



## Invited review

# Psychostimulants, antidepressants and neurokinin-1 receptor antagonists ('motor disinhibitors') have overlapping, but distinct, effects on monoamine transmission: The involvement of L-type $\text{Ca}^{2+}$ channels and implications for the treatment of ADHD



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## ABSTRACT

Both psychostimulants and antidepressants target monoamine transporters and, as a consequence, augment monoamine transmission. These two groups of drugs also increase motor activity in preclinical behavioural screens for antidepressants. Substance P-preferring receptor (NK1R) antagonists similarly increase both motor activity in these tests and monoamine transmission in the brain. In this article, the neurochemical and behavioural responses to these three groups of drugs are compared. It becomes evident that NK1R antagonists represent a distinct class of compounds ('motor disinhibitors') that differ substantially from both psychostimulants and antidepressants, especially during states of heightened arousal or stress. Also, all three groups of drugs influence the activation of voltage-gated  $\text{Ca}(v)1.2$  and  $\text{Ca}(v)1.3$  L-type channels (LTCCs) in the brain, albeit in different ways. This article discusses evidence that points to disruption of these functional interactions between NK1R and LTCCs as a contributing factor in the cognitive and behavioural abnormalities that are prominent features of Attention Deficit Hyperactivity Disorder (ADHD). Arising from this is the interesting possibility that the hyperactivity and impulsivity (as in ADHD) and psychomotor retardation (as in depression) reflect opposite poles of a behavioural continuum. A better understanding of this pharmacological network could help explain why psychostimulants augment motor behaviour during stress (e.g., in preclinical screens for antidepressants) and yet reduce locomotor activity and impulsivity in ADHD.

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## 1. Introduction

The substituted phenylalkylamines, d-amphetamine and methylphenidate, are psychostimulants that bind preferentially to noradrenaline (NET) and dopamine (DAT) transporters. D-Amphetamine is also a substrate for the translocation site on the transporter and so competes with noradrenaline and dopamine for uptake (Fleckenstein et al., 1999). The tropane alkaloid, cocaine, is another psychostimulant that blocks monoamine uptake, especially serotonin by comparison with either d-amphetamine or methylphenidate (Bosy and Ruth, 1989; Fleckenstein et al., 1999), but neither cocaine nor methylphenidate is a substrate for translocation.

Similarly, most antidepressants bind to monoamine transporters and inhibit uptake of these neurotransmitters, especially noradrenaline and serotonin (Table 1). In this respect, the pharmacodynamics of psychostimulants overlap with antidepressants and so it is not surprising that these two classes of drugs produce similar responses in preclinical screens for antidepressants (e.g., the swim test and mouse tail-suspension test: Porsolt et al., 1978; Steru et al., 1987; Cryan et al., 2005). Most of these procedures evaluate the effects of drugs on the motor response to stress (rather than 'depression-like' behaviour), which is strongly influenced by monoamine transmission. The positive behavioural response to d-amphetamine in these screens is not entirely spurious. In the pre-DSM era, this drug was used to treat 'depression', especially when the illness involved prominent 'fatigue': this could suggest that d-amphetamine relieves deficits in motor motivation and activity, which is a common feature of depression, rather than improves affective state (see: Rasmussen, 2006 and Section 6).

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**Table 1**  
Changes in extracellular monoamines in the prefrontal cortex following acute administration of psychostimulants, antidepressants or NK1R antagonists.

		Dopamine	Noradrenaline	Serotonin	
Psychostimulants	Amphetamine	↑↑	↑↑	↑	Rowley et al., 2014
	Methylphenidate	↑↑	↑↑		Koda et al., 2010
	Cocaine	↑↑	↑	↑↑	Shen et al., 2004; Pan et al., 1995; Pum et al., 2007
Antidepressants		↑	↑↑	↑↑	Jordan et al., 1994; Kobayashi et al., 2008
NK1R antagonists	Low arousal states	↑	↑	↑	Sections 2.2–2.4 (this article)
	High arousal states	↓	↓	↑↑	

Although d-amphetamine is not licensed as an antidepressant, it is still a first-line treatment for Attention Deficit Hyperactivity Disorder (ADHD), along with methylphenidate. Atomoxetine, a preferential noradrenaline reuptake inhibitor, is also endorsed as an effective treatment for ADHD. This raises interesting questions about neurobiological factors that are common to psychostimulants, antidepressants and drugs used to treat ADHD, which are discussed later.

Antagonists of the neurokinin-1 receptor (NK1R), for which substance P is the preferred endogenous ligand, comprise another group of compounds that increase motor activity in preclinical screens (e.g., Rupniak et al., 2001; Dableh et al., 2005; Yan et al., 2010). Not only do they resemble psychostimulants and antidepressants in these behavioural procedures, but they also increase the concentration of extracellular monoamines in the brain (especially serotonin: see below). On the basis of such evidence, NK1R antagonists have been investigated for antidepressant activity, but none has proved effective for this clinical indication so far.

However, early research of NK1R antagonists flagged the problem that the compound, CP 96345, binds to voltage-gated, L-type  $\text{Ca}^{2+}$ (v) channels ('LTCCs': Schmidt et al., 1992; Guard et al., 1993) as well as NK1R. It has long been acknowledged that this non-specific binding to LTCCs induces behavioural changes that resemble the response to antidepressants (and psychostimulants) in preclinical screens (Rupniak et al., 2001; Rupniak and Jackson, 1994). This binding to LTCCs is shared by many NK1R antagonists: those for which details have been published are listed in Table 2. However, two compounds that have been widely used in preclinical research, (S) GR 205171 and (S) SR 140333, can be regarded as selective NK1R antagonists because their binding affinity for the human NK1R is approximately  $10^5$ -fold higher than for LTCCs.

