Neuropsychopharmacology (2004) 29, 1585–1586

www.neuropsychopharmacology.org

Reply

M1 Receptor Agonism, a Possible Treatment for Cognitive Deficits in Schizophrenia

Katerina Zavitsanou*

Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD), Department of Biomedical Sciences, University of Wollongong, Northfields Avenue, NSW 2522, Australia

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 [^{3}H]pirenzepine binding to M1 and M4 muscarinic receptors in ACC samples taken post-mortem from patients with schizophrenia. In agreement with our results are post-mortem studies showing significant reductions of [^{3}H]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 [^{3}H]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.

*Correspondence: Dr K Zavitsanou, Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD), Department of Biomedical Sciences, University of Wollongong, Northfields Avenue, NSW 2522, Australia, Tel: +61 2 42213199, Fax: +61 2 42214096, E-mail: katerina_zavitsanou@uow.edu.au
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

REFERENCES

Anagnostaras SG, Murphy GG, Hamilton SE, Mitchell SL, Rahnama NP, Nathanson NM *et al* (2003). Selective cognitive dysfunction in acetylcholine M1 muscarinic receptor mutant mice. *Nat Neurosci* **6**: 51–58.

Buchanan RW, Summerfelt A, Tek C, Gold J (2003). An open-labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia. *Schizophr Res* **59**: 29–33.

Bush G, Luu P, Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* **4**: 215–222.

Crook JM, Tomaskovic-Crook E, Copolov DL, Dean B (2001). Decreased muscarinic receptor binding in prefrontal cortex from subjects with schizophrenia: a study of Brodmann's areas 8, 9, 10, and 46, and the effects of neuroleptic drug treatment. *Am J Psychiatry* **158**: 918–925.

Dean B, McLeod M, Keriakous D, McKenzie J, Scarr E (2002). Decreased muscarinic1 receptors in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry* **7**: 1083–1091.

Felder CC, Porter AC, Skillman TL, Zhang L, Bymaster FP, Nathanson NM *et al* (2001). Elucidating the role of muscarinic receptors in psychosis. *Life Sci* **68**: 2605–2613.

Friedman JI, Temporini H, Davis KL (1999). Pharmacologic strategies for augmenting cognitive performance in schizophrenia. *Biol Psychiatry* **45**: 1–16.

Goldman-Rakic PS (1987). Circuitry of the primate prefrontal cortex and the regulation of behavior by representational memory In: Plum F (ed). *Handbook of Physiology: The Nervous System, Higher function of the Brain*. American Physiological Society: Bethesda, MD. Vol **5** pp 373–417.

Liao DL, Hong CJ, Chen HM, Chen YE, Lee SM, Chang CY *et al* (2003). Association of muscarinic m1 receptor genetic polymorphisms with psychiatric symptoms and cognitive function in schizophrenia patients. *Neuropsychobiology* **48**: 72–76.

Raedler TJ, Knable MB, Jones DW, urbina RA, Gorey JG, Lee KS *et al* (2003). *In vivo* determination of muscarinic acetylcholine receptor availability in schizophrenia. *Am J Psychiatry* **160**: 118–127.

Zavitsanou K, Huang XF (2002). Decreased [^{3}H]spiperone binding in the anterior cingulate cortex of schizophrenia patients: an autoradiographic study. *Neuroscience* **109**: 709–716.

Zavitsanou K, Katsifis A, Mattner F, Huang XF (2004). Investigation of M1/M4 muscarinic receptors in the anterior cingulate cortex in schizophrenia, bipolar disorder and major depression disorder. *Neuropsychopharmacology* **29**: 619–625.

Zavitsanou K, Ward P, Huang XF (2002). Selective alterations in ionotropic glutamate receptors in the anterior cingulate cortex in schizophrenia. *Neuropsychopharmacology* **27**: 826–833.