stress-system appears to correlate with the dimensional personality characteristic that modulates sensitivity in social communication. Moreover, we have recently demonstrated that levels of hopelessness correlate with serotonine receptor functioning in the prefrontal cortex, which is involved in the generation and choice of response alternatives when confronted with particular problems, and with trait-dependent regulation of anxiety. It thus appears that two interrelated clusters of psychobiological characteristics are involved in the development of suicidal behaviour, i.e. (1) a sensitivity to interpersonal events and activation of the stress system and (2) prefrontal serotonine function, hopelessness and the regulation of anxiety.

S43.3

The stress-system and suicidal behaviour

L. Träskman-Bendz, B. Pendse, Å. Westrin. *Department Clinical Neuroscience, Section of Psychiatry, Lund University Hospital, Sweden*

The main objectives of our studies are to find adequate means of predicting recurrence of suicidal behaviour. In view of currently discussed theories on stress and kindling, we have lately concentrated on the role of stress in suicide attempts.

We study temperament, monoamines, steroids, and neuropeptides of patients who have deliberately harmed themselves, and we compare findings from them with findings from control populations.

Even though suicide attempters with major depression rate themselves significantly higher on trait anxiety than non-suicidal patients, suicide attempters form a heterogeneous group concerning temperament-ratings and biological findings. The most deviant patients (high trait anxiety, aggression, impulsiveness, suspiciousness combined with repeated suicide attempts) have low levels of steroids, monoamine-metabolites, and the neuropeptides CRH and NPY, while suicide attempters with normal temperament have high concentrations of e.g.cortisol, often corresponding with nonsuppression after dexamethasone administration.

We assume that "normal temperament" suicide attempters have not (yet?) reached the stage of sensitisation where the stress-system seems to be "burnt out". The genetic factors influencing body dissatisfaction and dieting-oriented behavior may constitute a part of the genetic vulnerability to eating disorders. These influences are likely to be age-specific and sex-specific.

S43.4

UK legislation on analgesic pack sizes: impact on suicidal behaviour

K. Hawton, E. Townsend*. *Centre for Suicide Research, University of Oxford, UK*

Because of the growing problem of self-poisoning with analgesics, especially paracetamol, in September 1998 legislation was introduced in the United Kingdom to limit the size of analgesic packs (of paracetamol, aspirin and their compounds). In this presentation the background and rationale for this legislation will be discussed. The results of a prospective investigation in which the impact of the legislation on subsequent mortality and morbidity associated with analgesic self-poisoning will be presented. This investigation has focused on changes in sales figures, self-poisoning with analgesics, impact of paracetamol overdoses on liver toxicity, referrals to liver units and liver transplantation, and finally and most importantly, the impact of the legislation on deaths from analgesic poisoning. Overall, the initial results seem to have been very positive. Thus there was a decrease in paracetamol overdoses and in large overdoses of both paracetamol and aspirin. There are fewer liver transplants due to paracetamol liver damage. Finally, deaths from both paracetamol and aspirin self-poisoning decreased substantially. The implications of these findings for future trends and research will also be considered.

S43.5

Efficacy of St. John's wort extract WS® 5570 in major depression – a double-blind, placebo-controlled trial

Y. Lecrubier[1]*, G. Clerc[2], R. Didi[3], M. Kieser[4]. [1]*Hôpital Pitié Salpêtrière, Unité INSERM 302, Paris;* [2]*CHS de Pontorson, Pontorson;* [3]*CHS La Chartreuse, Dijon, France*
[4]*Biometrical Department, Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany*

Objective: In a double-blind, randomized, placebo-controlled trial in 375 patients we investigated the antidepressant efficacy and safety of 3 x 300 mg/day hydroalcoholic Hypericum extract WS® 5570.

Method: The study participants were male and female, adult outpatients with mild to moderate major depression (single or recurrent episode; DSM-IV criteria). Following a single-blind placebo run-in phase, 186 patients were randomized to WS® 5570 and 189 to placebo and received double-blind treatment for 6 weeks. Follow-up visits were held after 1, 2, 4 and 6 weeks. The primary outcome measure was the change versus baseline of the 17-item Hamilton Rating Scale for Depression (HAM-D) total score. In addition, an analysis of responders (patients with =50% HAM-D total score reduction versus baseline) was carried out and subscale/subgroup analyses were conducted. The design included an adaptive interim analysis performed after randomization of a total of 169 patients with options for sample size adjustment or early stopping.

Results: WS® 5570 produced a sigificantly higher reduction in HAM-D total score and significantly more treatment responders than placebo. Hypericum extract was more effective in patients with higher baseline HAM-D scores and led to global reduction of depression-related core symptoms as investigated by the HAM-D melancholia subscale. Both groups were comparable regarding adverse events.

Conclusions: Hypericum extract WS® 5570 was found to be safe and more effective than placebo for the treatment of mild to moderate depression.

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S44. The dopamine D3 receptor and its ligands: psychiatric implications

Chairs: J.-C. Schwartz (F), G. Sedvall (S)

S44.1

Increased levels of D_3 dopamine receptor mRNA in blood lymphocytes of schizophrenic patients

S. Fuchs*. *Department of Immunology, The Weizmann Institute of Science, Rehovo, Israel*

Dopamine is a major neurotransmitter in the central nervous system and its receptors are associated with a number of neuropathological disorders such as Parkinson's disease and schizophrenia.

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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].

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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

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