Against this background, it is interesting to appraise the extent to which the pharmacology of NK1R antagonists resembles that of psychostimulants and antidepressants, *versus* the possibility that they represent a novel class of compounds with a distinct pharmacological profile. In so doing, this article will also consider how LTCCs could modify the neurochemical and behavioural responses to these three groups of compounds. The final sections will discuss the therapeutic implications of functional interactions between LTCCs and NK1R antagonists in the light of evidence that a deficit in activated NK1R in mice induces behavioural abnormalities that resemble those seen in ADHD.

## 2. Psychostimulants, antidepressants and NK1 receptor (NK1R) antagonists have distinct effects on extracellular monoamines (Table 1)

### 2.1. Psychostimulants and antidepressants augment serotonergic, noradrenergic and dopaminergic transmission

It is well established that acute systemic administration of the psychostimulants, cocaine, methylphenidate or d-amphetamine, increases the extracellular accumulation of monoamines in the

forebrain, especially the catecholamines, noradrenaline and dopamine (Chen and Reith, 1994; Kuczenski et al., 1995; Rowley et al., 2014). This action is thought to explain the motor arousing effects of these drugs. Cocaine also causes a prominent increase in extracellular serotonin, but methylphenidate is exceptional in that, despite binding to the same site as cocaine on the dopamine transporter, it has low affinity for the serotonin transporter and does not increase extracellular serotonin (Kuczenski and Segal, 1997; Pum et al., 2007; Fleckenstein et al., 1999).

Acute administration of antidepressants similarly causes an (impulse-dependent) increase the extracellular concentration of noradrenaline and serotonin in the forebrain, an action that is consistent with their high affinity for NET and/or SERT. However, they also increase the concentration of extracellular dopamine (e.g., Kitaichi et al., 2010; Hudson et al., 2012; Cadeddu et al., 2013). In most cases, this will be mediated indirectly through (synaptic) interactions with serotonergic or noradrenergic neurones because, with few exceptions, established antidepressants have negligible affinity for the DAT (see: Stanford, 1996a; Tatsumi et al., 1997).

An increase in the extracellular concentration of any of the monoamines could influence motor activity (Auclair et al., 2004; Rowley et al., 2014). However, an increase in dopaminergic transmission is likely to be essential for preventing anhedonia, impaired executive function and deficits in motivation, all of which are key features of depression (Argyropoulos and Nutt, 2013; Salamone and Correa, 2012).

### 2.2. NK1R antagonists augment serotonin transmission

All reports indicate that a functional deficit in NK1R increases serotonergic transmission in the brain. For instance, acute systemic administration of an NK1R antagonist increases extracellular serotonin in the frontal cortex (e.g., GR 205171 or L 733060: Lejeune et al., 2002; Guiard et al., 2005). An increase in serotonin release was also found in a study of freely-moving mice with functional ablation of the NK1R gene (NK1R<sup>-/-</sup>) (Froger et al., 2001). Moreover, local infusion of a NK1R antagonist into the forebrain augmented the serotonergic response to stress (Ebner et al., 2008).

Again, there is no evidence that NK1R antagonists inhibit monoamine transporters directly and so any increase in serotonergic transmission presumably arises from an increase in impulse-dependent release of transmitter. This could follow an increase in the firing-rate of raphe neurones projecting to forebrain regions, which depends on input from noradrenergic neurones (Haddjeri and Blier, 2008). However, it could also be mediated by preventing NK1R in the terminal field from activating a possible GABAergic inhibition of serotonin release (Ebner et al., 2008) (Fig. 1).

Although NK1R antagonists have not fulfilled expectations as antidepressants in their own right, they are still being developed as adjuncts to established antidepressant treatments (e.g., Lelas et al., 2013). However, it would probably be inadvisable to co-administer an NK1R antagonist with a selective serotonin reuptake inhibitor because the combined administration of drugs that increase

**Table 2**

Published reports of NK1R antagonist binding to different domains on LTCCs (pK<sub>i</sub> is specified when these are reported). 'Yes': substantial displacement of the radioligand by the NK1R antagonist has been reported. 'No': no evidence of displacement of the radioligand by the NK1R antagonist has been reported.

	Dihydropyridine [e.g. nifedipine]	Benzothiazepines [e.g. diltiazem]	Phenylalkylamine [e.g. verapamil]	References
CP 96345	CP 96345 reduces K <sub>D</sub> for [3H]-nimodipine binding	K <sub>i</sub> 22.5 nM (rat cerebral cortex)	Yes	Guard et al., 1993 McLean et al., 1993
CP 96345	No		Yes	Constantine et al., 1994
CP 96345	Yes	Yes	Yes	McLean et al., 1993
CP 96345	Yes	Yes	Yes	Lombet and Spedding, 1994 McLean et al., 1993
CP 96345 (Displacement of 0.25 nM [3H]desmethoxyverapamil)			IC50: 41 nM	
CP 99994 (Displacement of 0.25 nM [3H]desmethoxyverapamil)			IC50: 3.4 μM	McLean et al., 1993
CP 99994	No	No	Yes	Lombet and Spedding, 1994
GR 203040	No	No	No	Beattie et al., 1995
GR 205171 [rat brain]	pK <sub>i</sub> 5.6	pK <sub>i</sub> 5.6 pK <sub>a</sub> : 8.3	pK <sub>i</sub> < 5	Gardner et al., 1996
L 733060		IC50: 0.9 nM	IC50: 760 nM	Harrison et al., 1995
RP 67580	Yes	Yes	Yes	Lombet and Spedding, 1994
RP 67580		Yes		Rupniak et al., 1993
RP 67580 (Displacement of 0.25 nM [3H]desmethoxyverapamil)			210 nM	McLean et al., 1993

