ABSTRACTS

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Table of Contents

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ORAL PRESENTATIONS

SCNP WELCOME LECTURE 2011

Genetic susceptibility and environmental stressors in psychosis.

Sir Robin M.Murray

Abstract not available at printing

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SYMPOSIUM: OXYTOCIN; BALANCING ATTACH-MENT AND SUSPICIOUSNESS?

Brain oxytocin: modulator of emotional, neuroendocrine and neuronal stress responses

Inga D. Neumann

Brain neuropeptides, such as oxytocin (OXT), represent viable novel research candidates for the development of effective treatment strategies of affective and stress-related disorders. OXT is released within limbic target regions upon various stressful or social stimuli, where it regulates complex behavioural and hormonal stress responses including the activity of the hypothalamo-pituitary-adrenal (HPA) axis, anxiety-related or social behaviours[1]. OXT actions are mediated by G-protein-coupled receptors (GPCR), which are distributed in brain regions relevant for stress regulation. The anxiolytic effects of OXT within the PVN were found to be mediated via the mitogen-activated protein kinase (MAPK) / extracellular signal-regulated kinase 1/2 (ERK1/2) cascade[2]. The prominent stimulatory action of OXT on the ERK pathway in hypothalamic neurons may also mediate neuroplasticity of the neuroendocrine system during lactation, when the brain OXT system is highly activated[3]. Furthermore, OXT stimulation of hypothalamic cells led to the phosphorylation of Ca^{2+}/calmodulin-dependent protein kinases (CaMK). Translocation of both pERK and phosphorylated CaMK IV to the nucleus results in CREB phosphorylation and changes in gene expression patterns, which may account for long-lasting behavioural effects of OXT.
Importantly, anxiolytic effects of chronic OXT were also found in a psychopathological rat model, i.e. in rats selectively bred for high (HAB) anxiety-related behaviour further indicating the OXT system as a potential target for the development of therapeutic strategies to treat anxiety- and stress-related diseases[4]. Supported by the Deutsche Forschungsgemeinschaft (DFG) and BMBF.

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An Oxytocin Treatment Trial in Schizophrenia: Reduction of Social Cognitive Deficits and Psychotic Symptoms.

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Preclinical and Clinical Evidence for Oxytocin's Therapeutic Effects in Schizophrenia.

Kai MacDonald

Background:
Current psychopharmacologic treatments for schizophrenia, though effective for some patients and for some symptoms, still consistently fail to benefit certain patient groups and certain symptom clusters. Oxytocin is a neuropeptide that regulates

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many central processes (i.e. trust, social cognition) relevant to schizophrenia. Thus, oxytocin may have potential as treatment for symptoms of this condition.
Objectives:
To investigate the therapeutic potential of oxytocin and oxytocin analogs for schizophrenia in animal models of schizophrenia (animals with prepulse inhibition (PPI) deficits) and humans subjects afflicted with this condition.
Methods:
The effects of systemically administered oxytocin in reversing natural PPI deficits in certain strain of rats and mice were assessed. Based upon promising findings from these studies, clinical effects of 3 weeks of adjunctive intranasal oxytocin on core positive and negative symptoms, verbal learning and overall clinical improvement in patients with schizophrenia were studied in a placebo-controlled study.
Results:
Subcutaneous and intranasal oxytocin significantly increased PPI in Brown Norway and C57 mice consistent with the effects of antipsychotics in these animals. In patients with schizophrenia, 3 weeks of intranasal oxytocin caused significant therapeutic changes compared to placebo as measured by the Positive and Negative Symptom Scale (PANSS) and Clinical Global Impression (CGI), and demonstrated a salubrious effect on the California Verbal Learning Test (CVLT). In human trials, chronic oxytocin treatment was well-tolerated, without evidence of clinically significant laboratory abnormalities.
Conclusion:
These results, from both animal and human studies, are consistent with other preclinical and clinical studies of oxytocin and support the notion that oxytocin is a promising agent to treat schizophrenia. Many significant questions remain, however, before oxytocin's therapeutic potential can be exploited to help patients with psychotic illness. These questions include: 1) optimal dosing and duration; 2) use as a primary antipsychotic agent; 3) differential effects based on schizophrenia subtype, gender, and oxytocin receptor genotype; 4) more fine-grained examination of oxytocin's effects on different symptom domains (i.e. cognition, social cognition). To address these and other issues, large studies of oxytocin in schizophrenia are underway.

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SYMPOSIUM: ADHD, ARE WE TREATING THE RIGHT PATIENTS?

ADHD - Epidemiology, diagnostics, co-morbidity, and progress into adulthood

Pål Zeiner

Background:
Attention Deficit / Hyperactivity Disorder (ADHD) is characterized by symptoms of hyperactivity, impulsivity, and inattention and shows heterogeneity both with regard to etiological factors and clinical heterogeneity in terms of co-morbidities, gender effects, courses, and outcomes. During recent years there has been a large increase in the number of individuals diagnosed with ADHD. What should be the recommendations for best clinical practice?
Objectives:
1 To present different models for understanding the heterogeneity of ADHD in children, adolescents, and adults.
2. To discuss the diagnostic dilemmas regarding ADHD versus other psychiatric disorders in individuals with attention problems.
3. To discuss the clinical implications of comorbidity.
Methods:
Review of epidemiological and clinical studies.

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The problems with treating ADHD in substance abuse

Magnusson A

Background:
The worldwide prevalence of ADHD has been estimated as 5.2 %. The number of patients treated for ADHD has increased markedly during recent years. Methylphenidate is the most commonly used substance to treat this condition. It is

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currently the top selling medication in a Nordic country.
Objectives:
To discuss the problems associated with psychostimulant prescriptions, especially in patients with drug dependence.
Methods:
This presentation is based on clinical experience, analysis of drug databases and on novel research data. In Iceland, every medical prescription is entered into a central register and this was used for analysis of central stimulant prescriptions. Thirty-two i.v. drug users admitted for detoxification completed a questionnaire that probed for drug preferences.
Results:
Methylphenidate prescriptions have been rapidly increasing in Iceland and other Nordic countries. Iceland has now the highest prescriptions rates in the world. Most i.v. drug users in Iceland favor methylphenidate to cocaine and amphetamine. Diagnosing and treating ADHD in substance dependent patients is a complex process. A patient receiving social security benefits may double his income if he receives a diagnosis of ADHD and treatment with psychostimulants.
Conclusion:
There is a demand for prescription psychostimulants among drug users. Receiving a diagnosis of ADHD may have marked economical effects for a drug user. There has been a rapid rise in the number of psychostimulant prescriptions during recent years in many Nordic countries.

