de la Tourette syndrome and self-injurious behaviour were each present in only one patient.

It is concluded that not only major depression but also atypical bipolar disorder, so called unstable mood disorder, can frequently be observed in DS. Moreover, a range of psychiatric and somatic disorders are important in the differential diagnosis of behavioural abnormalities in DS patients.

S31.4

Neuroanatomy and psychopathology of co-morbid learning disability and schizophrenia

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Reasons for the higher frequency of schizophrenia in learning disabled populations are uncertain. They were investigated by clinical, imaging and genetic studies of matched patients with learning disability and schizophrenia (co-morbid group), schizophrenia alone and learning disability alone. The co-morbid group had more negative symptoms, episodic memory deficits, and soft neurological signs than the other two groups. Co-morbid subjects had a tendency to belong to multiply affected families and showed high rates of chromosomal variants. Structural scans of the three groups were compared with those of matched normal controls. The scans of the co-morbid subjects were closely similar to those of the subjects with schizophrenia alone. The amygdala hippocampus on both sides was significantly smaller than that of the normal controls. The brain of the learning disabled patients were generally smaller than those of the other three groups, but the amygdalo-hippocampal complexes were not reduced in size. Thus, in terms of brain structure, patients with co-morbid learning disability and schizophrenia resemble patients with schizophrenia and not those with learning disability.

S32. Clinical aspects of cholecystokinin research

Chairs: J. Shlik (FIN), T. Gunnarsson (S)

S32.1

Mice lacking CCK2 receptors display reduced anxiety in the plus-maze

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Studies on rodents suggest that the neuropeptide cholecystokinin (CCK) increases anxiety via CCK2 receptors. In the present study the exploratory behaviour of female mice, lacking CCK2 receptors, was analysed in the elevated plus-maze. Furthermore, the action of diazepam, a benzodiazepine agonist, was studied in these animals. Homozygous (-/-) CCK2 receptor deficient mice made more visits to open arms and spent greater time in the open parts compared to wild-type (+/+) littermates. The administration of diazepam (0.5–3 mg/kg) significantly increased the exploratory behaviour of wild-type mice. However, the action of diazepam was even stronger in mutant animals. Diazepam (0.5–1 mg/kg) significantly affected the ethological parameters of plus-maze exploration in homozygous mice, but not in wild-type animals. The highest dose of diazepam (3 mg/kg) reduced the number of closed arm entries in mutant mice. Nevertheless, mice lacking CCK2 receptors spent a significantly longer time in the open arms compared to wild-type mice. Accordingly, the targeted disruption of the CCK2 receptor gene reduces anxiety of mice in the plus-maze. The anxiolytic and motor suppressant action of diazepam are also increased in mutant mice.

S32.2

Natriuretic peptides modulate the psychometric and endocrine effects of cholecystokinin tetrapeptide in man

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While Atrial Natriuretic Peptide (ANP) has a high affinity for natriuretic A-type receptors, C-type natriuretic peptide (CNP) binds primarily to natriuretic B-type receptors. In pre-clinical studies these two peptides show opposite effects on stress hormone secretion and anxiety behavior: ANP displays an anxiolytic action in rodents, whereas CNP is anxiogenic.

We investigated the effects of ANP and CNP upon experimentally provoked panic attacks in humans using cholecystokinin tetrapeptide (CCK-4).

In different studies, panic patients and healthy controls were pretreated with intravenous infusions of ANP, CNP and or placebo from 11:40 to 11:10 in double-blind, randomized and balanced designs. At 11:00 all subjects were given CCK-4 as an intravenous bolus injection. Provoked panic and anxiety symptoms were assessed before and after CCK-4. Adenocorticotropic Hormone (ACTH) was measured in plasma using a radioimmunoassay.

By ANP pre-treatment, Acute Panic Inventory ratings after CCK-4 were significantly lowered compared to placebo pre-treatment in panic patients ($p<0.05$), but not in controls. The release of ACTH after CCK- 4 was significantly reduced in both patients and controls by ANP vs. placebo pre-treatment. CNP pre-treatment significantly increased visual analogue scale ratings for "anxiety", while no effect upon panic symptoms was observed in normal controls. The stimulated release of ACTH was significantly increased by CNP.

Also in man ANP has anxiolytic-like effects on CCK-4-induced anxiety symptoms and concomittantly reduces ACTH activation. In contrast, CNP increases the anxiogenic action of CCK-4 and enhances the ACTH surge after CCK-4. The pharmacotherapeutic potential of both A-type natriuretic peptide receptor agonists and B-type antagonists as novel anxiolytics needs further research.