serotonin release with a serotonin reuptake inhibitor risks inducing serotonin toxicity (Stanford and Stanford, 1999; Stanford et al., 2010).

### 2.3. NK1R antagonists blunt noradrenergic transmission during arousal/stress

NK1R antagonists, like psychostimulants and established antidepressants, can augment noradrenergic transmission but reports are not as consistent as those for serotonin. Acute administration of the selective antagonist, GR 205171, increased extracellular noradrenaline in rat forebrain in one study (Millan et al., 2001) but not others (Renoldi and Invernizzi, 2006; Bert et al., 2002).

Neither GR 205171 nor functional ablation of the NK1R gene in NK1R<sup>-/-</sup> mice affected extracellular noradrenaline in the prefrontal cortex of freely-moving mice (Zocchi et al., 2003; Fisher et al., 2007).

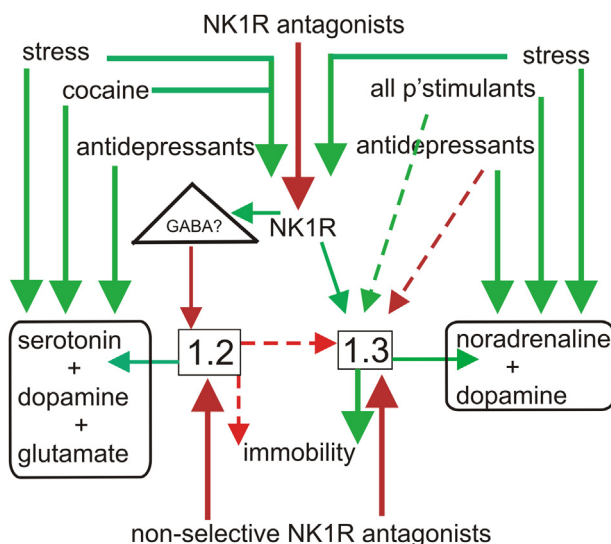
By contrast, chronic administration of the antagonist, L 760735, induced burst-firing of noradrenergic neurones in the locus coeruleus of anaesthetized subjects (Maubach et al., 2002). This is consistent with the greater concentration of extracellular noradrenaline in the frontal cortex of anaesthetized NK1R<sup>-/-</sup> mice, by comparison with their wildtypes (Herpfer et al., 2005; Fisher et al., 2007).

These findings could suggest that noradrenaline release increases only when there is a high degree of NK1R receptor occupancy by antagonists. A second explanation, for which there is some evidence (Fisher et al., 2007), is that a deficit in activation of NK1R blunts noradrenaline release in aroused animals. This proposal is consistent with the finding that, unlike serotonin, GR 205171 prevented a stress-induced increase in extracellular noradrenaline in the prefrontal cortex of freely-moving rodents (Renoldi and Invernizzi, 2006; Ebner and Singewald, 2007). It also fits with evidence that arousing/stressful stimuli increase release of substance P in the region of the locus coeruleus (Ebner and Singewald, 2007), which increases the firing-rate of noradrenergic neurones projecting from this nucleus (Guyenet and Aghajanian, 1977).

As discussed in detail elsewhere (Yan et al., 2009), a lack of functional NK1R would cause excessive noradrenergic transmission during low states of arousal, but a deficit in noradrenergic transmission as arousal increases. This bidirectional disruption of central noradrenergic transmission would impair the response to stressful stimuli, including cognitive performance ('selective attention': see also: Section 5).

### 2.4. NK1R antagonists blunt dopaminergic transmission during arousal/stress

There is one report that dopamine release is increased by local infusion of the non-selective NK1R antagonist, CP 96345, into the rat striatum (Gygi et al., 1993). However, the majority of studies have found that NK1R antagonists blunt dopamine transmission in this brain region. For instance, the NK1R antagonist, L 732138, prevented the dopamine-dependent decrease in the amplitude of inhibitory postsynaptic currents (IPSCs) in nucleus accumbens



**Fig. 1.** A schematic representation of a hypothetical network, incorporating functional communication between NK1R and Ca(v)1.2 and Ca(v)1.3 channels, that modulates motor activity and monoamine release during arousal/stress (e.g., the forced swim test and tail suspension tests). The scheme, which is based on evidence described throughout this article, could explain the overlap and key differences in the effects of NK1R antagonists, antidepressants and psychostimulants on motor immobility and monoamine release. Solid arrows indicate functional links for which experimental evidence already exists. Dotted arrows indicate functional links that are implied, but not confirmed, by experimental evidence. Green = activate; red = inhibit.

