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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.

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

Table 2
Effects of antidepressants on electroencephalography in rats, healthy subjects and depressed patients. Significant increases (↑) or decreases (↑). NC: no change. –: not reported.

Drug	Species	Dose	Wake	REM[a]	SWS	Delta	Theta	Alpha	Beta	Gamma	Ref.
Citalopram	Wistar	2 and 5 mg/kg (acute)	↑	↓	NC	–	–	–	↓	↓	1
	Wistar	15 mg/kg/day/35 days	↑	↓	NC	↓	–	↓	↓	–	1
	Sprague-Dawley	10 and 40 mg/kg (acute)	–	↓	–	–	–	–	–	–	2
	Healthy subjects	20 mg, 3 days	↑	↓	NC	–	–	–	–	–	3
	Healthy subjects	20 and 40 mg	–	–	–	↓	–	–	↓	–	4
	Depressed patients	20 mg	–	–	–	↑	NC	↑	↑	–	5
Escitalopram	Sprague-Dawley	1 and 2 mg/kg (acute)	NC	NC	↑	–	–	–	–	–	6
	Wistar	2 and 10 mg/kg (acute)	–	↓	–	–	↓	–	–	–	7
	Wistar	10 mg/kg/day/21 days	–	↓	–	–	–	–	–	–	7
	Sprague-Dawley	2 mg/kg (acute)	–	–	–	NC	NC	NC	NC	NC	8,9
Fluoxetine	Sprague-Dawley	10 mg/kg (acute)	–	↓	–	–	–	–	–	–	2
	Long-Evans	2 mg/kg (acute)	–	–	–	↓	NC	NC	NC	NC	10
	Healthy subjects	60 mg (acute)	–	↓	↓	–	–	–	–	–	11
	Healthy subjects	40 mg/3 weeks	–	–	–	NC	NC	NC	↑[b]	–	11
	Healthy subjects										12
	Depressed patients	40 mg/4 weeks	–	–	–	NC	NC	NC	↓	–	13
Fluvoxamine	Fischer	40 mg/kg (acute)				↓	↓	↓	↓	↓	14
	Wistar	20 mg/kg (acute)	↑	↓	NC	–	–	–	–	–	15
	Healthy subjects	50 mg (8 h postdose)	–	–	–	↓	↓	↓	↓	–	16
	Healthy subjects	100 mg (acute)	↑	↓	↓	–	–	–	–	–	17
Paroxetine	Fischer	2 mg/kg (acute)	–	–	–	↓	↓	↓	↓	↓	14
	Sprague-Dawley	2.2 mg/kg (acute)	NC	↓	NC	–	–	–	–	–	6
	Healthy subjects	20 mg, 3 days	↑	↓	NC	–	–	–	–	–	3,18
	Healthy subjects	20 mg (acute)	–	–	–	NC	NC	NC	NC	NC	19
	Depressed patients	20 mg/6 weeks				↑	↑	↓	↑		19
Sertraline	Healthy subjects	200 and 400 mg	–	–	–	↓	↓	NC	↑	NC	20,21
	Healthy subjects	200 and 400 mg	–	–	–	–	–	–	↑	–	22
Zimeldine	Wistar	20 mg/kg (acute)	↑	↓	NC	↓	NC	NC	↓	NC	23
	Healthy subjects	100 and 200 mg (acute)	↑	↓	↓	–	–	–	–	–	24
	Healthy subjects	100 mg (acute)	–	–	–	↓	↓	↑	NC	NC	20,21
Duloxetine	Sprague-Dawley	7.7 mg/kg (acute)	↑	↓	NC	–	–	–	–	–	6
	Sprague-Dawley	10 mg/kg (acute)	↑	↓	NC	NC	NC	↓	↓	NC	8,9
	Healthy subjects	80 mg/7days, 60 mg bid/7 days	–	↓	↓	–	–	–	–	–	25
Venlafaxine	Sprague-Dawley	20 and 40 mg/kg (acute)	↑	↓	NC	–	–	–	–	–	6
	Wistar	1, 5, and 10 mg/kg (acute)	↑	↓	↓	–	–	–	–	–	26
	Healthy subjects	37.5 and 75 mg bid/7 days	–	–	–	NC	NC	NC	NC	NC	27
	Healthy subjects	12.5,25 and 50 mg	–	–	–	–	–	–	↓	–	28
	Healthy subjects	< 225 mg/day/29 days	↑	↓	NC	–	–	–	–	–	29
Vortioxetine	Sprague-Dawley	5 and 10 mg/kg (acute)	↑	↓	NC	NC	↑	↑	NC	↑	8,9
	Sprague-Dawley	10 mg/kg/day/14 days	NC	NC	NC	–	–	–	–	–	9

1. Neckelmann et al. (1996), 2. Ivarsson et al. (2005), 3. Wilson et al. (2004), 4. Lader et al. (1986), 5. Saletu et al. (2010), 6. Sanchez et al. (2007), 7. Vas et al. (2013), 8. Sanchez et al. (2007) 9. unpublished observations, 10. Dringenberg et al. (2000), 11. Feige et al. (2002), 12. Saletu and Grunberger (1985), 13. Tarn et al. (1993), 14. Dimpfel (2003), 15. de St Hilaire-Kafi and Gaillard (1988),16. Saletu et al. (1996), 17. Wilson et al. (2000), 18. Bell et al. (2003), 19. Knott et al. (2002) 20. Saletu and Grunberger (1988), 21. Saletu et al. (1986), 22. Siepmann et al. (2003), 23. Bjorvatn et al. (1995), 24. Nicholson and Pascoe (1986), 25. Chalon et al. (2005), 26. Salin-Pascual and Moro-Lopez (1997) 27. Siepmann et al. (2008), 28. Saletu et al. (1992), and 29. Luthringer et al. (1996).

