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COMMENTARY

JP-1302: a new tool to shed light on the roles of α_{2C}-adrenoceptors in brain

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The discovery of JP-1302 as a selective, high affinity antagonist at the α_{2C}-adrenoceptor will enable researchers to probe the functional role and address the therapeutic utility of this potentially highly important adrenoceptor subtype.
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The subdivision of α-adrenoceptors into the major groupings of α_1 and α_2 and the knowledge that these groupings are themselves heterogeneous predates molecular cloning approaches that have since confirmed the existence of three subtypes of α_1: α_{1A};α_{1B} and α_{1D} and three subtypes of α_2: α_{2A}; α_{2B} and α_{2C} (Alexander *et al*., 2006). Although the therapeutic exploitation of adrenoceptor subtypes has been relatively successful with respect to the pathophysiological role of noradrenaline in the periphery, non-selective α_1 and/or α_2- adrenoceptor agonists and/or antagonists have proved of relatively little use in the treatment of psychiatric and neurological indications. As few would doubt the importance of noradrenaline to brain function, this is likely to reflect different and perhaps opposing roles and distributions of 'subtypes of subtypes' that make clinical potential difficult to define using non-selective agents. That is not to say that useful medicines for psychiatric and neurological disorders do not have impact on adrenergic pharmacology. However, this has been more by accident than design: many polyvalent antipsychotics and a small number of antidepressants have appreciable affinity for adrenoceptors, although the clinical benefit (or cost) those interactions provide is difficult to fathom. The 'prototypical' atypical antipsychotic, clozapine has, for example, very high affinity for α_2-adrenoceptors and this property may contribute to the lower potential of clozapine to induce extrapyramidal side effects (Kalkman *et al*., 1998; Kleven *et al*., 2005).

In the absence of selective tools, much has been learned by investigating the effects of genetic alteration of the expression of adrenoceptor subtypes in mouse brain. With respect to α_2-adrenoceptors, α_{2A} appears to be predominantly presynaptic and responsible for exerting the classical effects of non-selective α_2-adrenoceptor agonists on neurotransmitter release, blood pressure (hypotension), arousal, nociception and body temperature (Kable *et al*., 2000). The α_{2B} subtype is thought to underlie adrenergic-agonist-induced hypertension (Makaritsis *et al*., 1999) but difficulties in breeding homozygous knockouts has limited more extensive phenotyping of these animals. In contrast, mice that are homozygous for α_{2C} gene deletion or overexpression are viable and have been reasonably well-characterized. Overall, both strains of mouse confirm that α_{2C} is not responsible for the classical effects of non-selective α_2-adrenoceptor agonists (see Kable *et al*., 2000), although the subtype does have some influence on neurotransmitter release (Bucheler *et al*., 2002; Zhang and Ordway, 2003), even if less so than does α_{2A} (Bucheler *et al*., 2002). However, the transgenic phenotypes make definition of the potential clinical applications of α_{2C}-selective ligands somewhat problematic. Thus, whereas α_{2C} knockout animals exhibit an 'antidepressant-like' profile in the forced swim test (FST) and overexpressing mice show a response consistent with greater learned helplessness in this paradigm (suggesting that α_{2C}-adrenoceptor antagonists have potential for treating stress-related disorders such as depression; Sallinen *et al*., 1999), data on prepulse inhibition of the auditory startle response (PPI) predict that α_{2C}-adrenoceptor *agonism* might be beneficial in situations where this response is impaired, such as schizophrenia (Sallinen *et al*., 1998a). α_{2C}-Adrenoceptor knockout mice also show hyper-responsiveness to amphetamine (Sallinen *et al*., 1998b), again consistent with the idea that an agonist might have antipsychotic properties.

And then, along comes JP-1302 (acridin-9-yl-[4-(4-methyl-piperazin-1-yl)-phenyl]amine). In the paper by Sallinen *et al.* (2007) in this issue, JP-1302 is described as a novel, highly selective α_{2C}-adrenoceptor antagonist with a K_i at the human α_{2C}-receptor of 16 nM – about 100-fold higher affinity than for α_{2A} or α_{2B}. Although this is not the first α_{2C}-selective compound to be identified, (OPC-28326 (4-(*N*-methyl-2-phenylethylamino)-1-(3,5-dimethyl-4-proprionylaminobenzoyl) piperidine) was noted by Sun *et al.* (2001) as having a K_i

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of 13.7, 3840 and 633 nM at α_{2C}, α_{2A} and α_{2B}-adrenoceptors, respectively), it is the first to have been examined behaviourally in rodents. Sallinen *et al.* (2007) show that doses of JP-1302 in the range of 1–10 μmol kg^{-1} decrease immobility time in the FST to a level similar to that seen with 10–30 μmol kg^{-1} of the antidepressant desipramine: the data are thus consistent with the response of the α_{2C} knockout and overexpressing mice. In marked contrast, however, the compound did not disrupt PPI and even enhanced the measure somewhat after a dose of 30 μmol kg^{-1}. More impressively though, a dose of 5 μmol kg^{-1} JP-1302 was capable of complete reversal of the impairment in PPI induced in Sprague–Dawley rats by the psychotomimetic NMDA receptor antagonist, phencyclidine and similar results were found in Wistar rats.

How could these latter findings be compatible with results using transgenic animals? There are many possibilities, not the least being differences between rats and mice. The authors consider the possibility that the transgenic animal data are confounded by physiological compensation during maturation. Another (related) possibility is that the α_{2C}-adrenoceptor plays some key early developmental role that alters the vulnerability of animals to NMDA receptor antagonism (and other psychostimulants?) in later life. Whatever the explanation, it is clear that there are many as yet unanswered questions about JP-1302 in particular and about α_{2C}-adrenoceptors in general. Is the compound able to reverse other behavioural, neurochemical or electrophysiological effects of blocking NMDA receptors. What about the response to amphetamine? Do α_{2C}-adrenoceptors play a key role in the pathogenesis of schizophrenia, so often thought of as a developmental disorder? or is the behavioural response to JP-1302 idiosyncratic to its chemical structure and nothing to do with α_{2C}-adrenoceptors? Assuming this not to be the case, the compound certainly warns against simplistic interpretations of data generated by gene deletion or overexpression experiments. From this perspective, it will be interesting to see whether JP-1302 has any significant positive impact on cognitive processes, as is suggested by the reversal by the non-selective α_2-adrenoceptor antagonist, atipamezole of the disturbed spatial navigation seen in α_{2C} overexpressing mice (Bjorklund *et al.*, 1999).

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