*in vitro*, a response that is triggered by substance P (Kombian et al., 2003). Local infusion of CP 96345, or systemic administration of another antagonist, WIN 51708, similarly prevented the release of acetylcholine from striatal interneurons mediated by dopaminergic (D1) receptors. CP 96344, an enantiomer of CP 96345 that binds to LTCCs, but not NK1R, did not prevent acetylcholine release, confirming that the response to CP 96345 can be attributed to antagonism of NK1R (Anderson et al., 1994).

So far, only one study has monitored striatal extracellular dopamine in freely-moving NK1R<sup>-/-</sup> mice (Yan et al., 2010). There was no difference in basal efflux of dopamine in NK1R<sup>-/-</sup> and wildtypes but, notably, there was no increase in extracellular dopamine in NK1R<sup>-/-</sup> mice after treatment with d-amphetamine. This echoes a report that local infusion of the NK1R antagonist, L 733060, into the rat striatum prevented an increase in extracellular dopamine following systemic administration of cocaine (Loonam et al., 2003) (See also: Section 4.4).

A similar pattern is evident from studies of the prefrontal cortex. Systemic administration of GR 205171 increased baseline extracellular dopamine in one study of rats (Lejeune et al., 2002) but not another, using mice (Zocchi et al., 2003). However, as with noradrenaline (see above), GR 205171 abolished the dopamine response to arousal/stress (Renoldi and Invernizzi, 2006; Hutson et al., 2004). This could explain why, in a microdialysis study of freely-moving NK1R<sup>-/-</sup> mice, extracellular dopamine in this brain region was considerably lower than in wildtypes at baseline and why the higher concentration of extracellular dopamine in the wildtypes dissipated after administration of the antagonist, RP 67580 (Yan et al., 2010) (Fig. 1).

## 2.5. Summary

A functional deficit of NK1R seems to increase serotonin release, especially during arousal/stress. However, there is no consistent evidence that a lack of functional NK1R increases noradrenaline release in freely-moving subjects and such a response is even more uncertain for dopamine. Instead, the evidence suggests that NK1R antagonists prevent dopamine and noradrenaline responses to arousing/stressful stimuli as well as the striatal dopaminergic response to psychostimulants. These are interesting findings, not least because there is a well-established cross-sensitization of the behavioural and neurochemical responses to repeated exposure to stress and d-amphetamine (Antelman et al., 1980; Cruz et al., 2012), which suggests that these two stimuli could have neurobiological targets in common. Whether or not this is the case, any blunting of central dopaminergic (and possibly noradrenergic) transmission by NK1R antagonists distinguishes these drugs from psychostimulants (e.g., Kuczenski et al., 1991; Lillrank et al., 1999).

Disruption of the catecholamine response to stress by NK1R antagonists is also hard to reconcile with these compounds being regarded as putative antidepressants. This is mainly because established antidepressants augment, rather than reduce, monoamine responses to stress (e.g., Page and Lucki, 2002). Yet, NK1R antagonists evidently increase motor activity in behavioural screens for antidepressants: indeed, such a response in humans could have beneficial effects in treating psychomotor retardation in depression. However, as explained above, dopaminergic transmission makes an essential contribution to promoting motivation and cognition, as well as preventing anhedonia, and so any disruption of dopaminergic transmission by NK1R antagonists would limit their efficacy as antidepressants. Nevertheless, it is possible that the blunting of dopaminergic transmission contributes to the antiemetic effects of apripitant and other NK1R antagonists that are under development for this clinical application (see: Yoshikawa et al., 2001).

## 3. L-type Ca<sup>2+</sup> (v) channels (LTCCs) modulate monoamine transmission

### 3.1. LTCC activation

LTCCs are voltage-gated Ca<sup>2+</sup> channels (Ca(v)), which are defined pharmacologically by their high sensitivity to blockade by dihydropyridines (see below). Two subtypes are expressed in comparatively high densities in the brain: Ca(v)1.2 and Ca(v)1.3: Hirota and Lambert, 1997). About 90% of these are a splice variant of Ca(v)1.2 channels (Ca(v)1.2c; Sinnegger-Brauns et al., 2009), which are found mainly on cell bodies and proximal dendrites of glutamatergic neurones in the cortex and striatum and, to a lesser extent, the cerebellum (Hell et al., 1993).

Activation of LTCCs by BayK 8644 increases the release of all three monoamines in the striatum (serotonin, noradrenaline and dopamine: Sinnegger-Brauns et al., 2004; dopamine: Watanabe et al., 1998; Maruya et al., 2003; but see: Kasim et al., 2006). BayK 8644 also invariably augments K<sup>+</sup>-evoked release of serotonin (e.g., Middlemiss and Spedding, 1985), noradrenaline (Ginap et al., 1993; Sabrià et al., 1995) and dopamine (Woodward and Leslie, 1986; Watanabe et al., 1998) in the brain. This monoamine response to BayK 8644 is likely to contribute to the increase in motor activity on local infusion of this drug into the striatum (e.g., Watanabe et al., 1998; Maruya et al., 2003).