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Treatment of ADHD symptoms
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SYMPOSIUM: AUGMENTATION STRATEGIES IN TREATMENT RESISTANT DEPRES-SION.

Light exposure and sleep-wake cycle based therapies.
Timo Partonen

Light therapy, also called light treatment or phototherapy, involves exposure to artificial light. Bright-light therapy refers to the administration of visible light producing at least 2500 lx at eye level. Important parameters for light therapy include the intensity, duration of daily exposure, and timing of light exposure. A meta-analysis of data derived from controlled trials on a total of 332 patients with winter depression revealed that light of 2500 lx administered via a light-box device in 2-hour daily morning sessions for 1 week improved 67% of patients with mild, and 40% with moderate to severe depressive episodes. The use of higher intensities and shorter exposures has yielded similar response rates. In selected samples, a good treatment response has been achieved in 80% or more of the patients. Another meta-analysis applying the Cochrane systematic review method confirms the efficacy of bright-light therapy against placebo controls.
Sleep manipulations are antidepressants and options in the treatment of mood disorders. Sleep deprivation may be total, partial or targeted at REM sleep. 61 research articles involving over 1700 subjects have documented that 67% of the depressed with a major depressive episode and 48% of those with dysthymia respond to sleep deprivation. However, 83% of those who had an antidepressant response to sleep deprivation but no medication relapsed after one night of sleep. Naps of 10 to 90 minutes may activate relapses after successful sleep deprivation in 15% to 85% of the responders respectively.
Light therapies and sleep manipulations influence the circadian system that generates not only the circadian rhythms but also the sleep-wake cycle. Disrupted circadian rhythms and sleep patterns are common in depressive and bipolar disorders. Desynchronization of circadian rhythms leads to the decrease in amplitude seen in the principal circadian pacemaker and is hypothesized to

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contribute to depressive episodes. My lab has reported the primary finding that genetic variants in circadian clock genes associate with not only seasonal but also non-seasonal depressive disorders associate with *PER2* variants at the general population level, and that winter depression associates with *CRY2* variants and *CRY2* expression levels relate to the depressed state in patients with bipolar disorder. Since the circadian system tracks both dawn and dusk, these findings may explain why the phase angle (between sleep phase and circadian rhythms) is abnormal in winter depression, and why the rest-activity cycles are elastic indicative of a reset error of the circadian rhythms in these patients.

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Augmentation by combining antidepressant and antipsychotic drugs.

Torgny H. Svensson

Background:
Adjunctive treatment with antidepressant drugs is frequently used to augment the effects of antipsychotic drugs (APDs) in schizophrenia, particularly on negative and depressive symptoms but also on cognitive impairment. Moreover, low doses of atypical APDs are often used to augment the effects of antidepressant drugs, such as SSRIs, and speed their onset of action in mood disorders, including bipolar depression and major depressive disorder (MDD). Significantly, the atypical APD quetiapine can be used as monotherapy both in schizophrenia and bipolar disorder, including bipolar depression, and even in MDD.
Objectives:
The present set of experimental studies in rats were undertaken to clarify some of the neurobiological mechanisms which may help explain these synergistic effects with focus on dopaminergic and glutamatergic systems in the brain.
Methods:
We used the conditioned avoidance response (CAR) paradigm, a preclinical test with high predictive validity for clinical antipsychotic efficacy. EPS liability was examined using a catalepsy test. Dopamine outflow in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) was measured using *in vivo* microdialysis in awake and freely moving animals, and drug effects on cortical NMDA receptor-mediated transmission were examined by intracellular electrophysiological recordings in pyramidal cells of the mPFC *in vitro*.
Results:
Combined treatment with low doses of olanzapine and the selective norepinephrine transporter (NET) inhibitor reboxetine, a potent antidepressant drug, potentiated its antipsychotic effect and also enhanced prefrontal dopamine outflow and NMDA receptor-mediated transmission. Entirely analogous effects were obtained when combining reboxetine with low doses of quetiapine, which in humans, but not in rats, generate an active metabolite, norquetiapine, that is a potent NET inhibitor in itself. Finally, similar results were obtained when combining low dose risperidone with escitalopram, a potent and highly selective serotonin transporter (SERT) inhibitor.
Conclusions:
Combining certain antidepressants with atypical APDs generates enhanced prefrontal cortical dopamine efflux, subsequent activation of D1 receptors and an ensuing facilitation of prefrontal NMDA receptor-mediated transmission. Substantial evidence implicates prefrontal dopaminergic D1 receptors as well as NMDA receptors in the control of working memory and executive function, which are typically impaired in both schizophrenia and MDD. Recent data demonstrate a reduced expression of several NMDA receptor subunits, including NR1 and NR2A in both schizophrenia and bipolar disorder (BP) as well as in MDD. Thus, the combined use of selective NET or SERT inhibitors and low dose atypical APDs appears scientifically rational.

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Augmentation of antidepressant treatment – a practical clinical approach
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SYMPOSIUM: NEW TREATMENT OPTIONS IN NEUROPSYCHIATRIC DISORDERS

Antipsychotics for the elderly: how harmful are they?
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Alzheimer's drugs in the next decade
Niels Andreasen

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OSU 6162 shows effect on mental fatigue in clinical trial
Arvid Carlsson

Background:
Mental fatigue is a severe and frequently disabling chronic condition following upon e g head trauma, stroke and multiple sclerosis. The underlying pathogenetic mechanisms are not known. No effective treatment of this disorder is available.
Objective:
To test the possible efficacy of (-)-OSU6162, a partial agonist acting on dopaminergic and serotonergic receptors, on
mental fatigue symptomatology. According to our hypothesis the stabilising influence to be expected from a partial agonist acting on both dopaminergic and serotonergic systems will alleviate mental faigue.
Method:
Comparing (-)-OSU6162 with placebo in a double-blind
crossover study of 4 + 4 weeks duration in escalating dosage.
Effect measurement by means of self-assessment scales and a
battery of neuropsychological tests.
Results:
Twelve patients with mental fatigue following upon head
trauma (N=6) or stroke (N=6) completed the study. Seven patients showed a siginficant, in some cases marked improvement following (-)-OSU6162 in comparison with placebo. The response came already within a few days of treatment with the lowest dose (15 mg once or twice daily). The difference in self assessmment was statistcally significant ($p<0.05$), and a distinct trend for improvement showed up in certain neuropsychological tests.
Conclusion:
An extended study is warranted and is very likely to show significant improvement, when measured both by self assessmant and neuropsychological tests.

