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Reply MI Receptor Agonism, a Possible Treatment for Cognitive Deficits in Schizophrenia

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Neuropsychopharmacology (2004) 29, 1585–1586. doi:10.1038/sj.npp.1300509

Sir

There is now a great deal of evidence implicating the involvement of acetylcholine in cognitive processes relevant to schizophrenia (Friedman *et al*, 1999). This in turn provides potential for remediation strategies by manipulation of acetylcholine and/or its receptors. In response to our recently published paper in this journal (Zavitsanou *et al*, 2004), Brian Dean provided evidence that muscarinic M1 receptor agonism might be a possible treatment for cognitive deficits in schizophrenia.

Cognitive processes relevant to schizophrenia are mediated by the anterior cingulate cortex (ACC, Brodman's area 24), which plays an important role in attention control (Bush et al, 2000) and the prefrontal cortex, which is involved in working memory and executive function (Goldman-Rakic, 1987). In our recently published paper (Zavitsanou et al, 2004), we reported a decrease in [³H]pirenzepine binding to M1 and M4 muscarinic receptors in ACC samples taken post-mortem from patients with schizophrenia. In agreement with our results are postmortem studies showing significant reductions of [³H]pirenzepine binding within the prefrontal cortex (Brodman's area 8, 9, 10, and 46) of patients suffering with schizophrenia (Crook et al, 2001; Dean et al 2002). Taken together, these studies indicate similar deficits in muscarinic M1/M4 receptors in cortical areas involved in different aspects of cognition.

Unfortunately, without specific ligands it is difficult to assign a specific muscarinic receptor subtype to deficits observed in both post-mortem and neuroimaging studies (eg Raedler *et al*, 2003). Whereas in BA9, a decrease in

Received 27 April 2004; accepted 03 May 2004

Online publication: 15 May 2004 at http://www.acnp.org/citations/ Npp05150404200/default.pdf; http://www.acnp.org/citations/ Npp05150404089/default.pdf [³H]pirenzepine binding was associated with a decrease in M1 but not M4 receptor protein and mRNA (Dean *et al*, 2002), no data are available to support a similar association in the ACC. Studies with muscarinic receptor knockout mice have begun to offer some enhanced understanding of the role of muscarinic receptor subtypes in cognition and psychosis. In this context, it is of interest that M1 receptor knockout mice show abnormalities in memory-relative cognitive behaviors (Anagnostaras *et al*, 2003), whereas mice lacking the M4 receptor show a deficit in prepulse inhibition of the startle reflex, a measure of attention (Felder *et al*, 2001).

Recent studies using acetylcholinesterase inhibitors support the notion that activation of cholinergic receptors would be an effective approach to reversing the cognitive deficits in schizophrenia (Buchanan *et al*, 2003). As acetycholinesterase inhibitors are nonspecific in their effects, targeting both nicotinic and muscarinic receptors, it is difficult to assess the potential of each subtype as a target for remediation strategies and its role in side effects. The genetic study by Liao *et al* (2003) suggests that involvement of M1 receptors might be critical in the genesis of cognitive deficits in schizophrenia, and therefore M1 receptor agonism might be a good remediation strategy for the treatment of the cognitive dysfunction in schizophrenia.

In vivo neuroimaging studies using subtype selective radioligands with appropriate potency, efficacy, and pharmacokinetic properties are necessary for the better understanding of the role of each muscarinic receptor in cognitive processes. Future development of a muscarinic agonist that can produce improvements in cognitive performance without producing side effects is warranted and may prove useful in treating the cognitive deficits associated with schizophrenia. However, since abnormalities in noncholinergic systems that are modulated by acetylcholine have been reported in the ACC in schizophrenia (Zavitsanou and Huang, 2002; Zavitsanou *et al* 2002), pharmacologic treatment of cognitive symptoms through manipulations of these neurotransmitter systems merits investigation.

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