A series of important and highly relevant findings have emerged from studies of genetically-altered mice with functionally inactivated Ca(v)1.2 or Ca(v)1.3 channels. When Ca(v)1.2<sup>-/-</sup> mice were treated with BayK 8644, the release of noradrenaline was unaffected and the dopamine response was reduced, but the serotonin (and glutamate) response was abolished altogether. By contrast, in Ca(v)1.3<sup>-/-</sup> mice, the noradrenaline response was abolished and the dopamine release was again blunted, but the serotonin and glutamate response was unaffected (Sinnegger-Brauns et al., 2004). It was inferred from this work that activated Ca(v)1.3 channels augment noradrenaline release, whereas Ca(v)1.2 channel activation augments serotonin (and glutamate) release, and both channels augment dopamine release (see also: Sagala et al., 2012). It is striking that Ca(v)1.3 channels promote release of catecholamines (as do psychostimulants and antidepressants), whereas Ca(v)1.2 channels promote release of serotonin (as do empathogens and antidepressants).

As well as their role in BayK 8644-evoked release of monoamines, LTCCs modulate dendritic release of serotonin (Colgan et al., 2012; Trueta and De-Miguel, 2012). Serotonin released through this process is thought to activate somatodendritic 5-HT<sub>1A</sub> autoreceptors, which blunt serotonin release in the terminal field (Colgan et al., 2012). If, as is widely believed, activation of these 5-HT<sub>1A</sub> autoreceptors delays the onset of antidepressant, then prevention of dendritic release of serotonin by LTCC-blockers should reduce this therapeutic lag. Indeed, there is evidence that LTCC blockers do have beneficial effects in treating depression (Busquet et al., 2010; Casamassima et al., 2010).

LTCCs also influence postsynaptic monoaminergic neurotransmission. For instance, LTCC-opening underlies a prolonged after-hyperpolarisation in the prefrontal cortex, which is triggered by activation of dopaminergic (DRD2) receptors: this process regulates the excitability of pyramidal neurons, which are the conduit for cortical output (Gee et al., 2012). LTCCs contribute to a prolonged after-hyperpolarisation, which is triggered by activation of  $\beta_1$ -adrenoceptors in the hippocampus (Zhang et al., 2013), and they also modulate the response to activation of 5-HT<sub>2A</sub> receptors in the nucleus accumbens (Burattini et al., 2013).

In short, LTCCs influence monoamine transmission through several mechanisms, both up- and downstream of transmitter

release in the terminal field. As discussed below, evidence suggests that these processes modify animals' motor motivation and behaviour, especially during arousal/stress.

### 3.2. LTCC blockade

Three classes of drugs act as LTCC-blockers: *dihydropyridines* (e.g., nifedipine and nimodipine); *benzothiazepines* (e.g., diltiazem) and *phenylalkylamines* (e.g., verapamil). Dihydropyridines bind to all LTCCs but preferential binding of the phenylalkylamine, verapamil, defines Ca(v)1.2 channels, whereas diltiazem is used to define Ca(v)1.3 binding (see: Tuckwell, 2012). Some dihydropyridines promote, rather than prevent, LTCC channel-opening (e.g., BayK 8644) but an equivalent spectrum of action, from full channel-activators to full channel-blockers, has not been reported for benzothiazepines or phenylalkylamines. In fact, there is scope for a broad spectrum of responses to LTCC blockers. This is because there is negative allosteric coupling between the dihydropyridine site and the phenylalkylamine sites (i.e., diltiazem binding is reduced by phenylalkylamines), whereas the dihydropyridine and benzothiazepine sites are positively coupled (i.e., dihydropyridine binding is increased by benzothiazepines) (see: Rosenzweig-Lipson and Barrett, 1995).

LTCC blockers consistently prevent a BayK 8644-induced increase in monoamine release (Middlemiss, 1985; Pullar and Findlay, 1992; Dobrev and Andreas, 1997; El Ayadi et al., 2001; Zhu et al., 2004). By contrast, they do not have any prominent effects on K<sup>+</sup>-induced release of monoamines (c.f., Nordström et al., 1986; Pileblad and Carlsson, 1986; Viveros et al., 1996). On this basis, it has been suggested that the effects of LTCC blockade on monoamine transmission are especially important during states of heightened arousal (e.g., during stress), which recruit activated LTCCs (Schenberg et al., 2000; Zhu et al., 2004). This could explain why systemic doses of LTCC-blockers that do not affect spontaneous locomotor activity (e.g., Czyrak et al., 1990; Cohen et al., 1997; Zhang et al., 2003) can increase motor activity in the forced swim and tail suspension tests (Tazi et al., 1991; Cohen et al., 1997), which again predicts beneficial effects in treating motor retardation in depression (Busquet et al., 2010; Casamassima et al., 2010).

## 4. L-type Ca<sup>2+</sup>(v) channels (LTCCs) influence the responses to psychostimulants, antidepressants and NK1R antagonists

### 4.1. Acute response to psychostimulants

An early study of isolated snail neurones showed that cocaine and d-amphetamine increased inward Ca<sup>2+</sup> currents, a response thought to be mediated by LTCCs (Vislobokov et al., 1993). Since then, there have been remarkably few studies of how the response to psychostimulants might be influenced by LTCCs. There is one report that the dopamine response to cocaine is prevented by dihydropyridines, but not other classes of LTCC-blockers (Pani et al., 1990). There is no evidence that psychostimulants bind to these channels and so it was inferred that cocaine activates dihydropyridine-sensitive LTCCs indirectly. If so, this action could contribute to the prominent increase extracellular serotonin and dopamine induced by cocaine (Fig. 1).