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SCNP 2011 – LECTURE

Psychopharmacology, cognition and society
Barbara Sahakian

Cognitive enhancing drugs are needed to treat the cognitive impairments associated with debilitating neuropsychiatric disorders, such as Alzheimer's disease, schizophrenia and Attention Deficit Hyperactivity Disorder (Sahakian and Morein-Zamir, 2007). Such treatments will improve the quality of life and wellbeing for patients and their families and reduce the financial burden on society (Beddington et al, 2008).
Cognitive enhancement is of great interest to the general public and has implications for society, particularly in regard to the increasing use of cognitive enhancing drugs in school age children, and in young adults and academic staff at

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University (Greely et al, 2008; Maher, 2008; Sahakian & Mohamed, 2010; Sahakian and Morein-Zamir, 2007). Therefore, it is important to consider the potential harms of lifestyle use of these drugs, for example substance abuse, the unknown effects on the developing brain or coercion at school or work. Nevertheless, with the rapidly developing field of pharmacogenomics we may be able to gain maximum benefits with minimum harm to the individual and society as a whole. Certainly, the benefits of safe and effective cognitive enhancing drugs to society, including the ageing population and people with neuropsychiatric disorders and brain injury, are great (Beddington et al, 2008; The Academy of Medical Sciences Report, 2008). It is therefore important to engage the public in discussions of these neuroethical issues (Sahakian and Morein-Zamir, 2009; Morein-Zamir and Sahakian, 2010).

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ECNP EDUCATIONAL SYMPOSIUM: NEW AREAS FOR DRUG DEVELOPMENT

Biomarkers to guide drug development in neuropsychiatric disorders - example from Alzheimer's disease

Kaj Blennow

Research advances during the 25 years have given detailed knowledge on Alzheimer's disease (AD) pathogenesis. Detailed information is now by hand on the molecular mechanisms of APP processing and β-amyloid (Aβ) production, and the aggregation of Aβ with plaques development, a process believed to result in loss of synaptic integrity and progressive neurodegeneration. These research advances have also been translated into several new drug candidates with disease-modifying potential, several of which are now evaluated in clinical trials. This new type of drugs will logically most effective in the earlier stages of the disease, before the neurodegenerative process is too severe. Thus, the promise of causal treatment beyond symptomatic therapy also generates a need for diagnostic methods, to enable early diagnosis of AD.

The cerebrospinal fluid (CSF) is in direct contact with the extracellular space of the brain, and thus CSF assays reflect biochemical changes in the brain. The CSF biomarkers total tau (reflecting neuronal degeneration), Aβ42 (reflecting plaque formation), and phosphorylated tau (reflecting tau phosphorylation state and tangle formation), have been found to have a high diagnostic value for AD, and recent large multi-center studies also show that these CSF biomarkers can identify cases with prodromal AD in mild cognitive impairment (MCI) cohorts.

CSF biomarkers may also be valuable tools to identify and monitor the biochemical effect of new Aβ modulatory drug candidates directly in living AD patients. By CSF analyses, many aspects of the APP/Aβ metabolism can be monitored, including all Aβ isoforms (Aβ42, Aβ40 and others), APP isoforms (α-sAPP and β-sAPP). Recently, assays for Aβ oligomers in CSF have also been developed. The intra-individual variation for these CSF biomarkers is remarkably low, suggesting that they have the potential to identify very minor biochemical changes induced by Aβ modulatory treatment.

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Alteration of emotional processing as a marker of antidepressant action

Michael Browning

Background:
Depressed patients display characteristic negative habits of thought. For example, following a complex social event a patient may tend to remember and focus specifically on the worst aspects of the event. While these "negative processing biases" are explicitly targeted by some of the psychological treatments of depression, such as Cognitive Behavioral Therapy (CBT), little previous work has examined the impact of pharmacological treatments on such biases.
Objectives:
The current talk will present a series of studies which assess whether the mechanisms of action of antidepressant medication may be understood in terms of alteration of emotional processing biases. It will be suggested that the impact of these treatments on emotional processing biases may serve as a useful marker in drug discovery and treatment development.
Methods:
A series of experimental studies employing predominately non-clinical volunteers were conducted. These studies compared the impact of a number of different antidepressant (citalopram, mirtazapine, agomelatine and reboxetine) as well as non-antidepressant (diazepam) medications with placebo on measures of emotional processing biases. A further study tested the causal relationship between emotional processing biases and depressive symptoms by exploring the impact of a non-pharmacological modification of the biases on self reported symptoms in previously depressed patients.
Results:
Medications with antidepressant activity produced positive emotional memory biases whereas those without antidepressant activity did not. Inducing positive biases in previously depressed patients reduced self reported depressive and anxious symptoms.
Conclusion:
Both pharmacological and psychological interventions for depression alter measures of emotional processing bias. These measures may provide a useful assay when screening novel antidepressant compounds and developing treatment regimes.

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New genetics findings in psychiatry – can it facilitate drug development?

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Future applications of molecular imaging in drug development

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ELI LILLY SATELLITE SYMPOSIUM: PRESENT AND FUTURE CHALLENGES IN THE LONG-TERM MANAGEMENT OF SCHIZOPHRENIA

Challenges in the long-term management of schizophrenia.

Sir Robin M. Murray

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Removing the roadblocks. How to overcome the barriers to adherence.

Cecilia Brain

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Olanzapine long-acting injection. A review of clinical data.
Ole Kristian Kleivenes

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SYMPOSIUM: LITHIUM REVISITED

