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Review article

Antagonism of the 5-HT_6 receptor – Preclinical rationale for the treatment of Alzheimer's disease

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ABSTRACT

Antagonism of the 5-HT_6 receptor is a promising approach for the symptomatic treatment of Alzheimer's disease (AD). There is compelling preclinical evidence for the procognitive potential of 5-HT_6 receptor antagonists and several compounds are in clinical development, as adjunct therapy to acetylcholinesterase inhibitors (AChEIs). This manuscript summarizes the scientific rationale for the use of 5-HT_6 receptor antagonists as AD treatment, with some focus on the selective and high-affinity 5-HT_6 receptor antagonist idalopirdine (Lu AE58054).

The 5-HT_6 receptor is enriched in brain regions that mediate cognition, where expression predominates on glutamatergic and GABAergic neurons and subsets of GABAergic interneurons. It is proposed that 5-HT_6 receptor antagonism modulates the balance between neuronal excitation (glutamate) and inhibition (GABA), which may have widespread implications for neurotransmission and neuronal activity. This is supported by preclinical studies showing that 5-HT_6 receptor antagonists increase concentrations of multiple neurotransmitters, and strengthened by recent evidence that idalopirdine facilitates neuronal oscillations and contributes to the recruitment of several neuronal networks relevant in cognition. Some of these effects are observed with idalopirdine monotherapy, whereas others require concomitant treatment with an AChEI. Several hypotheses for the mechanism underlying the synergistic actions between 5-HT_6 receptor antagonists and AChEIs are discussed. Collectively, the current evidence suggests that 5-HT_6 receptor antagonism adds a unique, complementary mechanism of action to that of AChEIs. The facilitation of multiple neurotransmitters and neuronal activity in brain regions that mediate cognition, and the synergy with AChEIs, are proposed to mediate the procognitive effects of 5-HT_6 receptor antagonists in AD patients.

Contents

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Abbreviations

5-HT_6 receptor	5-hydroxytryptophan 6 receptor
5-HT_{3a} receptor	5-hydroxytryptophan 3a receptor
5-HT	5-hydroxytryptophan (serotonin)
ACh	acetylcholine
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ANOVA	analysis of variance
CB	calbindin
CNS	central nervous system
CR	calretinin
BOLD	blood oxygen level dependent
DA	dopamine
DPZ	donepezil
dBB	diagonal band of Broca
DRN	dorsal raphe nucleus
(q)EEG	(quantitative) electroencephalogram
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
IDL	idalopirdine
MoA	mode of action
nAChα7 receptor	α7 nicotinic acetylcholine receptor
NE	noradrenaline
NMDA	N-methyl-D-aspartate
nPO	nucleus pontis oralis
PK	pharmacokinetic
PV	parvalbumin
SEM	standard error of means
SST	somatostatin
Veh	vehicle
VIP	vasoactive intestinal peptide

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is a chronic, debilitating disorder with a significant impact on patients, caregivers and society. The prevalence of AD is steeply increasing due to the ageing population worldwide and significant efforts are being put into the development of novel therapeutic approaches. Currently, there is great emphasis on the development of disease-modifying therapies targeting pathological accumulation of either amyloid or tau proteins, key hallmarks of the pathogenesis of AD. So far, development of these disease-modifiers has been unsuccessful and there is a pressing need for more effective treatments to ameliorate symptoms.

Currently available symptomatic treatments for AD belong to two categories, targeting either cholinergic or glutamatergic signaling. Progressive degeneration of forebrain cholinergic neurons has long been understood to contribute to cognitive decline in AD (Davies and Maloney, 1976; Whitehouse et al., 1982). The use of acetylcholinesterase inhibitors (AChEIs; donepezil, rivastigmine and galantamine), inhibiting the breakdown of the neurotransmitter acetylcholine (ACh), remains the standard therapeutic approach to compensate for this loss of ACh. Memantine, an NMDA receptor antagonist aiming to correct an imbalance in glutamatergic signaling, represents an alternative possibility. Despite the fact that these agents improve cognition, function and even selected behavioral symptoms in AD patients, a significant unmet need remains (Birks and Harvey, 2006; Raina et al., 2008; Tan et al., 2014). AChEIs and memantine are increasingly used in combination, reflecting the growing understanding that a disease with a complex pathophysiology is best managed by combining several, complementary, approaches. Indeed, AD is characterized by degeneration of multiple neurotransmitter systems and a treatment targeting several of these and/or complementing existing therapies is expected to provide additional benefit. The current review discusses a novel concept for the treatment of AD - antagonism of the serotonin 6 (5-HT_6) receptor, which works through the regulation of multiple neurotransmitter systems and neuronal networks and demonstrates additional efficacy when combined with AChEI treatment.

2. The 5-HT_6 receptor and cognition

In the search for novel therapeutic approaches to ameliorate the cognitive decline in AD, the serotonergic system has gained increasing attention (Geldenhuys and Van der Schyf, 2011; Leiser et al., 2015). Indeed, serotonin plays an important role in the regulation of learning and memory (Meneses, 2013; Meneses and Liy-Salmeron, 2012; Schmitt et al., 2006) and there is substantial evidence for degeneration and dysfunction of the serotonergic system in AD (Arai et al., 1984; Bowen et al., 1983; Cross et al., 1983; Ichimiya et al., 1986; Lai et al., 2002; Nazarali and Reynolds, 1992). The serotonergic system provides a multitude of entry points for pharmacological intervention, including seven serotonin (5-HT) receptor families (5-HT_1 – 5-HT_7), together containing 14 receptors. Of the 14 known 5-HT receptor subtypes, the 5-HT_6 receptor has emerged as a particularly promising target for the treatment of cognitive disorders, due to a number of distinctive features described below (Benhamu et al., 2014; Mitchell and Neumaier, 2005; Ramirez, 2013; Upton et al., 2008).

The 5-HT_6 receptor was discovered in 1993 as a G-protein coupled receptor, positively linked to adenylate cyclase via the G-protein Gαs (Monsma et al., 1993; Ruat et al., 1993). Henceforth, the classical definition of agonist/antagonist on the 5-HT_6 receptor is based on the respective activation/inhibition of adenylate cyclase and the subsequent change in cellular cAMP levels. Later studies have revealed several alternative intracellular signaling cascades, including coupling to Gαo/Gi, regulation of Ca^{2+} signaling via a G-protein and coupling to Fyn tyrosine kinase and the mTOR pathway (Meffre et al., 2012; Riccioni et al., 2011; Wang et al., 2016; Yun et al., 2007; Zhang et al., 2003). The functional significance of each of the intracellular signaling cascades in different biological contexts and brain regions remains to be investigated as well as their mode of engagement by the various 5-HT_6 receptor ligands. Furthermore, constitutive activity of the 5-HT_6 receptor has been described in certain cellular systems, which suggests that 5-HT_6 receptor inhibition could also be achieved through inverse agonism resulting in neuropharmacological effects that are independent of the endogenous serotonergic tone (Duhr et al., 2014; Romero et al., 2007).

In contrast to several other members of the 5-HT receptor family, the 5-HT_6 receptor has no known functional isoforms. A single-nucleotide polymorphism (SNP) was identified in a non-coding region of the gene (C267T) and, in a selected few studies, linked with disorders such as AD, Parkinson's disease (PD) and schizophrenia (Messina et al., 2002; Tsai et al., 1999a, 1999b) and the response to treatment in affective disorders (Lee et al., 2005; Yu et al., 1999). These association studies remain to be replicated and the functional significance of the silent polymorphism is unknown.