The dopaminergic hypothesis of schizophrenia assumes that the illness results from excessive activity at dopamine synapses in the brain. However, the exact pathophysiology is still unknown. Since at present the diagnosis of schizophrenia relies on descriptive behavioral and symptomatic information, there is a crucial need for developing peripheral measurable markers for the diagnosis, evaluation and follow-up of schizophrenia. In recent years human peripheral blood lymphocytes have been found to express several dopamine receptors (D_3, D_4 and D_5) by employing molecular biology techniques and binding assays. It has been suggested that these dopamine receptors found on lymphocytes may reflect those receptors found in the brain. We have demonstrated a correlation between D_3 dopamine receptor on lymphocytes and schizophrenia and show a significant elevation of 2–6 folds in mRNA level of D_3 but not of D_4 dopamine receptor in the schizophrenic patients. This increase is not affected by different anti-psychotic drug treatments (typical or atypical). Moreover, non-medicated patients exhibit the same pattern, indicating that this change is not a result of the medical treatment. We propose the D_3 receptor mRNA on blood lymphocytes as a novel marker for the identification and follow-up of schizophrenia.

I will also discuss in my presentation some additional potential markers, for schizophrenia, in blood lymphocytes.

S44.2

Roles of the D3 receptor and brain-derived neurotrophic factor in behavioural sensitisation to psychomotor stimulants

O. Guillin*, N. Griffon, J. Diaz, P. Carroll, J.C. Schwartz, P. Sokoloff. *Unité de neurobiologie et pharmacologie moléculaire. U-109 INSERM, France*

In the post-mortem brain of cocaine addicts the dopamine D3 receptor (D3R) expression is elevated in nucleus accumbens[1] and in hemiparkinsonian rats, the overexpression of D3R in the denervated striatum mediates behavioural sensitization to levodopa[2]. The D3R gene expression is controlled by a factor distinct from dopamine, which we have now identified as being brain-derived neurotrophic factor (BDNF)[3].

Trk B, the receptor for BDNF, co-localizes with D3R in nucleus accumbens. Gene-targeted mice lacking BDNF have ablated D3R during development. Repeated administration of levodopa induces the D3R overexpression in hemiparkinsonian rats and behavioural sensitisation, which are both blocked by infusion of a selective BDNF antagonist. This behavioural sensitisation results of an overexpression of TrkB receptor in the denervated striatum and of an dopamine D1 receptor dependant overexpression of BDNF gene expression in the frontal cortex which is the brain area where striatal BDNF is synthesised[4]. Thus, BDNF controls D3R expression and behavioural sensitisation[3].

Our data suggest that BDNF elicits long-term neuronal adaptation by controlling the responsiveness of its target neurons to the dopamine. Progressive changes in BDNF expression occurring during drug-taking might induce drug conditioned responses, a key process in drug addiction[5].

(1) Staley JK et al. J Neurosci **16**, 6100–6106 (1996)
(2) Bordet et al. Proc Natl Acad Sci USA **94**, 3363–3367 (1997)
(3) Guillin O et al. Nature **411**, 86–89 (2001)
(4) Altar et al. Nature **389**, 856–60 (1997)
(5) O'Brien et al. Res Publ Assoc Res Nervous Mental Dis **70**, 157–177 (1992)

S44.3

The functions of dopamine D_3 receptors: their pharmacology and potential therapeutic applications

J.J. Hagan*. *Psychiatry Centre of Excellence for Drug Discovery, GlaxoSmithKline plc, Verona, Italy*

Mesocorticolimbic dopaminergic neurons have been extensively implicated in motivation and reinforcement. Since its discovery (Sokoloff *et al.*, 1990) the dopamine D_3 receptor has been implicated in addiction processes (Caine and Koob, 1993) and in mediating some aspects of drug abuse. Dopamine D_3 receptor mRNA is found in the nerve terminal areas of the mesocorticolimbic system within the ventral striatum, nucleus accumbens, dentate gyrus and cortex of rat and human brain. Autoradiographic studies, with a variety of ligands, confirm this distribution. Progress in this area has been hampered by a lack of selective pharmacological tools. We have recently identified SB-277011-A, which has high affinity and selectivity for cloned human (pKi=8) and rat dopamine D_3 receptors with 80 fold selectivity over hD_2 receptors (Reavill *et al.*, 2000). Extensive behavioural profiling reveals no overt effects on spontaneous locomotor activity or hyperactivity induced by amphetamine or PCP. Even at high doses, SB-277011-A (79 mg/kg p.o.) did not induce catalepsy or increase serum prolactin levels. Repeated administration (uid/ 21 consecutive days) of SB-277011-A (1, 3 and 10 mg/kg p.o.) significantly decreased the number of spontaneously active DA neurons in the ventral tegmental area, but not the substantia nigra, suggesting a selective pharmacological action of the compound on the mesocorticolimbic system. In studies of brain stimulation reward (BSR) the compound has been found to attenuate the enhancing effect of cocaine on BSR thresholds, but by itself produced no elevations of response thresholds. In studies of cocaine induced conditioned place preference (CPP) acute treatment with SB-277011-A produced dose-dependent attenuation of both acquisition and expression of cocaine-induced CPP, without producing significant place preference or aversion. In rats trained to intravenously self-administer cocaine, acute treatment with SB-277011-A produced a dose-dependent attenuation of cocaine-triggered reinstatement of previously extinguished self-administration behaviour. Finally, cocaine-seeking behaviour, measured using a second-order schedule of reinforcement, shows that SB-277011-A dose-dependently decreased responding in both the first, drug-free interval and following self-administered cocaine, with no effect on self-administration of the drug under a continuous reinforcement schedule. These data support the hypotheses that dopamine D_3 receptors play a role in regulating the functions of mesocorticolimbic dopaminergic neurons and in mediating at least some of the behavioural effects of cocaine which are thought to be predictive of its abuse liability.

S44.4

Potential clinical applications of BP 897, a partial dopamine D_3 agonist

J.-C. Schwartz*. *Unité de Neurobiologie et Pharmacologie Moléculaire (U.109) de l'INSERM, Centre Paul Broca, Paris, France*

The dopamine D_3 receptor (D_3R) is expressed in a rather discrete subpopulation of neurons in limbic brain areas receiving dopaminergic afferents from the ventral segmental area, e.g. shell of n.accumbens, amygdala, prefrontal cortex. More recently expression of the D_3R was detected within dopamine neurons themselves, implying an autoreceptor function which remains to be clarified.

BP 897, a phenylpiperazine derivative displays partial agonist activity at the D_3R and selectivity, being 50-fold less potent

https://doi.org/10.1016/S0924-9338(02)80312-1 Published online by Cambridge University Press