History of Lithium treatment
Lars von Knorring

Background :
Lithium is an accepted treatment for manic depressive illness. However, it took a long time from the its discovery and its first use till the treatment was generally accepted.
Objectives:
To follow the history from the discovery of Lithium till it was accepted as a treatment for manic depressive illness
Methods:
Review of the literature
Results:
Lithium was discovered 1817 by Johan August Arfwedson. Gout had been known since antiquity. In 1679 Antonie van Leeuwenhoek had described urate crystals in urine of gout patients. In 1848 Alfred Baring Garrod realized that this excess uric acid was the cause of gout. According to Garrod, "Irregular gout" included Mania, Depression and Anxiety. Around 1838, Jonathan Pereira suggested that gout could be trated by means alkali salts. Around 1840 A. Lipowitz demonstrated that lithium carbonate was the best to solve uric acid crystals (in vitro). Around 1860 Garrod introduced lithium salts as the most important preventive ingredient in the alkali treatment of periodic gout. In 1871, William A. Hammond introduced lithium bromide as a treatment for acute mania and acute melancholia. Around 1886 Carl Lange introduced lithium carbonate to treat ”the Periodic depression”. His brother, Fritz Lange introduced lithium salts in the treatment of inpatients with severe depressions.
However, in the beginning of the 20th century, Lithium treatment declined and instead Lithium was used in mineral water, beer and table salts. In 1949, Corcoran et al published a paper about Lithium poisoning fom the use of salt substitutes and in the same year FDA did forbid all use of lithium salts for humans.
In the same year, Lithium was rediscovered as a treatment for mania by John Cade. Later, 1967, Poul Christian Baastrup and Mogens Scou demonstrated that Lithium had a prophylactic effect against recurrent depressions and manic-depressive psychosis.
In 1970, US became the 50th country in the world to register Lithium. In 1975 lithium was approved as a prophylactic treatment for mania.
However, two years later, Hestbech J, Hansen HE, Amdisen A, Olsen S. published a paper Chronic renal lesions following long-term treatment with lithium. After the first period of Lithium panic in 1949, this paper started a second period of Lithium panic.
In 1987 Mogens Schou got the Albert Lasker award for his landmark systematic clinical trials of Lithium as therapy and prophylaxis for manic depressive illness, which initiated a revolution in the treatment of mental disease.
Conclusion:

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Preclinical mechanism of action
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Lithium - old and new evidence on its efficacy in bipolar disorder
Rasmus W. Licht

After more than 50 years, lithium is still a main treatment of bipolar disorder, even it has not been

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promoted by the pharmaceutical industry over the last decades. During the recent years the evidence base on lithium for treatment of bipolar disorder has been substantially increased by results from a number of trials. Therefore, a review of this evidence is timely.
An ideal mood stabilizer is able to control acute symptoms of mania and of depression and to prevent the reoccurrence of symptoms of either pole. As to the antimanic efficacy, modern parallel-group designed trials have confirmed earlier positive findings. However, due to the narrow therapeutic index requiring blood monitoring and due to a relatively late onset of action, which is related to the safety issues, lithium monotherapy generally has a limited place in the acute treatment of more severe manic states. For acute bipolar depression, there are conflicting results, in particular due to recent industry-generated studies showing no advantage of lithium over placebo. Recent long-term trials have added substantially to the documentation of the long-term stabilizing properties of lithium in bipolar disorder. In particular, it has now been shown, that lithium is efficacious as maintenance treatment independently of any acute response to the drug. It has also been convincingly demonstrated that lithium not only prevents mania, but also depression in bipolar disorder. It is still debated whether lithium has a specific antisuicidal effect beyond its recurrence preventive effects.
Beyond the beneficial clinical effects, lithium has multiple unwanted clinical effects involving other organ systems than the CNS. However, when lithium treatment is properly and skilfully managed and monitored, the more serious effects can usually be avoided.

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ASTRA ZENECA - SCNP YOUNG SCIENTIST SYMPOSIUM

A selective inhibitor of protein kinase A induces behavioural and neurological antidepressant-like effects in rats

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Background:
It is well established that cyclic adenosine monophosphate (AMP) signalling via cAMP-dependent protein kinase (PKA) within neurons plays an important role in depression and antidepressant treatment. However, the importance of several newly discovered targets that function independently from PKA, such as exchange protein activated by cAMP (Epac), remains unexplored in this regard.
Objectives:
In this study we used a cAMP analogue that inhibits PKA but not Epac (Rp-8-Br-cAMPS), to explore the modifying actions of these two targets on immobility in the forced swim test (FST) and cerebellar CREB phosphorylation in rats. In addition, we assessed central cAMP and cGMP levels and investigated the involvement of cGMP-dependent protein kinase (PKG) on any observed effects by using a selective PKG inhibitor (Rp-8-Br-PET-cGMPS).
Methods:
Rats were implanted with an i.c.v. guide cannula to the right lateral ventricle and were allowed 7 days for recovery. Animals were subjected to a 15 minute pre-swim followed by a 5 min test swim 24 hours later. Three 5 µl infusions of vehicle (Ringer's solution) or drug solution (Rp-8-Br-cAMPS (100 nmol), Rp-8-Br-PET-cGMPS (1 nmol) or both) were administered at 24, 6 and 1 hour before the final swim. Rats were decapitated and their brains dissected immediately following the test. Western blotting was used for the measurement of total and phosphorylated CREB levels in the cerebellum, whereas low pH ELISA kits (Sigma) were used for the measurement of cAMP and cGMP levels in hippocampus, frontal cortex and cerebellum regions.
Results:
Rp-8-Br-cAMPS potently reduced immobility in the FST and increased the phosphorylation of CREB in the cerebellum, effects that were unaltered by the co-administration of Rp-8-Br-PET-cGMPS. Furthermore, Rp-8-Br-cAMPS increased the accumulation of cAMP and cGMP in the hippocampus, frontal cortex and cerebellum of these rats.
Conclusion:
Together, these results suggest that PKA may not be the only mediator of cAMP-induced

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antidepressant activity, but that other mechanism(s) may play at least an equally important role in this regard. Based on the pharmacodynamic profile of Rp-8-Br-cAMPS, the relatively recently discovered Epac messenger molecule emerges as a likely candidate to fulfil this role. Therefore, this study identifies Epac as a promising novel antidepressant target.

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Concomitant NET inhibition enhances the antipsychotic-like effect of quetiapine in rats and enhances prefrontal dopamine output and cortical NMDA receptor-mediated transmission

