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Treatment of cognitive dysfunction in major depressive disorder—a review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetine

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ABSTRACT

Although major depressive disorder is primarily considered a mood disorder, depressed patients commonly present with clinically significant cognitive dysfunction that may add to their functional disability. This review paper summarizes the available preclinical data on the effects of antidepressants, including monoamine reuptake inhibitors and the multimodal antidepressant vortioxetine, in behavioral tests of cognition such as cognitive flexibility, attention, and memory, or in potentially cognition-relevant mechanistic assays such as electroencephalography, *in vivo* microdialysis, *in vivo* or *in vitro* electrophysiology, and molecular assays related to neurogenesis or synaptic sprouting. The available data are discussed in context with clinically relevant doses and their relationship to target occupancy levels, in order to evaluate the translational relevance of preclinical doses used during testing. We conclude that there is preclinical evidence suggesting that traditional treatment with monoamine reuptake inhibitors can induce improved cognitive function, for example in cognitive flexibility and memory, and that the multimodal-acting antidepressant vortioxetine may have some advantages by comparison to these treatments. However, the translational value of the reviewed preclinical data can be questioned at times, due to the use of doses outside the therapeutically-relevant range, the lack of data on target engagement or exposure, the tendency to investigate acute rather than long term antidepressant administration, and the trend towards using normal rodents rather than models with translational relevance for depression. Finally, several suggestions are made for advancing this field, including expanded use of target occupancy assessments in preclinical and clinical experiments, and the use of translationally valuable techniques such as electroencephalography.

1. Introduction

Major depressive disorder is a severe and disabling condition that often is accompanied by cognitive dysfunction (reviewed by McIntyre et al. (2013a)). Cognitive dysfunction in depression may include impairments in attention, executive function, memory, and processing speed (reviewed by McIntyre et al. (2013a) and Millan et al. (2012)). Moreover, cognitive dysfunction often persists as residual symptoms in patients who have achieved remission from their depression (Conradi et al., 2011), which could imply that currently used antidepressants do not offer adequate therapeutic efficacy with respect to cognitive symptoms and that there is a need for new treatment options (McClintock et al., 2011). However, few and mostly small clinical studies have been undertaken to assess the efficacy of currently used selective serotonin (5-HT) reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors on cognitive dysfunction in depression (reviewed by McIntyre et al. (2013a)). It therefore seems that there is an unmet need for large well-designed clinical studies of antidepressants' effects on cognitive dysfunction in depression, as well as for new antidepressants that offer efficacy through novel mechanisms of action.

The antidepressant vortioxetine acts through a multimodal mechanism. It is an antagonist at serotonergic 5-HT_{3A} (Ki = 3.7 nM),

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5-HT_7 (Ki=19 nM) and 5-HT_{1D} (Ki=54 nM) receptors, a partial agonist at serotonergic 5-HT_{1B} receptors (Ki=33 nM; intrinsic activity 55%), an agonist at serotonergic 5-HT_{1A} receptors (Ki=15 nM) and an inhibitor of the serotonin transporter (Ki=1.6 nM) in cell lines expressing human receptors or transporter (Bang-Andersen et al., 2011; Mork et al., 2012; Westrich et al., 2012). In two large, well-powered randomized double-blind clinical studies of depressed patients with cognitive dysfunction, vortioxetine has shown beneficial effects on several cognitive domains compared to placebo either as a pre-specified secondary outcome measure (Katona et al., 2012), or as the primary outcome measure (McIntyre et al., 2013b).

The aim of this review is to summarize and discuss the preclinical evidence for effects of selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and vortioxetine on cognitive function in mechanistic assays and animal models of depression.

2. Translational considerations

2.1. Target occupancy, a way to assess dose equivalence

Alignment between clinical and preclinical doses is an important factor for the translatability of pharmacodynamic measures. The advancement of positron emission tomography and other imaging techniques has allowed the determination of target occupancy levels at clinically effective doses. Several radioligands with a high selectivity for the serotonin transporter have been developed for human use and postiron emission tomography studies indicate that clinically effective doses of serotonin transporter inhibitors correspond to approximately 80% serotonin transporter occupancy (Meyer et al., 2004). Positron emission tomography studies of clinical vortioxetine doses (5–20 mg/day) at steady-state conditions revealed mean serotonin transporter occupancy of $\approx$50% at 5 mg/day, 65% at 10 mg/day, and $>$80% at 20 mg/day of vortioxetine (Areberg et al., 2012; Stenkrona et al., 2013).