[a] Decrease in rapid eye movement (REM) is observable either by a decrease in REM amplitude or an increase in onset latency. SWS=slow wave sleep.
[b] The increase in beta was observed only during non-rapid eye movement sleep.

clear differences between the three antidepressants. Consistent with previous studies (Katoh et al., 1995; Sanchez et al., 2007), duloxetine as well as vortioxetine increased vigilance (measured as time awake), yet their effects on brain rhythms were markedly different. Vortioxetine at a dose corresponding to 80% serotonin transporter occupancy increased delta, theta and gamma power significantly, whereas duloxetine at the same level of serotonin transporter occupancy decreased gamma. Similarly, Sebban et al. (1999) showed that increased noradrenergic activity decreased electroencephalographic spectral power in the rat. Escitalopram at a comparable level of serotonin transporter occupancy only moderately increased vigilance (Sanchez et al., 2007), but had no significant effect on elecetroencephalographic rhythms, a result that is also similar to previous studies. Unfortunately, clinical electroencephalography data is not available at this time with duloxetine or escitalopram. However, given the reproducible findings for other antidepressants shown in Table 2, it is likely that our preclinical findings will translate into humans. Furthermore, the fact that vortioxetine elicited increased hippocampal output (Dale et al., 2013), increased pyramidal neuron firing (Riga et al., 2013) and frontal cortical gamma oscillatory power in rats (Leiser et al., 2014) discussed in detail below indicate that the cellular framework for activating cortical neurons and eliciting gamma is engaged. Yet the effect in healthy human subjects, depressed patients, as well as in preclinical models of depression remains to be studied.

3. Preclinical behavioral models of cognitive function

As mentioned in Section 1, several cognitive domains are affected in depressed patients, including executive function, attention, processing speed, and memory. Several rodent assays have been developed to study these aspects of cognitive function. The following sections review the effects of selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors and vortioxetine on cognitive function in normal animals and in animal models of depression.

3.1. Preclinical models of executive function

Cognitive flexibility, which can be thought of as the ability to recognize and adapt to changing rules or environmental circumstances, is an aspect of executive function that is commonly disrupted in depression. In preclinical studies, the attentional set-shifting task is by far the most commonly used paradigm to assess cognitive flexibility, although more simple tasks also exist, such as reversal learning paradigms. In normal rats, the effects of serotonin transporter inhibitors on performance in these paradigms are inconsistent. Brown et al. (2012) demonstrated that acute escitalopram treatment improved performance in a spatial reversal learning task at a therapeutically relevant dose of 0.3 mg/kg and at 1 mg/kg (see Table 1 for information on therapeutically relevant doses of serotonin transporter inhibitors). However, Bari et al. (2010) found that acute citalopram treatment at 1 mg/kg impaired and at the very high dose of 10 mg/kg improved reversal learning. In contrast, there appears to be consensus that norepinephrine transporter inhibitors such as desipramine can improve the performance of normal rodents in operant reversal learning tasks (Seu and Jentsch, 2009; Seu et al., 2009). Furthermore, chronic, but not acute administration of desipramine improved extra-dimensional shift performance in the set-shifting task (Lapiz et al., 2007). However, the lack of clinically validated positron emission tomography radioligands to establish the level of norepinephrine transporter occupancy at clinically relevant doses impairs our ability to evaluate the clinical relevance of the doses used in these preclinical studies. Up to this point, vortioxetine's effects on reversal learning tasks have not been studied in normal rats.

The attentional set-shifting task seems to be reliably impaired in one way or another in response to repeated stress paradigms, *i.e.*, impaired extra-dimensional shift performance after repeated restraint stress (Nikiforuk, 2012, 2013; Nikiforuk and Popik, 2011), or chronic unpredictable stress (Bondi et al., 2008) and impaired reversal learning after chronic intermittent cold stress (Lapiz-Bluhm and Morilak, 2010; Lapiz-Bluhm et al., 2009). These studies show that acute administration of selective serotonin reuptake inhibitors attenuates stress-induced impairments in set-shifting performance (Lapiz-Bluhm and Morilak, 2010; Lapiz-Bluhm et al., 2009; Nikiforuk and Popik, 2011). However, it is not certain that the acute doses used in these experiments are in a clinically relevant range (Table 1). Escitalopram reversed the effects of repeated restraint stress at doses of 1 and 3 mg/kg, but not at 0.3 mg/kg (Nikiforuk, 2012, 2013; Nikiforuk and Popik, 2011) and 5 mg/kg citalopram reversed chronic intermittent cold stress-induced set-shifting impairments (Lapiz-Bluhm and Morilak, 2010; Lapiz-Bluhm et al., 2009). Since the attentional set-shifting task takes a long time to complete, it is difficult to clearly interpret the role of serotonin transporter inhibition in alleviating stress-induced deficits in behavioral flexibility without more data on exposure or serotonin transporter occupancy. A chronic dosing study of 10 mg/kg/day escitalopram administered *via* osmotic minipumps (s.c.), which corresponds to full serotonin transporter occupancy (Pehrson et al., 2013b), also showed recovery of cold stress-induced impairment of reversal learning (Bondi et al., 2008).

The ability of norepinephrine transporter inhibitors to reverse stress-induced deficits may depend on the type of impairment. In models that impair the extradimensional shift portion of the set-shifting task (*i.e.*, repeated restraint and chronic unpredictable stress), acute or chronic treatment with desipramine reduced the stress-induced deficits (Bondi et al., 2008; Naegeli et al., 2013; Nikiforuk and Popik, 2011). Chronic administration of the serotonin–norepinephrine reuptake inhibitor milnacipran was also able to reverse the chronic unpredictable stress-induced impairment in extradimensional shift performance (Naegeli et al., 2013). However, in the chronic intermittent cold stress model, acute and chronic administrations of desipramine were ineffective in restoring reversal learning deficits (Lapiz-Bluhm and Morilak, 2010). In the chronic intermittent cold stress model, chronic vortioxetine dosing at serotonin transporter occupancy levels as low as 60% restored function in the reversal learning task to the level of control animals (Wallace et al., 2014). Thus, it may be that vortioxetine's direct action at serotonergic receptors plays a role in counteracting cold stress-induced deficits in reversal learning. However, additional studies are needed to investigate this possibility.