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Background:
Quetiapine is a second-generation antipsychotic drug, structurally similar to clozapine. Like clozapine, quetiapine alleviates both positive and negative symptoms as well as certain cognitive impairments in schizophrenia despite a relatively low D_2-receptor occupancy. Quetiapine has also shown efficacy in bipolar depression and major depression. Quetiapine also generates a major metabolite in humans, norquetiapine, which is a potent norepinephrine transporter (NET) inhibitor.
Objectives:
Since quetiapine is not metabolized to norquetiapine in rodents, we investigated, in rats, the effects of adjunct NET inhibition by concomitant administration of reboxetine and quetiapine.
Methods:
Antipsychotic-like activity was assessed using the conditioned avoidance response (CAR) test, dopamine output in the medial prefrontal cortex and the nucleus accumbens was measured using in vivo microdialysis in freely moving animals, NMDA receptor-mediated transmission was measured using intracellular electrophysiological recordings in pyramidal cells of the medial prefrontal cortex *in vitro*.
Results:
Reboxetine (6 mg/kg i.p.) potentiated the suppression of CAR by a low dose of quetiapine (3 mg/kg i.v., $p<0.05$) but did not further enhance the suppression of CAR of a higher dose of quetiapine (6 mg/kg i.v.). Concomitant administration of quetiapine (6 mg/kg i.v.) and reboxetine (6 mg/kg i.p.) produced a significant increase in cortical dopamine output when compared to quetiapine or reboxetine alone. However, concomitant NET inhibition did not significantly enhance the quetiapine-induced accumbal dopamine output. Administration of low concentrations of quetiapine (60 nM) and reboxetine (20 nM) together produced a substantial enhancement of NMDA receptor-mediated transmission as compared to either drug alone, an effect that was prevented by the D_1-receptor antagonist SCH23390 ($p< 0.05$).
Conclusion:
The present results propose that concomitant NET inhibition by norquetiapine may not only contribute to the antidepressant effect of quetiapine, but also help to maintain its antipsychotic effect in spite of a relatively low level of D_2-blockade. Clinically, blockage of the NMDA receptor by low, nonpsychotic doses of ketamine impairs verbal working memory, which is frequently impaired in schizophrenia and major depression. Recent post mortem studies demonstrate a reduced expression in cortical areas of several NMDA receptor subunits, including NR1 and NR2A, in schizophrenia, bipolar disorder and major depression. In addition, clinical and preclinical evidence propose an impaired prefrontal dopamine projection in schizophrenia. Consequently, the marked facilitation of prefrontal dopamine output and cortical NMDA receptor-mediated transmission produced by quetiapine combined with a NET inhibitor may contribute to its overall efficacy in schizophrenia, bipolar disorder and major depression, including its cognitive-enhancing action.

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The ghrelin signalling system is involved in the consumption of sweets as wel as of alcohol

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Background:
The gastric-derived orexigenic peptide ghrelin affects brain circuits involved in energy balance as well as in reward. Indeed, ghrelin activates an important reward circuit involved in natural- as well as drug-induced reward, the cholinergic-dopaminergic reward link. It has been hypothesized that there is a common reward mechanism for alcohol and sweet substances in both animals and humans. The mechanisms involved in alcohol use disorders are complex and recently ghrelin and its receptor (GHS-R1A) were shown to be required for alcohol-induced reward as well as moderate alcohol consumption in mice. Further, a single nucleotide polymorphism in the GHS-R1A gene has been associated with high alcohol consumption in humans.
Objectives:
The effects of GHS-R1A antagonists on operant self-administration of alcohol and sucrose in rats as well as for high alcohol, sucrose as well as saccharine consumption in rodents were studied. The effects of peripheral grelin administration on sucrose intake in rats were also examined. In an attempt to translate the preclinical data regarding ghrelin, sucrose and alcohol into humans, a group of alcohol-consuming individuals was investigated for genetic variants of the ghrelin signalling system in relation to both their alcohol and sucrose consumption.
Methods:
Here we used the operant self-administration model for alcohol as well as for sucrose. Additionally, the intermittent access alcohol or sucrose two-bottle-choice drinking paradigm and continuous- and limited-access two-bottle choice drinking paradigms in rodents were used. Genotyping was performed using TaqMan Pre-Designed SNP Genotyping Assays® on the ABI PRISM 7900HT Sequence Detection System using the TaqMan Allelic Discrimination technology.
Results:
Here we found associations with the ghrelin gene haplotypes and increased sucrose consumption, and a trend for the same association was seen in the high alcohol consumers. The preclinical data show that a GHS-R1A antagonist reduces the intake and self-administration of sucrose in rats as well as saccharin intake in mice. Further, ghrelin increases the intake of sucrose in rats. The GHS-R1A antagonist, JMV2959, was found to reduce the operant self-administration of alcohol in rats and to decrease high alcohol intake in Long-Evans rats as well as in high alcohol preferring AA rats.
Conclusion:
Collectively, our data provide a clear indication that the GHS-R1A antagonists reduces and ghrelin increases the intake of rewarding substances and hence, the central ghrelin signalling system provides a novel target for the development of drug strategies to treat addictive behaviours such as alcohol dependence.

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Acute Behavioral stress affects the readily releasable pool of vesicles in prefrontal/frontal cortex.

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Background:
Abnormalities of glutamatergic transmission are considered a core feature of stress-related neuropsychiatric disorders, such as schizophrenia, depression and anxiety. However, the mechanisms whereby behavioral stress and glucocorticoids affect synaptic glutamate homeostasis still need to be elucidated. In a recent study, unpredictable foot-shock stress was found to induce an increase of glutamate release from prefrontal/frontal cortex synaptosomes (1).The increase in glutamate release was completely prevented by chronic antidepressant treatment.
Objectives:
Aim of the present work was to assess if acute foot-shock stress-induced change in glutamate release is mediated by an increasing in the number of vesicles docked to the presynaptic membrane, affecting therefore the overall distribution of vesicles among different presynaptic pools. Indeed a widely accepted view agrees that the mature glutamatergic presynaptic terminal is composed of three pools of synaptic vesicles, generally termed as the readily releasable pool (RRP), the recycling pool and the reserve pool.
Methods:

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Rats were chronically treated with vehicle or desipramine and then subjected to a standard footshock-stress protocol (1). Using superfusion technique in purified synaptosomes, we measured glutamate release evoked by depolarization and hypertonic sucrose, as a measure of RRP. The number of vesicles docked to the presynaptic membrane in prefrontal/frontal cortex was evaluated using electron microscopy. Changes in vesicle mobilization were measured in prefrontal/frontal cortex synaptosomes from control rats incubated with corticosterone by Total Internal Reflection Fluorescence (TIRF) microscopy.
Results:
Foot-shock stress induced a marked and significant increase in glutamate release from prefrontal/frontal cortex synaptosomes, evoked by both depolarization and hypertonic sucrose, suggesting therefore an increase in the RRP from stresses rats. Chronic treatment with desipramine completely prevented the increase of glutamate release evoked by depolarization but not by hypertonic sucrose. Preliminary results from electron microscopy suggest that foot-shock stress increases the number of docked vesicles in prefrontal/frontal cortex synaptosomes, partially prevented by chronic desipramine treatment. Preliminary experiments from TIRF microscopy suggest that incubation in vitro of prefrontal/frontal cortex synaptosomes with corticosterone increases the size of the RRP.
Conclusion:
The previous results suggest that acute foot-shock stress upregulates glutamate release by increasing the number of vesicles docked to presynaptic membrane and ready for release and that the dampening effect of antidepressants involves downstream mechanisms regulating vesicle fusion.

References
Musazzi L et al. (2010). Acute stress increases depolarization-evoked glutamate release in the rat prefrontal/frontal cortex. The dampening action of antidepressants. *PloS ONE* 5(1):e8566.