S32.3

Cholecystokinin-serotonin interactions

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Cholecystokinin (CCK) extensively interacts in the brain with other neurotransmitter systems. The relationship between CCK and serotonin (5-HT) is important for various brain functions including the regulation of anxiety, pain, food intake and neuroendocrine stress response. Furthermore, CCK neurotransmission may be involved in the mechanism of action of the 5-HT-acting medications that are increasingly used in the treatment of numerous psychiatric disorders. The studies so far suggest that treatment with drugs that enhance 5-HT transmission attenuates CCK-4-induced panic attacks in patients with panic disorder and indicate a possible role

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for 5-HT3 receptor in mediating the CCK-induced anxiety. On the other hand, a decrease in 5-HT neurotransmission after tryptophan depletion augments CCK-4-induced neuroendocrine activation. To further explore the spectrum of CCK-5-HT interactions we study the biochemical and behavioural markers of CCK activity under conditions of an altered presynaptic availability of 5-HT. Specifically, we investigate in separate studies the effect of tryptophan depletion on the composition of CCK peptides in the cerebrospinal fluid and the influence of a serotonin precursor 5-HTP on the CCK-4-induced panic attacks in healthy volunteers.

S32.4

Cholecystokinin and anxiety disorders

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There is evidence for the role of the cholecystokinin (CCK) neurotransmitter system in the neurobiology of panic disorder. The CCK receptor agonist, CCK-tetrapeptide (CCK-4) fulfils criteria for a panicogenic agent and there is evidence that panic disorder might be associated with an abnormal function of the CCK system. CCK receptors, which have been cloned, have been classified into two subtypes: CCK-1 and CCK-2. Recently, it has been reported that genetic dissection of the CCK system suggests that CCK-2 receptor gene variation and CCK peptide gene variation may be factors in the neurobiology of panic disorder. These findings support the hypothesis that panic disorder might be associated with an anomalies of the CCK peptide and CCK-2 receptor system. This session will review research to date on the role of CCK in anxiety disorders, suggests future research strategies and review potentials for therapeutics.

S32.5

Cholecystokinin in cerebrospinal fluid

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Cerebrospinal fluid (CSF) concentrations of the cholecystokinin (CCK) tetrapeptide (CCK-4) and the sulphated octapeptide (CCK-8S) were analysed in three groups of healthy subjects, in hypothyroid patients before and during treatment, and in panic disorder (PD) patients.

On performing lumbar puncture with the patient in the sitting position, the concentrations of CCK-4 and CCK-8S were influenced by age, bedrest prior to lumbar puncture, neuraxis distance, position during lumbar puncture, height, atmospheric pressure and storage time. No such influences were found when lumbar-puncturing the subjects in the decubitus position. This might imply that lumbar puncture in the decubitus position is to be recommended when performing CSF studies on CCK.

In hypothyroid patients, serum levels of thyroid hormones correlated with both CCK peptides in the CSF. A negative correlation between CCK-4 and the subjects level of anxiety was found.

In PD patients, suicidal ideation correlated positively with CCK-4. There was also a positive correlation between tyrosine and CCK-8S. No other correlations were found between monoamines and CCK peptides in any of our studies.

S32.6

Pentagastrin, anxiety and personality

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Rationale: CCKB receptor agonists such as pentagastrin or CCK-4 have panic-like anxiogenic effects in humans. It has also been shown that CCK-4 can stimulate insulin release and thus C-peptide release from pancreatic islet cells. Combined, these mechanisms may provide a basis for a bio-assay.

Objectives: Our aim was to study if a pentagastrin bolus injection evokes C-peptide release, correlating to the anxiogenic effect of pentagastrin and whether personality characteristics might predict the response.

Methods: Bolus i.v. pentagastrin was administrated at increasing doses. The Karolinska scale of personality (KSP) and anxiety sensitivity index (ASI) were used to characterize the individuals. Pentagastrin-induced discomfort was rated.

Results: A significant increase in the plasma level of C-peptide, heart rate (HR) and galvanic skin response (GSR), accompanied by increases in discomfort rated on SAS, were observed within the same time-frame (2–4 minutes) following pentagastrin. ASI correlated to the increase in discomfort following pentagastrin.

Conclusions: The results support the predictive value of ASI for fearfulness and indicate that C-peptide levels in plasma might predict the biological response to pentagastrin.

SAL08. Current and Future Treatments for Dementia

SAL08

Current and future treatments for dementia

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Cholinesterase inhibitors (ChEI) are currently the most established treatment strategy in Alzheimer's Disease (AD). The treatment effect appears mainly to be symptomatic. Nicotinic agonists may have cytoprotective effects. Glutamatergic (NMDA)-antagonists (memantine) have been successfully tested in severe dementia. Estrogen replacement therapy may give a lower risk for AD in elderly women. However, the reported treatment studies on AD have been negative. Anti-inflammatory drugs have shown to reduce risk for AD. Growth factors are important for neuronal development and maintenance. Nerve growth factor (NGF) stimulates outgrowth of cholinergic neurons but gave severe side effects. Anti-amyloid substances might be used to target directly to the production of Aβ in order to increase the removal of Aβ and/or to decrease the aggregation of Aβ. Immunisation studies of APP transgenic mice with Aβ42 before the onset of pathology prevented development of β amyloid plaques and when given to mice already with pathology, the progression was reduced. This might open the way for immunisation/vaccination against AD. Clinical studies have started.

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