In preclinical animal studies, target occupancies are determined by *in vivo* or *ex vivo* radioligand binding methods. Table 1 summarizes the selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor, and vortioxetine doses that correspond to 80% serotonin transporter occupancy 30 min after a subcutaneous (s.c.) injection in rats and mice. The occupancies were determined by *in vivo* displacement of [^{3}H]-2-(2-dimethylamino-methyl-phenylsulfanyl)-5-methyl-phenylamine. In the following sections the preclinical results are discussed relative to the serotonin transporter occupancy values in Table 1.

Table 1
In vivo serotonin transporter binding potencies of antidepressants in rat and mouse brain determined by *in vivo* displacement of [^{3}H] N,N-dimethyl-2-(2-amino-4-methylphenylthio) benzylamine administered i.v. Doses producing 80% serotonin transporter occupancy (ED_{80}) are shown.

Drug	ED_{80} (mg/kg, s.c., 30 min)	
	Rat[a]	Mouse[b]
Citalopram	0.52	0.44
Escitalopram	0.26	0.28
Fluoxetine	Not tested	8.0
Fluvoxamine	Not tested	1.8
Paroxetine	0.28	0.20
Sertraline	1.4	1.0
Duloxetine	2.9	1.0
Venlafaxine	2.4	3.3
Vortioxetine	3.4	6.0[a]

[a] LT Brennum unpublished data;
[b] Calculated from Larsen et al. (2004).

2.2. Quantitative electroencephalography and cognition

Although there has been advancement in the ability to assess target occupancy in a translatable manner, there is very limited insight linking these target occupancies with neurotransmission and cognitive endpoints, particularly across species. One important methodology that holds promise to bridge this gap is electroencephalography. Quantitative electroencephalography enables specific characterization of defined cellular and cerebral circuitries during wakefulness and cognitive functions through investigation of changes in the oscillatory properties of the brain (Basar et al., 1999, 2000; Basar and Guntekin, 2008; Leiser et al., 2011; Millan et al., 2012).

Raw electroencephalographic outputs are separated into component oscillatory bands during analysis, and some fundamental ideas about the biological underpinnings and role of each band have emerged, although these ideas are complex and still evolving (Basar et al., 1999, 2000, 2001; Leiser et al., 2014; Steriade, 2005). Delta waves (1–4 Hz) are believed to be generated by the summation of long-lasting after-hyper-polarizations in pyramidal neurons (layers II–III or V) and it has been posited that increases in delta power reflect greater synaptic input from subcortical areas. Frontal cortical theta waves (4–8 Hz) have been proposed to reflect coordinating neural networks involved in monitoring behavior and the environment, as well as in facilitating task-specific adaptive changes in performance. Alpha (8–12 Hz) and beta (12–30 Hz) waves can be viewed holistically as neural synchrony generated by coordination between afferent input to, and efferent output from, the cortex. Gamma ($>$30 Hz) synchronization occurs across the network between neurons and may reflect crosstalk between inhibitory interneurons and excitatory pyramidal neurons.

Importantly, the inherent cellular machinery and neuronal circuits involved in generating these oscillations are relatively conserved across mammalian species and can therefore provide a framework for translating findings from animal to clinical studies. As can be seen in Table 2, preclinical electroencephalography findings are often replicated in clinical trials using healthy subjects or depressed patients. With few exceptions, selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors decreased rapid eye movement sleep and suppressed cortical spectral power in rats, healthy subjects and depressed patients.

Given that each oscillatory band is tied to the activity of differentiable biological generators, it can be expected that performance of cognitive processes will be coupled to changes in the oscillatory behavior of the brain. And indeed this is what is observed. Altered delta rhythms have been associated with internal concentration (Harmony, 2013). Additionally, theta and gamma rhythms have been related to memory encoding and retrieval, alpha and gamma rhythms with attention or focusing, and gamma synchrony with conscious awareness (Ward, 2003). If changes in these oscillatory bands reflect the engagement of the cellular networks involved in driving these cognitive processes, then it may be reasonable to expect that pharmacological treatments capable of modulating oscillations in a given frequency band also alter performance in the associated cognitive functions. From this perspective, an understanding of how antidepressant treatments modulate these rhythms may have predictive value for their effects on cognitive function.

A comparative quantitative electronencephalography study of escitalopram, duloxetine and vortioxetine in rats showed clear differences between the three antidepressants. Consistent with previous studies (Katoh et al., 1995; Sanchez et al., 2007),

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