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Cardiovascular risk factors during second generation antipsychotic treatment are associated with increased immune markers

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Background:
Severe mental disorder and cardiovascular disease (CVD) are often associated, and inflammation is implicated in both disorders.
Objectives: The aim of this current study was to investigate whether there is a relationship between CVD risk factors and inflammation in schizophrenia or bipolar disorder, and if second generation antipsychotics (SGAP) are associated with these factors.
Methods:
We included 361 patients with schizophrenia or bipolar disorder in a naturalistic cross-sectional study. Fasting plasma levels of cytokines, such as high sensitivity CRP (hsCRP), soluble tumor necrosis factor receptor 1 (sTNF-R1), osteoprotegerin (OPG), soluble CD40 ligand (sCD40L), interleukin-1 receptor antagonist (IL-1Ra), von Willebrand factor (vWf) and interleukin-6 (IL-6), all known to be involved in CVD and severe mental disorders, were measured. CVD risk factors including metabolic parameters (lipids and glucose), body mass index (BMI) and blood pressure (BP) were measured and current medication recorded.
Results:
High BMI was associated with increased hsCRP ($p<0.001$), whereas elevated fasting plasma levels of triglycerides were associated with increased hsCRP ($p<0.001$), sTNF-R1 ($p=0.009$) and vWf ($p=0.004$). Elevated plasma glucose was significantly associated with higher hsCRP ($p=0.041$). Low HDL-cholesterol was significantly associated with elevated levels of sTNF-R1 ($p<0.001$). There was a significant interaction between SGAP and BMI ($p=0.023$) and glucose ($p=0.002$) on hsCRP levels, also after adjustment for confounders.
Conclusion:
Several CVD risk factors in patients with severe mental disorder were associated with elevated levels of immune markers. SGAP-related

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overweight and hyperglycemia were associated with higher levels of hsCRP. This indicates that CVD risk factors related to SGAP are associated with immune activation involving the CRP pathway.

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Serotonin transporter gene polymorphism, childhood trauma and cognition in patients with psychotic disorders

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Background:
The 5-HTTLPR polymorphism found in the promoter region of the 5-HTT/SLC6A4 serotonin transporter gene has been linked to an altered stress response. In response to stressful experiences, the short (s-) allele is associated with greater negative psychological reaction and increased stress hormone compared to the long (l-) allele. High stress levels are associated with cognitive impairments in a variety of clinical and experimental settings. Patients with psychotic disorders are characterized both by an increase in childhood traumatic events and abnormal stress response, and by significant but highly variable cognitive dysfunction.
Objectives.
5-HTTLPR as well as long-term effects of childhood trauma interact and may contribute to at least some of the variation in cognitive abnormalities in patients with psychotic disorders.
Methods:
118 non-chronic patients with broad DSM-IV schizophrenia spectrum psychotic disorders (mean±age:32.2±11.3; gender: 54% males), were consecutively recruited to the Thematically Organized Psychosis research study. History of childhood abuse was obtained using the Childhood Trauma Questionnaire (CTQ). Cognitive function was assessed through a standardized neuropsychological test battery. The *5-HTT* gene *polymorphism was analyzed using standard PCR.*
Results:
We observed a significant interaction of 5-HTTLPR variants and childhood trauma on cognitive dysfunction across cognitive domains; homozygote s-carriers exposed to childhood physical neglect or abuse had significantly poorer cognitive functioning than all other groups.
Conclusion:
Our results need replication, but underline the necessity of investigating stressful events and its interaction with genetic markers when studying the mechanisms behind cognitive dysfunction in patients with psychosis.

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SCNP EDUCATIONAL LECTURE:

Depression and heart disease – common biology?

Poul Videbech

A statistical association between major depression and heart diseases has been noticed for nearly a century.
Ischaemic heart disease (IHD) is thus more often than expected followed by depression, and if myocardial infarction is complicated by depression, this increases the mortality substantially. Furthermore, patients who have had a depression have increased risk of IHD. Recent evidence behind these facts will be presented.
Several mechanisms can underlie these associations. Lifestyle factors such as tobacco smoking, inflammatory processes, hypercortisolemia, to mention a few, are interesting candidates.
Another putative mechanism is arteriosclerotic damage to small vessels. In the brain this leads to white matter lesions and increased susceptibility for depression, and the same pathological process in the coronary circulation is known to cause IHD.

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This could explain the increased mortality from heart diseases in patients with so-called silent infarctions, which is frequently found in the brains of patients with major depression.

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SCNP 2011 FRONTIERS LECTURE

Emotional processing in depression

Guy Goodwin

Background:
Symptoms and observable signs offer an important way of measuring the severity of depression and estimating recovery. However, a shift to understanding the cognitive neuroscience underlying the clinical picture can be achieved by studies of emotional processing.
Objectives :
To use measures of cognitive function and emotional bias to inform the neurobiological basis of the onset, relapse and effective treatment of patients with mood disorder
Methods:
We have conducted a series of studies using neuropsychological and neuroimaging approaches to identify cognitive abnormalities in patients and in young subjects at risk of mood disorder
Results :
Patients with depression have impaired attention, memory and executive function that offer a way of identifying abnormal brain states or structure. They also have negative emotional biases but measurement of such effects is confounded by these global impairments and may be secondary to a primary change in mood. Early effects of antidepressants treatments in healthy volunteers and depressed patients appear to target such mechanisms specifically.
Conclusion :
It remains to be established how far the risk phenotypes for mood disorder and the properties of antidepressants are defined by effects on emotional processing both in relation to successful treatment and in the potential for emotional side effects, or blunting of experience, after recovery from depressive symptoms.

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SYMPOSIUM: EARLY TREATMENT STRATEGIES IN SCHIZOPHRENIA– ARE WE THERE YET?

The case for prevention in psychotic disorders.