Another animal model that may be related to the biology of depression is serotonin depletion. Depletion of central serotonin stores in humans using acute dietary tryptophan depletion induces depressed affect in vulnerable populations and reliably induces deficits in some types of cognitive function, most notably memory (see Delgado et al. (1990)). In preclinical studies, serotonin depletion may be achieved using dietary tryptophan depletion, which has high translational value, or *via* inhibition of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis. To our knowledge, only one group has attempted to investigate the effects of serotonin depletion in the attentional set-shifting model to date. Lapiz-Bluhm et al. (2009) demonstrated that the profound serotonin depletion induced by the tryptophan hydroxylase inhibitor 4-chloro-DL-phenylalanine methyl ester hydrochloride (PCPA) produced selective deficits in reversal learning revealed by the attentional set-shifting task, and citalopram failed to reverse the deficits. Acute or 3-day vortioxetine administration at a dose corresponding to the highest clinically relevant level of target engagement counteracted the serotonin depletion-induced deficit in reversal learning (Wallace et al., 2014).

Sub-chronic administration of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine, is another preclinical model that is commonly used to induce impairments in executive function. It is generally thought of as a model of schizophrenia-like cognitive impairments (Jenkins et al., 2010), and we were not able to identify any published studies investigating antidepressant effects in this model. However, there is a bourgeoning literature supporting a mechanistic role for altered glutamate (Pehrson and Sanchez, 2014) and γ-aminobutyric acid (GABA) neurotransmission (Croarkin et al., 2011) in the etiology or treatment of depression, and for a modulatory role of serotonin on glutamate and GABA signalling (Pehrson and Sanchez, 2014). Thus, it could be that the glutamatergic (Lindahl and Keifer, 2004) and GABAergic (Pratt et al., 2008) changes induced by sub-chronic PCP administration are relevant to the action of antidepressants on depression-related cognitive dysfunction. In the attentional set-shifting task, sub-chronic phencyclidine administration reliably induces a selective impairment in extra-dimensional shift performance. Early results from our laboratory show that acute treatment with vortioxetine over a clinically relevant dose range (1–10 mg/kg, s.c., 1 h prior to testing) reversed the subchronic phencyclidine-induced deficits in set-shifting performance (Pehrson et al., 2013a), and this effect was also seen using chronic administration (unpublished observations).

Overall, these data may support a role for serotonin or norepinephrine transporter inhibitors in improving executive function. However, in some cases the translational value of these data may be questioned either due to 1) the use of high doses or uncertainty of exposure/target engagement levels at relevant time points, 2) the use of normal rats rather than models with translational relevance for depression, or 3) the use of acute rather than sub-chronic or chronic treatment. Thus, based on these data it is difficult to clearly evaluate the mechanisms associated with traditional antidepressants in animal models of executive function.

3.2. Preclinical models of attention

Depression is commonly associated with impaired attention, so much so that it is one of the diagnostic criteria (DSM-V) (American Psychiatric Association, 2013). However, in the preclinical space there has been very little work done to model depression-like deficits in attention performance, perhaps due to the complexity of attention-related tasks such as the 5-choice serial reaction time task or the visual signal detection task. Preclinical models of depression induced by stress or serotonin depletion failed to induce deficits in preclinical models of attention (Blokland et al., 2002; Torregrossa et al., 2012), perhaps suggesting that these preclinical models have limited translational value for the cognitive functions impaired in clinical depression populations. A small amount of work has been published on antidepressant effects on attention in normal rodents. For example, acute citalopram at 1 mg/kg had no effects on attention-related endpoints in the 5-choice serial reaction time task (Baarendse and Vanderschuren, 2012). Another group similarly found that citalopram had no effect on attention performance, but showed increased response latency at 1 and 3 mg/kg (Humpston et al., 2013). Fluoxetine and paroxetine selectively increased response omissions, each at 3 mg/kg (Humpston et al., 2013) and venlafaxine had no effect on attention performance at doses up to 3 mg/kg (Humpston et al., 2013). Thus, in normal animals, selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors appear to either have no effect or may actually impair attention and nothing is known about their effects in preclinical models of depression.

3.3. Preclinical models of memory

The effects of antidepressants on memory function have mostly been studied in normal animals and investigations in depression-related models have focused primarily on stress-induced memory impairment. Furthermore, the vast majority of studies in normal rats have been conducted with fluoxetine and the results are inconsistent (Table 3). The acute effects range from impairment (Bridoux et al., 2013; Carlini et al., 2007), to no effect (Degroot and Nomikos, 2005; Eriksson et al., 2012; Jansen and Andrews, 1994) or improvement (Burghardt et al., 2007; Flood and Cherkin, 1987; Montezinho et al., 2010; Schilstrom et al., 2011). In some studies the improving or impairing effects occur at doses that are much higher than those needed to fully occupy the serotonin transporter (Schilstrom et al., 2011; Bridoux et al., 2013; Table 1). Chronic dosing studies of selective serotonin reuptake inhibitors are also inconclusive (Carlini et al., 2012; Deschaux et al., 2011; Grunbaum-Novak et al., 2008; Karpova et al., 2011; Lebron-Milad et al., 2013; Melo et al., 2012). Acute vortioxetine treatment improved memory performance in a fear conditioning task as well as in a novel objection recognition test, in both cases at doses that are clinically relevant (Mork et al. 2013). Serotonin–norepinephrine reuptake inhibitors have been studied very little in preclinical tests of memory function with relevance to depression. An acute study reported that the selective norepinephrine transporter inhibitor atomoxetine counteracts the positive effect of escitalopram in a rat fear conditioning test (Montezinho et al., 2010), and in a chronic dosing study venlafaxine was found to have no effect in a passive avoidance test (Carlini et al., 2012). Vortioxetine has not been tested in memory tests after repeated dosing of normal rodents. Memory impairment induced by sub-chronic phencyclidine treatment was reported to be restored after repeated dosing with fluvoxamine but not with paroxetine (Hashimoto et al., 2007). However, the fluvoxamine and paroxetine doses were 10–20 times higher than those needed to fully occupy the serotonin transporter (Table 1). In conclusion, selective serotonin reuptake inhibitors appear to have limited effect on memory performance in normal animals. There are very few studies with serotonin–norepinephrine reuptake inhibitors and, at least acutely, the increase of extracellular norepinephrine after acute treatment with these drugs may counteract the effect of serotonin transporter inhibition.

