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

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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].

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(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

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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

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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

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and devoid of intrinsic activity at the D_2R. This original pattern, evidenced on recombinant human receptors, was confirmed *in vivo* in rodent models in which the drug was active at doses $\leq$ 1 mg/kg p.o. either as agonist or antagonist depending on the test.

Following successful preclinical and Phase I clinical studies, BP 897 is now submitted to clinical trials in order to assess the potential of this novel class of drugs in neuropsychiatry. The potential antipsychotic activity of BP 897 is consistent with i) the localisation of the D_3R, ii) its enhanced expression in brain of schizophrenic patients, iii) association studies of a D_3R polymorphism in schizophrenia, iv) occupancy of the D_3R by all antipsychotics, v) efficacy of BP 897 in rodent schizophrenia "models". A double-blind placebo-controlled study of BP 897 in schizophrenic patients has been initiated.

Potential applications in drug abuse are consistent with i) localisation of the D_3R, ii) efficacy of BP 897 in rodent models of drug seeking behaviours, i.e. cue-conditionned responses related to cocaine, morphine or nicotine.

Double-blind placebo-controlled clinical trials were initiated assessing relapse in tobacco smokers and alcohol abusers and are planned in cocaine addicts.

S44.5

Eye movement disturbances and dopamine D3 receptor gene

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Eye movement disturbances occur in a majority of patients with schizophrenia and in a proportion of their first-degree relatives and they have been postulated as a phenotypic marker of this illness. Molecular genetic studies of dopaminergic system may suggest a possible involvement of dopamine D3 receptor (DRD3) gene in some aspects of schizophrenia. The aim of the study was to measure an association between the intensity of eye movement disturbances (fixation and smooth pursuit) and the Ser9Gly polymorphism of DRD3 gene in 119 schizophrenic patients (74 male, 45 female). Eye trackings were measured by the infrared reflectometry method and the intensity of disturbances was quantified on 0–3 scale. The mean intensity of both kinds of disturbances was highest in Ser/Ser, significantly lower in Ser/Gly and lowest in Gly/Gly genotype. Ser/Ser genotype was more prevalent in patients with higher intensity of both fixation and smooth pursuit disturbances, and Ser/Gly genotype frequency was lower in patients with higher fixation disturbances. The results suggest that DRD3 gene polymorphism may be a contributing factor to eye movement disturbances, a phenotypic marker in schizophrenia.

S45. Internet strategies for a non-governmental organisation

Chairs: C.B. Pull (L), N. Lindefors (S)

S45.1

Information technology and future society

K. Olausson*. *The Interactive Institute, Sweden*

The Interactive Institute, a national, interdisciplinary research institute working in the borderland between art, technique and communication. Kenneth Olausson is president for the company which is free-standing, independent and is supported by funds from the Swedish industry, universities and college organizations and The Swedish Foundation for Strategic Research, who also own the Institute. The Institute is built gradually, shaped as studios around the country. Today there are studios in Stockholm, Malmö, Gothenburg, Umeå, Piteå, Visby and Växjö and approximately 150 researchers are today tied to the Institute.

The activities in a studio are characterized by innovative use of art and technique. Every studio has a unique aim, with the basic idea that a mixture of different disciplines creates totally new activity within research and development that no one earlier dared, which in return will lead to new products, services and companies. More information about The Interactive Institute can be found on http://www.interactiveinstitute.se.

S45.2

Using Internet in clinical and epidemiology studies

J.-E. Litton*. *Stockholm, Sweden*

The Internet clearly has a role to play in today's information age and will become increasingly important in our communications, our work life and our daily activities.

The medical use of the Internet presents enormous opportunities and challenges. Some of the promises that the Internet holds for medicine has been tentatively explored. However, the Internet potential as a mean in clinical and epidemiology studies remains largely untapped.

Using information technology in clinical and epidemiology studies new creative research strategies to advance digital forms can be used. It is not only web-forms on Internet that can be used, mobile phones, digital TV and PDA are others examples of items in the new electronic village that will give new possibilities in this studies. Not only new studies can be performed, the speed and access to database solutions using software like Extensible Markup Language (XML) will also change the way clinical and epidemiology strategies will be handled in next decade. XML is on its way to become a global standard for the representation, exchange, and presentation of information on the Web. More than that, XML is creating a standardisation framework, in terms of an open network of meta-standards and mediators that allows for the definition of further conventions and agreements in specific domains. This story of the evolution of a standardisation framework doubtlessly will end successfully in the case of XML, and I suggest that it should be considered as a generic model for standardisation processes in the future for clinical and epidemiology studies using new menus for digital forms.

S45.3

Treatment of mental disorders via the Internet

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Self-help treatment for mental disorders has gained increased popularity. Until recently, computer mediated therapies have been offered without any patient-therapist interaction. However, there now seems to have been a shift toward using the World Wide Web (WWW), to inexpensively administer self-help treatment instructions, in conjunction with some sort of text-based human interaction (e-mail). In our research program we have conducted seven randomized controlled trials for different conditions (e.g.,

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