Ingrid Melle

Background:
Psychotic disorders are serious, costly, and disabling. They typically emerge in late adolescence and early adulthood, a critical phase of neurological, psychological and social development. Many patients display significant impairment already at start of first treatment, and outcome is poorer in those who come late into treatment. Recent studies indicate that it is possible to identify patients with psychotic disorders or with a high risk of developing a psychotic disorder at an earlier point of time.
Objectives:
To give an overview of the background of early intervention in schizophrenia and other psychotic disorders.
Methods:
Review of published early intervention and high risk studies.
Results:
The TIPS study show that treatment can be initiated significantly earlier in psychotic disorders, and this is in turn associated with less severe psychotic symptoms, suicidality and functional disabilities at first treatment . Follow-ups show long-term advantages in the form of less severe negative symptoms, depressive symptoms and global dysfunction. In the past decade it has also been possible to reliably identify clinical constellations with clear power to predict the onset of psychotic disorder within the near future. These ultra high risk (UHR) individuals exhibit either attenuated positive symptoms and/or have high genetic risk combined with functional deterioration. In studies using these criteria,

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preliminary reports found a 40-50% annual rate of conversion to psychosis. A later study from Melbourne found conversion rates of 35% in a large sample of UHR subjects while the more recent North American Prodromal Longitudinal Study (NAPLS), using similar assessment methods, found a conversion rate of 28%. Recent reports document a falling trend for conversion rates to psychosis among consecutive annual samples. The decline was not correlated with symptom levels or functional capacities but with a decrease in the duration of symptoms prior to intake. This might imply that even attention to ongoing mental state and supportive follow-along may reduce the potential for conversion into psychosis.
Conclusion:
If valid, these results suggest that psychosis might be tied to a time-limited process in UHR individuals and that intervening early might normalize that process - in parallel with findings that shortened duration of untreated psychotic symptoms may ameliorate outcome.

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Current treatment strategies in high-risk patients
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Abstract not available at printing

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Stage dependent effect of omega-3 fatty acids in emerging psychosis
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SYMPOSIUM: SUICIDE – IMPULSIVITY. A RECENT UPDATE

New evidence of predictors of suicidality.
Lil Träskman-Bendz

Background:
Predictors of suicidal behaviour have been discussed for ages and from various perspectives. Our studies have mainly focused on psycho-biological factors associated with deliberate self-harm and/or suicide. The advantage of studying suicidal behaviour rather than psychiatric diagnoses per se is the fact that psychiatric diagnostics is based on empirical data, and therefore far from established.
Objectives:
Our studies deal with alterations in monoamine, inflammatory and stress-related systems of importance for suicidality.
Methods:
Throughout the years we have collected data from suicide attempters, non-suicidal depressed individuals and healthy controls. This data bank has offered unique possibilities to try different hypotheses concerning prediction of suicidal behaviour. Based on significant results in the beginning of the 90:ies, we have now established possibilities for extensive translational studies of the immune-system.
Results:
Brain-imaging and genetic studies of the serotonin-transporter reveal a possible association with impulsive suicidality, and globus pallidus seems to be a region of particular interest. Studies of cytokines show increased levels of soluble interleukin 2 (IL-2) receptors as well as decreased IL 2 in plasma of suicide attempters as compared to healthy controls, and this is regardless of diagnosis. Increased interleukin 6 (IL-6) in CSF was also noted in suicide attempters, and especially among those who used violent methods.
Conclusion:
We assume that one important reason for our results could be genetic aberrations harming significant parts of the brain, which in turn stimulate microglia and/or make that part of the brain vulnerable for astrocyte damage. These

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events could be the reason for suicidality or treatment-resistance during treatment with conventional antidepressants. Therefore our next step is to introduce anti-inflammatory add-on regimens for suicidal depressed patients.

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Impulsivity is affected by serotonergic neurotransmission, the 5-HTTLPR gene and sex.

EspenWalderhaug

Background:
The neurotransmitter serotonin (5-HT) is implicated in the regulation of impulsivity. Acute tryptophan depletion (ATD) is a widely used paradigm to study the effects of reduced 5-HT transmission on behaviour. ATD depletes tryptophan from the periphery, subsequently decreasing brain 5-HT synthesis and release. The 5-HTTLPR (serotonin transporter linked promoter region) is a polymorphism in the promoter region of the SLC6A4, the gene that codes for the serotonin transporter. The 5-HTTLPR results in a short (S) or long (L) allele. The S allele is associated with decreased transcriptional efficiency compared with the L allele, and is proposed to be a marker of less efficient 5-HTT functioning.
Objectives:
To investigate the effect of ATD and the 5-HTTLPR on a neuropsychological measure of impulsivity in healthy men and women.
Methods:
39 healthy men and 44 women participated in a randomized, double-blind, parallel group, ATD study. Behavioral measures of impulsivity were obtained using Continuous Performance Tests (CPT).
Results:
The ATD intervention lead to the expected reduction in plasma free and total tryptophan levels. Men and women showed opposite directions in their responses to ATD as indicated by a statistically significant sex × ATD – interaction. Compared with the same-sex placebo control group, women became more cautious during ATD, whereas men became more impulsive. There were no statistically significant main effects or interactions involving genotype on impulsivity when all the participants were included. Analyzing the male participants separately, we found a dose-dependent effect for the S-allele of the 5-HTTLPR on impulsivity. Men with the S'/S' genotype were more impulsive than individuals with the L/S' genotype. Men with the L/S' genotype were more impulsive than those with the L/L genotype.
Conclusion:
ATD increased impulsivity in men, and decreased impulsivity in women. Our data demonstrate that reduced serotonergic tone, as a result of either experimental ATD or 5-HTTLPR genotype, are both independently and additively associated with elevated impulsivity in Caucasian men.

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Antidepressants and suicide revisited

Gøran Isacsson

Background and objectives:
Definitely proving that the use of antidepressants prevent suicide is not possible. Strong data on the group level, however, suggest that the advent of the modern drugs has led to a world-wide decrease in suicide.
Proving causality requires data on antidepressant medications received by imaginary individuals, i.e. "prevented suicides". However, if such individuals *do* exist (hypothesis), their number must be subtracted from the theoretical number of completed suicides with detections of antidepressants in toxicology if no suicides had been prevented. Based on the latter assumption, we have constructed three reasonable "null-hypotheses":
Suicides with detections of antidepressants in *post-mortem* toxicological screening increase proportionally to the increasing use of antidepressants in the population. *Rationale: If not proportional, a good explanation of that would be needed.*
Patients hospitalized for depression who later commit suicide do more often have post-mortem

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toxicological detections of antidepressants than hospitalized patients diagnosed with other disorders than depression. *Rationale: Depression is the main indication for antidepressant medications.*
Patients hospitalized for depression have higher risks of subsequent suicide than do patients hospitalized for non-depression disorders. *Rationale: Depression is a main diagnostic risk factor for suicide.*
The first two null-hypotheses were tested in studies published in 2009 and 2010. In both cases the null-hypotheses failed and the results were better explained by the hypothesis that antidepressants *do* prevent suicide.
Methods: The third "null-hypothesis" was tested in a controlled record-linkage study of 18,922 suicides in Sweden 1992-2003. Each suicide was matched (age, sex, county) to ten population controls.
Results:
The social factors "unemployed", "not married" and "low income" were weak risk factors for suicide with adjusted ORs 2.1, 1.7 and 1.27. The clinical factor "hospitalized with a psychiatric diagnosis during the last 5 years" was a strong risk factor with OR 6.5. When the psychiatric hospitalizations were split into eight diagnostic groups and adjusted for the social variables, Depression had OR 4.1, "Other psychoses" including Bipolar disorder OR 4.0, and the remaining diagnoses ORs 5.2 – 8.9.
Conclusion:
The third null-hypothesis must be rejected. Our interpretation is that although depression indeed is a main risk factor for suicide, it is often well treatable after diagnosis which decreases the risk. In conclusion, the three studies support the assumption that there are, in the general population, individuals diagnosed with depression and treated with antidepressants, who without this treatment had committed suicide.