Despite the observation that stressors not only induce a depression-like behavior but also impair memory performance in rodents (Conrad, 2010), there are relatively few studies of antidepressants on memory-related deficits in stress models of depression (Table 4). These studies were mostly conducted with fluoxetine and involve repeated dosing, and again the outcomes are inconsistent. Paroxetine at the very high dose of 10 mg/kg/day for 3 weeks improved object recognition memory but did not improve depression-like behavior in mice (Elizalde et al., 2008). This high dose of paroxetine will likely also inhibit the norepinephrine transporter (Sanchez et al., 2014). The serotonin–norepinephrine reuptake inhibitor venlafaxine reversed memory deficits induced by chronic mild stress and maternal separation (Briones et al., 2012; Martisova et al., 2013). Vortioxetine's effects on stress-induced memory deficits have not been studied. In conclusion, while the effect of fluoxetine on stress-induced memory deficits varies, serotonin–norepinephrine reuptake inhibitors may potentially produce more consistent effects. However, there is a need for studies that directly compare different classes of antidepressants at doses that produce clinically relevant target engagement.

The effect of serotonin depletion on memory depends on the type of memory being studied. Spatial memory and passive avoidance were intact in tryptophan-depleted animals (Blokland et al., 2002; Lieben et al., 2004; Stancampiano et al., 1997); however deficits were observed in object recognition memory (Jans et al., 2010). To our knowledge there are no published studies on the effects of selective serotonin or serotonin–norepinephrine reuptake inhibitor antidepressants on tryptophan depletion-induced memory deficits. Studies showed that tryptophan hydroxylase inhibition by PCPA treatment caused deficits in some aspects of spatial memory, for example in the spontaneous alternation test (Alkam et al., 2011; du Jardin et al., 2014; Jensen et al., 2014), but not in the Morris water maze (Beiko et al., 1997; Richter-Levin and Segal, 1989). PCPA also induced deficits in novel object recognition performance (du Jardin et al., 2014; Jensen et al., 2014). Neither escitalopram nor duloxetine was effective in reversing PCPA-induced memory deficits, but acute vortioxetine treatment was effective over a large range of doses that included the entire clinically relevant range (*i.e.*, 1–10 mg/kg s.c. 1 h before testing; du Jardin et al., 2014; Jensen et al., 2014). Furthermore, the positive effect of vortioxetine was sustained after dosing for 2 weeks in the novel object recognition test (du Jardin et al., 2014). Although more studies will be beneficial, those studies that are available suggest that depletion of central serotonin reliably impairs some aspects of memory, for example object recognition memory, while leaving other aspects of memory relatively untouched. Furthermore, merely blocking the reuptake of serotonin or norepinephrine appears to be insufficient to restore serotonin depletion-induced memory deficits.

Depressive symptoms are commonly accompanied by cognitive dysfunction in elderly humans (McDermott and Ebmeier, 2009; Reppermund et al., 2011). Population-based studies with older adults have reported an association between depressed mood and performance in several cognitive domains, including sensorimotor function and processing speed, attention, learning and memory and executive function (Baune et al., 2006; Biringer et al., 2005; Reppermund et al., 2011; Vinkers et al., 2004). The age-related depression and cognitive dysfunction may be linked through a shared pathology. Elderly depressed subjects tend to have a smaller hippocampal volume and abnormalities in white matter and the temporal lobe than age-matched controls. Importantly, these structural changes are associated with progressive cognitive decline (Benavides-Piccione et al., 2013; Dotson et al., 2009;

Table 3
Effects of antidepressants on memory in normal animals.