As regards the influence of LTCCs on the behavioural response to psychostimulants, some reports suggest that dihydropyridines and diltiazem prevent cocaine-induced hyperactivity but not that induced by d-amphetamine (Moore et al., 1993; Ansah et al., 1993, 2002), which again points to activation of LTCCs by cocaine. Others have found LTCC-blockers do not affect the behavioural response to either cocaine (Rogério and Takahashi, 1990) or d-amphetamine (Rosenzweig-Lipson and Barrett, 1995; Bourson et al., 1989),

whereas a primate study found that verapamil prevented certain spontaneous or d-amphetamine-induced behaviours (aggression, hypervigilance, stereotypy, oral hyperkinesia and tachypnoea) but not others (Palit et al., 2001). However, LTCC blockers from different classes produce distinct shifts in the dose/response profiles for motor behaviour triggered by BayK 8644 and psychostimulants (Rosenzweig-Lipson and Barrett, 1995). This is likely to be because of differences in their allosteric modulation of LTCC function (Section 3.2).

Clearly, there is a need for more research in this area to reconcile these disparate reports.

### 4.2. Chronic treatment with psychostimulants (sensitization)

There is stronger evidence that LTCCs contribute to the behavioural sensitization that develops on chronic administration of psychostimulants. This is not least because repeated administration of the LTCC-activator, BayK 8644, alone, sensitizes rats to a subsequent dose of cocaine (Licata et al., 2000).

All classes of LTCC blockers prevent the development and/or expression of behavioural sensitization to d-amphetamine at doses that do not affect the response to acute treatment (Karler et al., 1991; Pierce et al., 1998). LTCC-blockers also prevent development of d-amphetamine-induced conditioned place preference (Pucilowski et al., 1993, 1995). Even verapamil prevented the enhanced dopamine response to locally infused d-amphetamine in cocaine-sensitized rats (Pierce et al., 1998), despite its poor penetration of the brain.

This evidence that LTCCs are needed to develop and/or express behavioural sensitization to psychostimulants is underpinned by studies of (null-function) Ca(v)1.2<sup>-/-</sup> or Ca(v)1.3<sup>-/-</sup> mice (reviewed by: Striessnig et al., 2006). Foremost is the finding that Ca(v)1.3<sup>-/-</sup> mice do not develop sensitization to d-amphetamine (Giordano et al., 2006). By contrast, Ca(v)1.2<sup>-/-</sup> mice do develop sensitization to cocaine and amphetamine. However, expression of sensitization is prevented by nifedipine in wildtypes but not Ca(v)1.2<sup>-/-</sup> mice (Giordano et al., 2010). This could be explained if activation of Ca(v)1.2 channels leads to inhibition of Ca(v)1.3 channel-opening (Fig. 1).

Overall, these findings suggest that Ca(v)1.3 channels are essential for development and/or expression of behavioural sensitization to psychostimulants and that blockade of Ca(v)1.2 channels prevents expression of a pre-existing sensitized response (Giordano et al., 2010). It is interesting that Ca(v)1.3 channels, which augment noradrenaline and dopamine release (as do psychostimulants), are essential for development of sensitization during chronic treatment with psychostimulants. The possibility that this sensitization rests on an increase in catecholamine release following activation of Ca(v)1.3, versus some other downstream factor, merits further investigation.

This proposal prompts the question of what endogenous factor could link psychostimulants with activation of LTCCs? Substance P is a promising candidate not least because low doses of methamphetamine increase the concentration of extracellular substance P in the striatum (Hanson et al., 2002) and d-amphetamine increases immunoreactive substance P in the ventral striatum (Furmidge et al., 1993). Furthermore, local infusion of substance P into the striatum increases dopamine efflux (Reid et al., 1991) whereas infusion of the NK1R antagonist, L 733060 prevents a cocaine-induced increase in extracellular dopamine (Kraft et al., 2001; Loonam et al., 2003). It seems that release of substance P, acting via NK1R, could augment the dopamine response to psychostimulants. In fact, it has even been suggested that substance P has psychogenic actions, along the lines of psychostimulants (Kombian

et al., 2003). Evidence that binding of substance P to NK1R activates LTCCs is discussed below (Section 4.3).

#### 4.3. Antidepressants

A report that LTCCs are targeted by antidepressants emerged from the finding that antidepressants from different classes blunted the response of the guinea-pig ileum to substance P, an action that was attributed to convergence of their effects on LTCCs (Boselli et al., 2007). Although it is the Ca(v)1b splice variant that is expressed in intestinal smooth muscle, antidepressants also prevent LTCC-opening in synaptosomes derived from several regions of the forebrain, which will express mainly the Ca(v)1.2c and/or Ca(v)1.3 subtypes (e.g., Deák et al., 2000; Lavoie et al., 1994, 1997).

Furthermore, mice with functionally inactivated Ca(v)1.3<sup>-/-</sup> show less immobility than their wildtypes in the swim test (Sinnegger-Brauns et al., 2004), suggesting that activation of Ca(v)1.3 channels exacerbates this immobility (Fig. 1). Indeed, this is consistent with the finding that BayK 8644 increases the immobility of Ca(v)1.2<sup>-/-</sup> mice in this test (Sinnegger-Brauns et al., 2004). However, a reduction in immobility in Ca(v)1.3<sup>-/-</sup> mice does not rule out the possibility that activation of Ca(v)1.2 increases motor activity directly and/or inhibits the immobility induced by Ca(v)1.3 channel-opening (Fig. 1).

