

## Letter to the Editor

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

Brian Dean\*

The Rebecca L Cooper Research Laboratories, The Mental Health Research Institute of Victoria, Victoria, Australia

Neuropsychopharmacology (2004) 29, 1583–1584. doi:10.1038/sj.npp.1300508

Sir

The recent report in this journal of a decrease in [<sup>3</sup>H]pirenzepine binding in Brodmann's area (BA) 24 from subjects with schizophrenia (Zavitsanou *et al*, 2004) adds to a growing body of evidence that implicates muscarinic receptors in the pathology of schizophrenia (Dean *et al*, 2003). The significance of these most recent data on [<sup>3</sup>H]pirenzepine binding is that they show that changes in M1/M4 receptors have some diagnostic specificity as they are not present in bipolar disorder or major depression.

Studies of muscarinic receptors in schizophrenia have advanced to allow interpretation of [<sup>3</sup>H]pirenzepine binding to go beyond simple commentary on changes in M1/M4 receptors in schizophrenia. Of significance to findings on cortical [<sup>3</sup>H]pirenzepine binding are recent data showing that a decrease in binding of that radioligand in BA 9 from subjects with schizophrenia was associated with a decrease in M1, but not M4, receptor protein and mRNA (Dean *et al*, 2002). It is therefore intriguing to postulate that decreased [<sup>3</sup>H]pirenzepine binding in the cortex from subjects with schizophrenia is reflective of widespread decreases in levels of M1 receptors. This hypothesis is supported by a study that has shown a decrease in mRNA for the M1 receptor in BA 6 from subjects with schizophrenia (Mancama *et al*, 2003).

One of the problems in post-mortem CNS studies in schizophrenia is translating findings on changes in receptor densities to functional outcomes relating to the symptoms of the disorder. In the case of the M1 receptor, it is significant that one of the prominent features of M1 receptor knockout mice is that they show abnormalities in cognitive-related behavior (Anagnostaras *et al*, 2003). This suggests that the M1 receptor has a significant role in

maintaining normal cognitive function; this is especially significant given that subjects with schizophrenia have cognitive deficits (Pantelis *et al*, 1999) and low levels of cortical M1 receptors (Dean *et al*, 2002). The hypothesis that deficits in cortical M1 receptors may be related to cognitive deficits in schizophrenia has been further advanced by a recent study that showed that a C267C genotype at a A276C single-nucleotide polymorphism in the M1 receptor gene was associated with poor cognitive function in subjects with schizophrenia (Liao *et al*, 2003). Importantly, the C267C genotype was not associated with either schizophrenia or the severity of positive and negative symptoms. It would therefore seem that the M1 receptor is likely to play an important role in the genesis of cognitive deficits in schizophrenia.

Radioligands specific to the M1 receptor that can be used in neuroimaging have yet to be developed. However, a decrease in [<sup>3</sup>H]QNB binding to the global family of muscarinic receptors has been demonstrated in the prefrontal cortex, and other CNS regions, in drug-free subjects with schizophrenia using single photon emission tomography (Raedler *et al*, 2003). These data, plus data from post-mortem studies, strongly suggest there is a decrease in M1 receptors in the frontal cortex of subjects with schizophrenia, which could result in an underactivation of cholinergic pathways in the CNS of subjects with the disorder. It therefore seems logical that activation of the muscarinic/cholinergic pathways in the CNS would be an effective approach to reversing the cognitive deficits in schizophrenia. This approach is supported by recent studies using acetylcholinesterase inhibitors to increase acetylcholine levels in the CNS that have resulted in improved cognitive function in schizophrenia (Buchanan *et al*, 2003) and schizotypal personality disorder (Kirrane *et al*, 2001). Conversely, anticholinergic agents that block muscarinic receptors impair cognitive function in subjects with schizophrenia (Minzenberg *et al*, 2004). Thus, experimental neuropsychopharmacological and basic research findings support the hypothesis that activating muscarinic receptors will be a pharmacological intervention that will alleviate some of the cognitive deficits in schizophrenia. Moreover, post-mortem and genetic studies now suggest that activat-

\*Correspondence: Dr B Dean, The Rebecca L Cooper Research Laboratories, The Mental Health Research Institute of Victoria, 155 Oak Street, Parkville, Victoria 3052, Australia, Tel: + 613 9389 2940, Fax: + 613 9387 5061, E-mail: bdean@mhri.edu.au  
Received 1 March 2004; accepted 3 May 2004  
Online publication: 15 May 2004 at <http://www.acnp.org/citations/Npp05150404200/default.pdf>; <http://www.acnp.org/citations/Npp05150404089/default.pdf>

ing the M1 receptor would be the preferred mechanism by which cognitive deficits could be reversed in schizophrenia. This hypothesis should soon be testable with the development of agonist with increasing specificity for specific members of the muscarinic receptor family (Cao *et al*, 2003).

## 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.
- Cao Y, Zhang M, Wu C, Lee S, Wroblewski ME, Whipple T *et al* (2003). Synthesis and biological characterization of 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivatives as muscarinic agonists for the treatment of neurological disorders. *J Med Chem* **46**: 4273–4286.
- Dean B, Bymaster FP, Scarr E (2003). Muscarinic receptors in schizophrenia. *Curr Mol Med* **3**: 419–426.
- 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.
- Kirrane RM, Mitropoulou V, Nunn M, Silverman J, Siever LJ (2001). Physostigmine and cognition in schizotypal personality disorder. *Schizophr Res* **48**: 1–5.
- 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 schizophrenic patients. *Neuropsychobiology* **48**: 72–76.
- Mancama D, Arranz MJ, Landau S, Kerwin R (2003). Reduced expression of the muscarinic 1 receptor cortical subtype in schizophrenia. *Am J Med Genet* **119B**: 2–6.
- Minzenberg MJ, Poole JH, Benton C, Vinogradov S (2004). Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry* **161**: 116–124.
- Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW (1999). Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. *Schizophr Res* **37**: 251–270.
- 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, Katsifis K, Filomena M, Huang X-F (2004). Investigation of M1/m4 muscarinic receptors in the anterior cingulate cortex in schizophrenia, bipolar disorder, and major depression disorder. *Neuropsychopharmacol* **29**: 619–625.