Drug and dosing	Animals	Memory task	Results	Ref.
Acute dose				
Fluoxetine 5 mg/kg i.p. 30 min	Wistar male rats	Passive avoidance, novel object recognition	Impaired memory retention	1
Citalopram 5, 10 mg/kg, i.p. 6 h	C57Bl male mice	Passive avoidance, Y-maze	Impaired memory function	10
Fluoxetine 10 mg/kg s.c., 60 min	C57Bl male mice	Passive avoidance	No effect	9
Fluoxetine 0.625–10 mg/kg s.c. 30 min	Long-Evans male rat	Delayed matching to position	No effect	2
Citalopram, fluoxetine 10 mg/kg i.p. 1 h	Sprague-Dawley male rat	Fear conditioning	Citalopram, fluoxetine improved memory consolidation	3
Fluoxetine 15 mg/kg i.p. 1 h	Sprague-Dawley male rat	Shock-probe burying	No effect on memory	4
Fluoxetine 15 mg/kg, s.c. 1 h	CD-1 male mice	Passive avoidance, active avoidance	Improved memory retention and retrieval but not acquisition	5
Escitalopram 5 mg/kg, citalopram 10 mg/kg, s.c. 30 min	Sprague-Dawley male rats	Novel object recognition 24 h delay	Escitalopram: improved memory function. citalopram: no effect	6
Escitalopram 0.5, 1, 5 mg/kg s.c.	Sprague-Dawley male rats	Fear conditioning	Facilitation of fear memory	7
Vortioxetine 5, 10 mg/kg, i.p. 1 h	Sprague-Dawley male rats	Fear conditioning, novel object recognition	Improved memory acquisition and consolidation	8
Repeated dosing				
Fluoxetine or venlafaxine 10 mg/kg p.o. 4 weeks	Swiss-SWR/j male mice	Novel object recognition 24 h delay	Fluoxetine: deficit; Venlafaxine: no effect	11
Fluoxetine 15 mg/kg p.o. 3 weeks	Wistar male rats	Water maze	No effect	12
Fluoxetine 0.08 g/l p.o. *via* drinking water 2 or 3 weeks	C57BL male mice	Fear conditioning	Effect on fear extinction only in combination with extinction training, no effect by itself	13
Fluoxetine 7 mg/kg i.p. >2 weeks	Wistar male rats	Auditory fear conditioning	Facilitation of fear extinction	14
Fluoxetine 10 mg/kg acute or 2 weeks	Sprague-Dawley male/female rats	Fear conditioning	Facilitate extinction only in metestrus/diestrus female. No effect in proestrus/estrus female or in male rats	15
Fluoxetine 20 mg/kg i.p. 19 d	Wistar female rats	Plus-maze discriminative avoidance task	Facilitation of fear extinction	16
Fluvoxamine 20 mg/kg, paroxetine 10 mg/kg i.p. acute or 2 weeks	ICR male mice	Novel object recognition 24 h delay after sub-chronic phencyclidine 10 mg/kg	Fluvoxamine: acutely no effect; 2 week treatment reverses phencyclidine effectParoxetine: no effect	17

1. Carlini et al. (2007), 2. Jansen and Andrews (1994), 3. Burghardt et al. (2007), 4. Degroot and Nomikos (2005), 5. Flood and Cherkin (1987), 6. Schilstrom et al. (2011), 7. Montezinho et al. (2010), 8. Mork et al. (2013), 9. Eriksson et al. (2012), 10. Bridoux et al. (2013), 11. Carlini et al. (2012), 12. Grunbaum-Novak et al. (2008), 13. Karpova et al. (2011), 14. Deschaux et al. (2011), 15. Lebron-Milad et al. (2013), 16. Melo et al. (2012), and 17. Hashimoto et al. (2007).

Steffens et al., 2011). Thus, a more naturalistic approach to model cognitive dysfunction in depression might be to study old animals, which exhibit depression-like behavior, cognitive deficits (Bordner et al., 2011; Malatynska et al., 2012; Topic et al., 2008) and structural changes in the hippocampus and dendritic morphology similar to elderly humans (Driscoll et al., 2006; Vila-Luna et al., 2012). A limited number of studies of antidepressants have been undertaken in old animals. Treatment of 16-month old rats with amitriptyline (average daily dose approximate 8 mg/kg in drinking water) prevented the cognitive deficits measured in the Morris Water maze test (Yau et al., 2002). Similarly, 1-month treatment of 12-months old female C57Bl mice with a clinically relevant vortioxetine dose *via* food produced an antidepressant-like effect in the forced swim test as well as a beneficial effect on cognitive performance in an object placement test (Li et al., 2013). In contrast, fluoxetine had neither an antidepressant-like activity nor a beneficial effect on cognitive performance in this study. Overall, studies of selective serotonin reuptake inhibitors showed inconsistent results, and there is a shortage of systematic studies of serotonin-norepinephrine reuptake inhibitors, on memory functions in preclinical models. More studies are warranted, particularly using doses that are relevant for blocking neurotransmitter transporters only.

4. Mechanistic studies

4.1. Neurochemistry

Monoamine neurotransmission is thought to play an important role in the regulation of cognitive function. Long-held hypotheses suggest that dopamine and norepinephrine have direct roles in the regulation of the prefrontal cortex mediated cognitive functions such as attention, working memory, and cognitive flexibility (reviewed in Robbins and Arnsten (2009)). Additionally, serotonergic neurotransmission is also thought to play a role in memory function (du Jardin et al., 2014; Jensen et al., 2014) and some aspects of cognitive flexibility (Lapiz-Bluhm et al., 2009). It is generally thought that the relationship between prefrontal cortex catecholamine neurotransmission and cognitive function can be described as an "inverted U", with either too much or too little activation leading to suboptimal performance (Robbins and Arnsten, 2009). Furthermore, current theories suggest that each cognitive domain will have independent "inverted U" curves, with the optimal level of stimulation differing, for example, in memory and cognitive flexibility tasks. From this perspective, it may be important to understand the ways that extracellular monoamine concentrations are affected by models of depression and antidepressant treatment.

Neurochemical studies have shown that extracellular concentrations of serotonin (Dazzi et al., 2005; Fujino et al., 2002), dopamine (Cuadra et al., 1999; Gresch et al., 1994) and norepinephrine (Dazzi et al., 2005; Gresch et al., 1994) increase in the prefrontal cortex in response to an acute stressor. Studies investigating the effects of chronic stress paradigms on extracellular norepinephrine and dopamine have generally found that while basal concentrations are not affected (Finlay and Zigmond, 1997; Gresch et al., 1994; Jett and Morilak, 2013), chronic stress engenders a significant sensitization of the increases in norepinephrine and dopamine levels elicited by an acute stressor (Cuadra et al., 1999, 2001; Di Chiara et al., 1999; Finlay and Zigmond, 1997; Jett and Morilak, 2013). We were not able to identify any studies that examined the effects of an acute stressor on prefrontal cortex serotonin release in chronically stressed rats;

Table 4
Effects of antidepressants in animal models of depression.