The lack of any difference in spontaneous activity of Ca(v)1.3<sup>-/-</sup> mice and their wildtypes (Busquet et al., 2010) suggests that reduced immobility (increased motor activity) in Ca(v)1.3<sup>-/-</sup> mice, compared with wildtypes, is apparent only when the animals are aroused or stressed, as would be the case in the swim test (Benedict et al., 1979; Stanford, 1995, 1996b). Blockade of Ca(v)1.3 channels by antidepressants could contribute to the reduction in immobility in these preclinical behavioural screens, therefore. Such an action would distinguish antidepressants from psychostimulants, which seem to augment rather than blunt LTCC-activation.

#### 4.4. NK1R antagonists

The evidence that activated Ca(v)1.3 channels increase immobility in the swim test (Sinnegger-Brauns et al., 2004) again points to Substance P as an endogenous factor that triggers this process during arousal/stress. First, release of substance P in the region of the locus coeruleus, at least, is increased by stress (e.g., Ebner and Singewald, 2007). Secondly, there is evidence that this peptide opens LTCCs: an action mediated by G<sub>q/11</sub> protein-coupled NK1R (Endoh, 2006). There is the additional possibility that activation of NK1R blunts Ca(v)1.2 channel opening, which would disinhibit immobility mediated by Ca(v)1.3 channels (Fig. 1).

If, as proposed, substance P augments Ca(v)1.3 channel-opening, then selective NK1R antagonists would diminish this response by blocking the cascade that couples activation of NK1R with these channels (Fig. 1). In view of evidence that activation of Ca(v)1.3 channels augments noradrenaline and dopamine, but not serotonin, release (see: Section 3.1), NK1R antagonists would be predicted to diminish the catecholamine response, but not the serotonin response, to arousal/stress (Fig. 1). Indeed, this could explain the prevention of the dopaminergic and noradrenergic, but not serotonergic, response to stress in mice lacking functional NK1R (Section 2; Fig. 1). Non-selective NK1R antagonists would be expected to be even more effective inhibitors of the immobility and catecholamine response during arousal/stress. This is because the effects of Ca(v)1.3 channel blockade on these responses would be additive with those of NK1R antagonism.

The evidence that NK1R antagonists blunt the catecholamine response, but augment the serotonergic response, to stress suggests that the functional coupling of these NK1R to Ca(v)1.2 (augments

serotonin and dopamine release) and Ca(v)1.3 (augments noradrenaline and dopamine release) recruits different second messengers, or neuronal networks, or both. The scheme in Fig. 1 explains how the influences of these channels could converge in the regulation of motor activity during stress. Evidence described in the next section suggests that activation of LTCCs is also involved in the modulation of motor impulsivity by NK1R.

### 5. Implications for the causes and treatment of ADHD

The possibility that a functional network, along the lines of that proposed in Fig. 1, could affect response control, as well as stress-induced motor behaviour, has emerged from recent studies of genetically-altered mice that lack functional NK1R (NK1R<sup>-/-</sup>).

As described above, regulation of catecholamine and serotonin release is disrupted in both NK1R<sup>-/-</sup> mice and wildtypes that have been treated with an NK1R antagonist (see Section 2). NK1R<sup>-/-</sup> mice also express locomotor hyperactivity (Yan et al., 2010). Furthermore, when tested in the 5-Choice Serial Reaction Time Task (5-CSRTT), NK1R<sup>-/-</sup> mice displayed deficits in cognitive performance and response control (Yan et al., 2011). Specifically, NK1R<sup>-/-</sup> mice carried out more *premature responses* (an index of impulsivity) and *omission errors* (an index of inattentiveness) than wildtypes. Because *hyperactivity*, *impulsivity* and *inattentiveness* are core diagnostic features of ADHD, we have proposed that impairment of NK1R function disrupts cognitive performance/response control in these mice and could do so in ADHD patients also. This is supported by evidence that the *TACR1* gene (the human equivalent of NK1R) is associated with ADHD, with four markers showing allelic association. Two haplotypes were also associated with ADHD, suggesting more than one disease mutation (Yan et al., 2010).

These findings led us to propose that behavioural abnormalities of NK1R<sup>-/-</sup> mice should be replicated in wildtypes that have been treated with an NK1R antagonist (RP 67580 or L 733060). As predicted, both these drugs increased locomotor activity in wildtypes, but not NK1R<sup>-/-</sup> mice (Yan et al., 2010). However, the behavioural effects of these antagonists in the 5-CSRTT were more complex. Whereas a low dose of either RP 67580 or L 733060 exacerbated *premature responses* by wildtypes, a higher dose of either drug prevented this increase (Weir et al., 2013). Moreover, the higher dose of RP 67580 increased *omission errors* in both genotypes. Because this increase occurred in both mouse genotypes, we inferred that it might have arisen from blockade of LTCCs by the (non-selective) NK1R antagonists and that LTCC-blockade could also mask the increase in *premature responses* induced by the lower drug doses. This proposal was confirmed by another study in which the LTCC-blocker, nifedipine, similarly reduced *premature responses* and increased *omission errors* in both NK1R<sup>-/-</sup> and wildtype mice (Dudley et al., 2013).

