and SB-200646 (5-HT\textsubscript{2B/2C}), has allowed a more detailed investigation on the role and therapeutic significance of these subtypes in cognitive functions. The amino acid sequences of 5-HT\textsubscript{2} receptors (Barnes and Sharp, 1999; Martin \textit{et al.}, 1998) have a high degree of homology within the seven transmembrane domains, being structurally distinct from other 5-HT receptors, sharing a characteristic of all genes in having either two (5-HT\textsubscript{2A} and 5-HT\textsubscript{2B} receptors) or three (5-HT\textsubscript{2C}) introns in the coding sequence. All three are coupled positively, via G\textsubscript{q}, to phospholipase C and increased accumulation of inositol phosphates and mobilize intracellular Ca\textsuperscript{2+}; though, 5-HT\textsubscript{2B} receptor in the gut is not associated with G\textsubscript{q} and the phospholipase C pathway.

As above mentioned, whether 5-HT\textsubscript{2A/2B/2C} an agonistic, antagonistic, and/or inverse agonistic action modulates learning and memory is unclear. For instance, post-training administration of 5-HT\textsubscript{2A/2B/2C} receptor drugs with moderate to high affinity at 5-HT\textsubscript{2} receptors, including 1-(3-chlorophenyl)piperazine (mCPP), mesulergine, 1-(naphtyl)piperazine (1-NP), and N-(3-trifluoromethylphenyl)piperazine (TFMPP), impaired memory consolidation, while (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) and ketanserin improved performance (see Meneses, 1999). Accordingly, the effects induced by all these drugs were blocked by MDL100907, a selective 5-HT\textsubscript{2A} receptor antagonist (Kehne \textit{et al.}, 1996). Since most of the above compounds also display relatively high affinity at 5-HT\textsubscript{2B/2C} receptors (see Table I), a possible role for these receptors in learning was hypothesized (Meneses \textit{et al.}, 1997). To further explore this hypothesis, the present study analyzed the effects of selective 5-HT\textsubscript{2B/2C} receptor antagonist, SB-200646 (Kennett, 1993; Shen \textit{et al.}, 1993), and those of the nonselective 5-HT\textsubscript{2/7} receptor antagonist, LY215840 (Cushing \textit{et al.}, 1996), on a pavlovian/instrumental autoshaping test (an associative learning task, see Meneses, 2002, for review), which combines both classical (pavlovian) conditioning (i.e., the pairing of a light lever with the delivery of food) and instrumental conditioning (i.e., delivery of food upon pressing a lever) procedures. Likewise, SB-200646 or LY215840 were coadministered with mCPP, mesulergine, 1-NP, TFMPP, DOI or ketanserin. Furthermore, in order to model the potential therapeutic benefits of 5-HT\textsubscript{2} receptor blockade in some types of dementias related with learning and memory dysfunctions, e.g., Alzheimer’s disease, it also determined the SB-200646 effects alone and in