Drug	Model	Assay/memory task	Result	Ref.
Fluoxetine 10 mg/kg i.p.; 4 weeks	Social isolation; Lister Hooded male rats	Novel object recognition 1 h delay	No effect	1
Fluoxetine 5 mg/kg i.p.; more than 2 weeks	Social isolation; Sprague Dawley male rats	Water maze Novel object recognition 24 h delay	Water maze: no effect Novel object recognition: caused deficits	2
Fluoxetine 10 mg/kg i.p.; 2 weeks+	Social isolation; ICR male mice	Water maze	Reversal of deficits	3
Venlafaxine 20 mg/kg p.o.; 15 days	Maternal separation; Wistar male rats	Novel object recognition 1 h delay	Reversal of deficits	4
Citalopram 340–410 mg/kg food, p.o.; 3 weeks	Flinders sensitive line rats of both sexes	Passive avoidance	Reversal of deficits	5
Venlafaxine 20 mg/kg p.o.	Chronic mild stress; Wistar male rats	Novel object recognition 1 h delay	Memory restored in rats susceptible to stress	6
Paroxetine 10 mg/kg; 3 weeks	Chronic mild stress; C57BL male mice	Novel object recognition 1 h and 24 h delay	Reversal of deficits at 1 h but not 24 h delay	7
Fluoxetine 10 mg/kg i.p. b.i.d.; 2 weeks	Learned helpless, chronic mild stress; ICR male mice	Water maze	Reversal of deficits	8
Fluoxetine 15 mg/kg	Chronic mild stress mice	Water maze, radial arm maze	Water maze: no effect Radial arm maze: impairment	9
Fluoxetine 10 mg/kg; 30 min prior to testing trial	Predator stress; Swiss male mice	Novel object recognition 1 h delay	Reversal of stress-induced memory deficits	10
Fluoxetine 10 mg/kg i.p.; 2 weeks	Time dependent sensitization model of posttraumatic stress disorder; Sprague Dawley male rats	Water maze	Prevented stress-induced spatial memory deficit	11
Fluoxetine 18 mg/kg/day p.o.; 4 days or 3 weeks	Single housing and shortened circadian cycle; B6/129 male mice	Novel object recognition 1 h delay	Memory restored in short light cycle group	12
Vortioxetine 1–10 mg/kg s.c. 1 h	Serotonin depletion	Novel object recognition 1 h delay Spontaneous alternation	Reversal of deficits in both tasks	13
Escitalopram 2 mg/kg, s.c. 1 h	Serotonin depletion	Novel object recognition 1 h delay Spontaneous alternation	No effect on deficits	13
Duloxetine 10 mg/kg, s.c. 1 h	Serotonin depletion	Novel object recognition 1 h delay Spontaneous alternation	No effect on deficits	13

1. Bianchi et al. (2009), 2. Valluzzi and Chan (2007), 3. Ibi et al. (2008), 4. Martisova et al. (2013), 5. Eriksson et al. (2012), 6. Briones et al. (2012), 7. Elizalde et al. (2008), 8. Song et al. (2006), 9. Gumuslu et al. (2013), 10. El Hage et al. (2004), 11. Harvey et al. (2004), 12. LeGates et al. (2012), and 13. du Jardin et al. (2014).

however, similar results have been reported in hippocampal serotonin concentrations (reviewed in Linthorst and Reul (2008)). Interestingly, the sensitizing effect of chronic stress on dopamine and norepinephrine release could be blocked by chronic administration of fluoxetine (Cuadra et al., 2001) or desipramine (Cuadra et al., 2001; Di Chiara et al., 1999). Similarly, Dazzi et al. (2005) have found that chronic administration of antidepressants such as fluvoxamine can blunt the increases in serotonin or norepinephrine, in response to an acute stressor. One way of interpreting these data is that chronic stress leads to a sensitization of phasic monoaminergic responses to external stimuli, or in another sense an increased signal-to-noise ratio, which chronic treatment with antidepressants can reverse. If these sensitized responses to stressful stimuli occur in a more generalized manner, then it may be that some of the chronic stress-induced impairments in memory or executive function are due to monoamine neurotransmission being beyond the "optimal window" of stimulation in the theorized inverted U functions noted above. Antidepressant treatment could theoretically normalize this effect of stress for some aspects of cognitive function. However, it is unlikely that these effects would be generally beneficial to cognitive function if monoamine neurotransmission becomes overall less responsive to external stimuli. But these ideas are entirely speculative, and should be considered with caution. Unfortunately, it is very difficult to draw clear data-driven conclusions on the relationship between monoamine neurotransmission and cognitive function in models of depression given the relative paucity of research that has been done in this area.

4.2. Electrophysiology

Serotonin has been shown to modulate prefrontal cortex functions *via* regulation of glutamatergic and especially GABAergic transmission (Andrade, 2011; Ashby et al., 1991; Komlosi et al., 2012; Puig et al., 2010; Yan, 2002; Zhong and Yan, 2004, 2011; Zhou and Hablitz, 1999). This may be important for cognitive function from the perspective that treatments that positively modulate postsynaptic glutamate neurotransmission tend to improve performance in a broad set of preclinical cognition models (Betry et al., 2013). Application of 5-HT increases the firing rate of fast-spiking interneurons and decreases the firing rate of pyramidal cells in rat prefrontal cortex brain slices (Zhong and Yan, 2011). Chronic treatment with fluoxetine (10 mg/kg for 21 days, i.p.) alters serotonergic regulation of GABA transmission and overall increases the excitability of fast-spiking interneurons in brain slices (Zhong and Yan, 2004, 2011). Accordingly, chronic, but not acute, treatment with fluoxetine (10 mg/kg for 21 days, i.p.) suppresses the firing of prefrontal cortex pyramidal neurons *in vivo* (Gronier and Rasmussen, 2003). Consequences of the reduction in firing rate of pyramidal cells on cognitive functions were not tested in these studies. Given the variable effects of fluoxetine on cognitive function (see Section 3), the impact of a decrease in pyramidal cell output remains unclear. A recent study by Riga et al. (2013) showed that vortioxetine can increase the firing rate of pyramidal neurons in the medial prefrontal cortex. Vortioxetine was tested at 0.1–1.6 mg/kg, i.v. and its maximal effect began at a dose of 0.4 mg/kg. In the same study, escitalopram tested at doses that fully occupied the serotonin transporter

(0.1–1.6 mg/kg, i.v.) did not alter the firing rate of pyramidal neurons (Riga et al., 2013). Additional experiments are required to elucidate whether the vortioxetine-mediated increase in the pyramidal cell output is involved in the cognition-enhancing effects observed with this drug.