It is widely accepted that disruption of serotonergic transmission in corticostriatal circuits exacerbates impulsivity (e.g., Dalley et al., 2002). If this is the case in NK1R<sup>-/-</sup> mice, then the scheme in Fig. 1 points to *premature responses* arising primarily from disruption of Ca(v)1.2 channel-opening because these channels augment serotonin release. This is supported by the additional finding that the potency of nifedipine for reducing *premature responses* was lower in NK1R<sup>-/-</sup> mice than the wildtypes (Dudley et al., 2013). This could be explained by a compensatory increase in LTCC activation in NK1R<sup>-/-</sup> mice, which would echo findings in studies that have compared the Spontaneously Hypertensive Rat (SHR), an established rodent model of ADHD, with their Wistar Kyoto (WKY) controls (Ohya et al., 1998; Pratt et al., 2002). It would also fit with the greater density of [<sup>3</sup>H]nifedipine binding sites in the striatum of SHR rats, compared with their WKY controls (Ross and Monis, 1988). Alternatively, because nifedipine has greater

efficacy at Ca(v)1.2 channels, the lower potency of this drug in NK1R<sup>-/-</sup> mice could reflect a shift to a greater influence of Ca(v)1.3 channels on this behaviour (see: [Sinnegger-Brauns et al., 2009](#)).

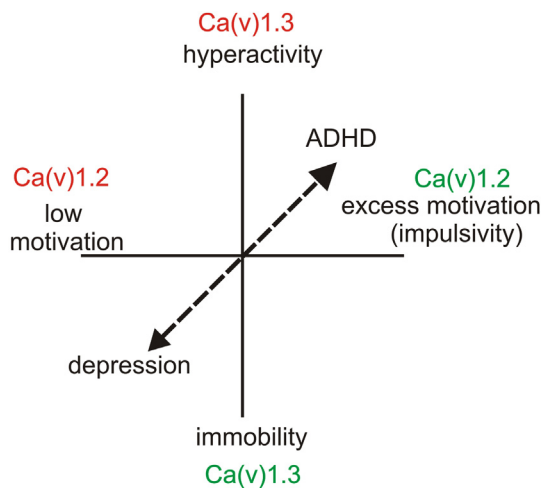
Collectively, this evidence further indicates that LTCC blockers could have beneficial effects in treating ADHD. Indeed there is already evidence to support this proposal in rats ([Meneses and Hong, 1998](#)), adult humans ([Schwartz et al., 1997](#); [Hanyu et al., 2007](#)) and children with renal hypertension ([Krause et al., 2009](#)). The findings described here suggest that LTCC-blockers might be most effective in relieving the predominantly hyperactive/impulsive subtype of this disorder.

However, it is possible that these channels modulate attention as well as motor activity and response control. Noradrenergic transmission from the locus coeruleus to the prefrontal cortex has a key role in regulating this aspect of cognitive performance ([Aston-Jones et al., 1999](#); [Dayan and Yu, 2006](#)). Expression of Ca(v)1.3-channels is comparatively dense in brainstem regions, especially in the locus coeruleus and motor nuclei ([Sukiasyan et al., 2008](#)), and all noradrenergic cell bodies in the locus coeruleus express NK1R ([Ma and Bleasdale, 2002](#)).

## 6. Conclusions

The evidence outlined in this article suggests that NK1R antagonists increase motor activity, as do psychostimulants, and prevent immobility in the swim test, as do both psychostimulants and antidepressants. NK1R antagonists also resemble antidepressants in that they augment release of serotonin but, unlike antidepressants and psychostimulants, they seem to blunt the catecholamine response during arousal. This makes it unlikely that NK1R antagonists qualify as either antidepressants or psychostimulants, but points to their forming a new class of compounds: 'motor disinhibitors'.

The neurochemical and behavioural responses to psychostimulants (during sensitization, at least), antidepressants and NK1R antagonists during arousal/stress, all seem to involve Ca(v)1.2 and Ca(v)1.3 channels to some extent. These channels preferentially augment impulse-dependent release of serotonin and noradrenaline, respectively, especially during arousal. Published findings point to the possibility that Ca(v)1.2 channels predominantly augment motor motivation, which reflects evidence that



**Fig. 2.** The association between serotonergic and catecholaminergic transmission and impulsivity/motor activity suggests that Ca(v) 1.2 and Ca(v)1.3 channels could have a key role in governing a continuum of motor behaviour, ranging from psychomotor retardation (depression) to high impulsivity/hyperactivity (ADHD). Channel labelling: red = low channel activation; green = high channel activation.

serotonergic transmission in the brain gates motor activity: *i.e.*, response control ([Jacobs and Azmitia, 1992](#)). On the other hand, Ca(v)1.3 channels seem to influence motor activity more directly.

As part of an integrated network, convergence of NK1R on these two LTCCs could influence a spectrum of motor responses to stress. A lack of motivation to respond *versus* excessive motivation (impulsivity), influenced by Ca(v)1.2 channels, would interact with immobility *versus* hyperactivity, influenced by Ca(v)1.3 channels ([Fig. 2](#)). If this is the case, it is possible that the psychomotor retardation in depression and motor hyperactivity/impulsivity in ADHD reflect opposite poles of a behavioural continuum.

To understand the functional interaction between NK1R and Ca(v) channels and their role in the regulation of motor behaviour could hold the key to explaining why psychostimulants augment the motor response to stress (*e.g.*, the swim test) and yet have beneficial (calming) effects in ADHD and why antidepressants offer little, if any, benefit in treating this disorder.

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