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SYMPOSIUM: TRENDS AND TREATMENT IN ADDICTION

Mechanisms involved in ethanol´s interaction with the brain reward system.

Bo Söderpalm

Background:
Alcoholism is a chronic recurring brain disorder causing the afflicted a multitude of social and health problems and enormous costs to society. The psychosocial and pharmacological treatment options available have but small to moderate effect sizes, underlining the great need for new effective remedies. Alcohol like all other drugs of abuse acutely activates the mesolimbic dopamine system and, upon chronic administration, produces functional alterations of this important part of the brain reward system. Available data suggests that the mesolimbic dopamine system is involved both in the positive and negative reinforcing effects of ethanol. It hence becomes imperative to understand *how* ethanol interferes with this system. Increased knowledge about these mechanisms may open up for new targets for pharmacotherapies.
Objectives:
To investigate the tentative involvement of cys-loop ligand-gated ion-channels, which ethanol is known to interact with in relevant concentrations, in the mesolimbic dopamine activating and reinforcing effects of ethanol.
Methods:
Experimental studies in the rat: In vivo microdialysis coupled to analysis of extracellular levels of dopamine, taurine, glycine, and □-alanine, home cage free choice two-bottle alcohol consumption model, reversed microdialysis, rt-PCR, immunohistochemistry, electrophysiology
Results:
Our data from a large number of studies are consistent and indicate that a neuronal circuitry involving glycine receptors in the nucleus accumbens, and, secondarily, nicotinic acetylcholine receptors in the ventral tegmental area, is involved in the mesolimbic dopamine activating and reinforcing effects of ethanol. Manipulations of both of these receptor populations have the potential to modulate ethanol consumption.

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Conclusion:
The proposed neurocircuitry has implications for understanding ethanol conditioned dopamine activation, chronic effects of ethanol on the mesolimbic dopamine system and the overall role/importance of dopamine and the nucleus accumbens for the reinforcing effects of ethanol. Two new pharmacological treatment principles are currently undergoing clinical trials based on the present findings.

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Can the smoking cessation agent varenicline be used for treatment of alcohol dependence?
Elin Löf

Background:
Nicotinic acetylcholine receptors (nAChRs) are involved in ethanol reinforcement in animal models and make interesting targets for new treatments of alcohol dependence. Non-specific nAChR antagonists such as mechamylamine reduce ethanol´s dopamine (DA) enhancing effects in the mesolimbic DA system, responding with conditioned reinforcement to ethanol and ethanol consumption in rats. In healthy volunteers, it reduces the self-reported rewarding effects of alcohol, but is associated with substantial side effects, emphasizing the need for new, more selective nAChR modulators for treatment of alcoholism. Varenicline (Champix®/Chantix®) is a medication for smoking cessation. It acts as a partial agonist for several nAChRs, slightly increasing the activity of the mesolimbic DA system, while blocking the reinforcing DA-stimulatory properties of nicotine. Moreover, varenicline significantly reduced alcohol seeking and consumption in alcohol high-preferring animals as well as alcohol self-administration in heavy-drinking smokers.
Objectives:
The aim of the experiments was to further investigate varencline as a new treatment for alcohol dependence by means of animal studies and a clinical trial.
Methods: Using the *in vivo* microdialysis method, we investigated various doses of varenicline and its interaction with ethanol on extracellular DA levels in the neuronal terminals (the nucleus accumbens; nAc) of the rat mesolimbic DA system. We have also performed an investigator-initiated, randomized, placebo controlled, double-blind, two-armed clinical trial of parallel-group design investigating 12 weeks of oral varenicline on alcohol consumption in 170 alcohol dependent women and men in Sweden.
Results:
Our pre-clinical data demonstrate that varenicline alone or ethanol alone significantly increased the levels of DA in the rat nAc compared to baseline, saline or varenicline + ethanol. Co-administration of varenicline and ethanol prevented the respective drug's stimulatory effects on nAc DA. The clinical trial data is currently under analysis and may be presented.
Conclusion:
Our pre-clinical data demonstrate an interaction between alcohol and varenicline on the activity of the mesolimbic DA system in the rat. The effect of varenicline on ethanol-induced DA overflow in the rat nAc resembles the effect of varenicline on nicotine-induced DA overflow in the same brain area, suggesting varenicline as an equally valuable treatment of alcohol dependence.

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The pharmacological treatment of drug craving – are we getting anywhere?
Jørgen Bramness

Background:
Worldwide several million people are abusing alcohol, narcotics and prescription drugs. This constitutes a significant burden individually, socially and economically in all countries. It is a common clinical experience that more difficult than getting people off drugs is getting them to stay off drugs for an extended period of time. The

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relapse rate for many addictions is high. In a neurobiological perspective the understanding of this phenomenon relies on lasting changes in mesolimbic dopaminergic neurons projecting from the ventral tegmental area (VTA) in the extended medulla to nucleus accumbens (NAc) and prefrontal cortex. The mechanism of action and potential clinical use for many, but not all, anti craving drugs are possible to understand within this paradigm
Objectives:
To give an overview of the most used and most promising drugs used to treat drug craving and to prevent drug use in drug addicted persons.
Methods:
The research is based on a non systematic review of the literature including a search of the Pubmed library
Results:
Information on the biology and clinical utility of the following drugs will be presented; drugs working within the mesolimbic dopaminergic system; opioid receptor antagonists (naltrexone), cannabinoid receptor antagonists (rimonabant) and other drugs influencing endogenic cannabinoid regulation (FAAH inhibitors), dopamine metabolizing inhibitors (disulfiram) and drugs influencing other receptor systems, such as GABA-ergic neurons (baclofen) and NMDA receptors (acamprosat)
Conclusion:
Several drugs show promising results as anti craving drugs, but no major breakthrough has been achieved.

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