In the hippocampus, exposure to stress has been shown to impair long-term potentiation, a model of synaptic plasticity that correlates with learning and memory (reviewed in Kim and Diamond (2002), Pittenger and Duman (2008) and Popoli et al. (2002)). Interestingly, in naïve non-stressed animals, application of serotonin and acute treatments with selective serotonin reuptake inhibitors also blocks hippocampal long-term potentiation recorded in brain slices and *in vivo* (Corradetti et al., 1992; Mnie-Filali et al., 2006; Shakesby et al., 2002; Staubli and Otaky, 1994; Stewart and Reid, 2000). We have shown that, in contrast to escitalopram, acute treatment with vortioxetine can reverse the serotonin-induced inhibition of *Cornu Ammonis* area 1 (CA1) pyramidal cells and enhance theta-burst long-term potentiation in hippocampal slices (Dale et al., 2013).

Prolonged treatments with selective serotonin and serotonin–norepinephrine reuptake inhibitors have a variable effect on long-term potentiation. For instance, chronic treatment with fluoxetine (1.0 mg/kg, i.p for 15 days) or escitalopram (0.34 g/kg in chow for 3 weeks) attenuated long-term potentiation recorded from the hippocampus (Ryan et al., 2009; Stewart and Reid, 2000). However, Matsumoto et al. (2005) showed that chronic, but not acute, treatment with milnacipran (30 mg/kg PO for 14 days) reversed the long-term potentiation impairment produced by fear conditioned stress in the hippocampus (Matsumoto et al., 2005). Finally, vortioxetine reversed stress-induced impairment of hippocampal long-term potentiation *in vivo* (Haddjeri et al., 2012).

In conclusion, vortioxetine distinguished itself from escitalopram in these studies by increasing the firing rate of prefrontal cortex pyramidal cells and enhancing hippocampal long-term potentiation. However, additional research is required, especially in animal models of depression, to determine whether changes in prefrontal cortex pyramidal cell function or long-term synaptic plasticity in the hippocampus correlates with the reversal of cognitive impairments in depression.

5. Molecular mechanisms underlying cognitive enhancing effects of antidepressants

Numerous studies have begun to dissect the molecular and cellular mechanisms underlying the antidepressant effects of selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, but the mechanisms by which they modulate cognitive function remain unclear. Neurogenesis has been linked with hippocampal-dependent memory formation in tasks such as fear conditioning and spatial memory (Burghardt et al., 2012; Denny et al., 2012; Drew et al., 2010; Saxe et al., 2006; Shors et al., 2002). Chronic treatment with selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and vortioxetine induces neurogenesis in normal animals and can restore impaired neurogenesis in stress paradigms, possibly leading to enhanced plasticity and cognitive function. Chronic administration of fluoxetine (5 or 10 mg/kg, i.p.) to rats led to an increase in cell proliferation and neurogenesis in the dentate gyrus (DG; Khawaja et al., 2004; Malberg et al., 2000). However, chronic fluoxetine administration (10 or 18 mg/kg/day in drinking water) to male 129/SvEv but not BALB/cJ mice led to an elevated density of bromodeoxyuridine-positive and doublecortin-positive cells, a marker of neuronal maturation (Holick et al., 2008; Santarelli et al., 2003). Chronic venlafaxine (10 mg/kg, i.p. or 40 mg/kg/day, s.c. *via* an osmotic minipump) also increased bromodeoxyuridine-positive cells in the subgranular zone in rats (Khawaja et al., 2004; Mostany et al., 2008). Similarly, chronic vortioxetine (5 mg/kg, p.o.) in mice elevated the number of doublecortin-positive cells, survival of bromodeoxyuridine-positive cells in the dentate gyrus, and increased dendritic branching at a dose of 20 mg/kg, p.o. (Guilloux et al., 2013). Fluoxetine (18 mg/kg, p.o.) also promoted neurogenesis in this study, but failed to induce dendritic branching (Guilloux et al., 2013). In a chronic corticosterone model of depression in mice, chronic fluoxetine administration (18 mg/kg/day, p.o.) restored cell proliferation and the density of doublecortin-positive cells in the dentate gyrus (David et al., 2009). Rats subjected to chronic mild stress displayed impaired neurogenesis, and chronic fluoxetine treatment (10 mg/kg, i.p.) restored the density of bromodeoxyuridine-positive and doublecortin-positive cells, and the levels of Ki67-positive cells, an endogenous marker of cell proliferation, in the subgranular zone (Bessa et al., 2009). In addition, this treatment regimen increased dendritic branching in the dentate gyrus and *Cornu Ammonis* area 3 (CA3) regions of the hippocampus and the density of mature dendritic spines in prefrontal cortex and CA3.

Selective serotonin reuptake inhibitor and serotonin–norepinephrine reuptake inhibitor treatment of normal animals can induce gene expression of various targets that play a role in neurogenesis, synaptic plasticity, and synapse formation, including growth factors, receptors, and signalling proteins. These targets, including the cyclic AMP response element binding (CREB), brain derived neurotrophic factor (BDNF), Calcium/calmodulin depenendant kinase II, Wnt family of proteins and glutamatergic NMDA receptor subunits, can play critical roles in various forms of memory and learning such as long-term memory, consolidation, spatial learning, episodic memory and other hippocampal-dependent tasks (Barco and Marie, 2011; Dincheva et al., 2012; Elgersma et al., 2004; Silva et al., 1998; Tang et al., 1999; Vargas et al., 2014; von Engelhardt et al., 2008). Chronic (10 mg/kg, i.p.) fluoxetine treatment promotes cyclic AMP response element (CRE)-mediated gene expression in the cortex and hippocampus, as assessed by β-galactosidase immunoreactivity (Thome et al., 2000), in C57BL6 CRE-LacZ transgenic mice. Furthermore, chronic fluoxetine (5 mg/kg, i.p.) and sertraline administration (10 mg/kg, i.p.) elevated CRE activity in rats accompanied by increased mRNA levels of CREB, BDNF, and the BDNF receptor tyrosine receptor kinase B (Nibuya et al., 1996). Other chronic fluoxetine treatment regimens in rats (10 mg/kg *via* an osmotic minipump or i.p., b.i.d.) as well as paroxetine or sertraline (5 mg/kg, i.p., b.i.d.) also increased CREB and BDNF mRNA levels in the hippocampus (Coppell et al., 2003; Tiraboschi et al., 2004). Similarly, venlafaxine administration (10 mg/kg, i.p.) induced BDNF mRNA expression in the granular cell layer of the hippocampus. Microarray analysis of gene expression following fluoxetine (5 mg/kg, i.p., b.i.d.) or venlafaxine (15 mg/kg, i.p., b.i.d.) administration led to upregulation of Wnt2, Wnt7, Frizzled9, a receptor for the Wnt ligand, and the protein kinase B 1 (Akt1) (Okamoto et al., 2010). In addition, citalopram treatment (15 mg/kg, i.p., b.i.d.) increased mRNA levels of Wnt2 and the adhesion molecule β-catenin, implicating a role for selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors in synaptogenesis. Vortioxetine's effect on plasticity-related proteins has not been studied extensively. However, in a comparative study of acute vortioxetine and fluoxetine treatment at clinically-relevant doses in rats, only vortioxetine upregulated mRNA levels of metabotropic glutamate receptor 1 and targets involved in protein synthesis (du Jardin et al., 2013).

Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors can also modulate neurogenesis- and synaptic plasticity-related targets at the protein level. Proteomic analysis of hippocampal lysates from rats subjected to chronic fluoxetine or venlafaxine (10 mg/kg, i.p.) treatment revealed increases in targets related to neurogenesis, such as Insulin

Growth Factor-1, trafficking and plasticity, such as Ras-related proteins 1a and 4a (Rab1a/4a) and Heat Shock Protein 10, metabolism, and the proteasome degradation pathway (Khawaja et al., 2004). Further studies have confirmed that selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors can induce increased expression of plasticity-related targets and activation of signalling proteins. Chronic fluoxetine treatment (10 mg/kg *via* minipump) augmented phosphorylation of CREB at serine 133, a site that activates gene expression and is implicated in plasticity, in nuclear fractions of the hippocampus and prefrontal cortex. Additionally this treatment increased the enzymatic activity and phosphorylation of Calcium calmodulin dependant kinase IV (Tiraboschi et al., 2004). Moreover, total extracellular signal regulated kinase 1/2 levels were increased in the cortex, suggesting activation of the Mitogen activated protein kinase pathway. Fluoxetine (5 mg/kg, i.p., b.i.d.) or venlafaxine (15 mg/kg, i.p., b.i.d.) administration elevated phospho-glycogen synthase kinase 3B levels, downstream of the Wnt signalling pathway, in the hippocampus (Okamoto et al., 2010). Also, chronic venlafaxine administration (10 or 40 mg/kg/day, s.c. *via* minipump) elevated total and nuclear expression of other components of the Wnt pathway, extracellular signal regulated kinase, and Akt in membrane fractions of the hippocampus (Mostany et al., 2008). Chronic treatment with fluvoxamine (15 mg/kg, i.p.) or paroxetine (5 mg/kg, i.p.) increased phosphorylation and activity of Calcium/calmodulin dependant kinase IIα (Popoli et al., 1997). Furthermore, chronic paroxetine administration (10 mg/kg, i.p.) increased membrane-associated levels of the glutamatergic α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) receptor subunit GluA1 in the hippocampus (Martinez-Turrillas et al., 2002, 2005).

Taken together, the above studies reveal that several plasticity-related proteins are modulated by selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors. However, studies using more clinically relevant doses are warranted, given that the ones reviewed here tended to be outside the clinically relevant dose range. Preliminary results with vortioxetine at clinically relevant doses support neurogenesis and plasticity promoting effects. Finally, it remains to be established whether antidepressants can induce changes in signalling in animal models that incorporate both depression and cognitive deficits.

6. Overall conclusions and future perspectives

Similar to the clinical literature, there is a need for programmatic investigation into the effects of antidepressants on cognitive function in preclinical models of depression. Moreover, the available literature tends to use doses that are outside the clinically relevant range, and to use normal animals preferentially over validated depression-related models. In order to advance the field, it is essential to use biologically relevant depression models and appropriate antidepressant doses, which would require an expansion of techniques focused on measuring target occupancy or brain exposure. Additionally, it is important to develop direct links between the mechanistic effects of antidepressants and their effects on cognitive function. Finally, it is important to create these links using techniques that are capable of direct studies in both preclinical and clinical settings, for example quantitative electroencephalography.

Although vortioxetine has not been extensively studied preclinically, the available data suggests that it may have advantages over existing antidepressants in terms of its effects on cognitive function or in mechanistic models that are potentially related to cognitive function, although in many cases direct links have yet to be made between preclinical and clinical results.

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