CONGRESS REPORT

ACNP (American College of Neuropsychopharmacology) 49th Annual Meeting

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The ACNP (American College of Neuropsychopharmacology) 49th Annual Meeting was held on December 5–9, 2010 in Miami Beach, Florida. The program included plenary lectures, panels, plenary session, study groups, posters.
Traditionally the program started with hot topics. Let us have a look at some clinical hot topics.

DNA methylation signatures of human cortical samples across the lifespan

DNA methylation is a major epigenetic modification playing an important role in the regulation of gene expression. The DNA methylation level was studied in the promoter region of a number of schizophrenia susceptibility genes (n74) in the human dorsolateral prefrontal cortex (DLPF) of non-psychiatric subjects across the lifespan. Only 7% of loci were virtually completely methylated across the lifespan. There were 7 genes showing significant changes in methylation over six weeks of the 2nd trimester of gestation, 2 genes during childhood and 10 genes showed methylation level changes during adult life. In summary, the results show a lifespan change in the methylation state of a number of schizophrenia susceptibility genes in the DLPF on nonpsychiatric controls. The result suggests the possibility that developmental changes in methylation status also could be related to the pathophysiology of schizophrenia.

Ondansetron augmentation in treatment of pharmaco-resistant obsessive-compulsive disorder (OCD)

About 40% of OCD patients do not respond to the first line serotonin reuptake inhibitor (SRI) treatment. Ondansetron, the 5-HT_3 antagonist, modulates dopamine turnover in nucleus accumbens and reduces striatal dopamine repetitive behaviour. By down regulation dopamine release in the cortico-mesolimbic pathway of the brain, ondansetron has the potential to augment therapeutic benefits of SRIs in patients who fail to adequately respond to monotherapy. Twenty-one patients with a treatment resistant OCD therapy received 12 weeks of single-blind ondansetron augmentation. Twelve of the 21 (57%) patients experienced a treatment response.

Oxytocin treatment improves social cognition and reduces psychotic symptoms in schizophrenia

Social dysfunction is the most common symptom as well as the primary cause of disability in schizophrenia and remains unresponsive to currently available antipsychotic medications. Decades of animal research have established that oxytocin has many pro-social effects. In recent human studies acute intranasal oxytocin administration increased interpersonal trust, eye contact, performance as well as social reciprocity in normal and autistic subjects. David Feifel recently reported that oxytocin treatment of subject s with schizophrenia for 3 weeks decreased Positive and Negative Syndrome Scale (PANSS) scores. Recently, in a randomized, double blind, placebo-controlled study in subjects with paranoid or undifferentiated schizophrenia oxytocin led to significant reduction in PANSS total score. The mean scores on an a priori subset of

PANSS items relevant to social functioning decreased more than any other variable.

Treatment of neurotrophic infectious agents to alleviate cognitive deficits in schizophrenia: a test of concept randomized double blind placebo controlled trial

Treatment of neurotrophic infectious agents may alleviate cognitive deficits in schizophrenia. An association between cognitive impairment in schizophrenia and exposure to neurotrophic herpes simplex virus, subtype 1 (HSV 1) was observed. These observations were made on individuals without a history or evidence of encephalitis suggesting that asymptomatic exposure to HSV 1 may be of significance. Valacyclovir, an effective medication available to treat herpes infections, was added to treatment for early course schizophrenic subjects. The patients showed a modest improvement in cognitive tests. If the results of the study are replicated, this approach could provide a new strategy to treat a major therapeutic challenge in schizophrenia.

Kenneth Kendler had a challenging lecture on the topic of Reflections on Psychiatric Genetic Research 1980–2010. Mr Kendler made some controversial statements. He stressed what matters – environment, mind, cultural and social issue, development (gene dynamic, shift of sources). Genes do not respect Diagnostic and Statistical Manual of Mental Disorders (DSM). Gene effect sizes for psychiatric illnesses are small – 1 500 genes could be significant under 0.5 significance level. Concerning the conceptual things we need philosophy, we need to become explanatory pluralists –we need both decompose and then re-compose. We have impoverished our psychopathological world. We are flighty – we look for new simple solutions and we have done a bad job without theories.

Several symposia focused on new drug development

1. Recent advances in glutamatergic treatment in schizophrenia

Schizophrenia appears to be associated with glutamatergic synaptic abnormalities that compromise N-methyl –D-aspartate (NMDA) glutamate receptor function. NMDA dysfunction may be a potential underlying feature of negative symptoms and cognitive deficit in schizophrenia.

Targeting the allosteric glycine site of the NMDA receptor has been proposed as an approach to enhance NMDA receptor functioning. Studies with full and partial agonists at the glycine site and sarcosine, a naturally occurring inhibitor of the glycine transporter $type_1$ have provided initial support for this hypothesis. RG_{1678} is a potent and non-competitive inhibitor of the glycine transporter $type_1$ which demonstrated a robust and clinically meaningful effect on negative symptoms and functioning compared to placebo.

Selective positive allosteric modulators of the metabotropic glutamate receptor $mGluR_2$, $mGluR_5$ subtypes and M_1 muscarinic acetylcholine receptor are all effective in modulating specific aspects of glutamatergic signaling in forebrain regions in brain slids and in vivo. This finding provides strong support for the hypothesis that modulation of glutamatergic signaling in limbic and forebrain regions may provide an exciting approach for treatment of schizophrenia.

2. Discovery of small molecules for research on neurosychiatric disorders: Target validation and drug discovery

Recent studies have shown a direct interaction of schizophrenia risk gene Disrupted-in-Schizophrenia$_1$ ($DISC_1$) with glycogen synthase $kinase_3$ (GSK_{-3}, a kinase that mediates the phosphorylation of proteins). Wnt/GSK_{-3} signaling playes a fundamental role in CNS through the regulation of diverse processes rating from neurogenesis to behaviors relevant to cognition. Genetic and pharmacological findings suggest that dysregulation of Wnt/GSK_{-3} signaling may play an important role in the pathophysiology of neuropsychiatric disorders. The small-molecule probes will provide a means to better understand the cellular and circuit level consequences of altering Wnt/GSK_{-3} signaling in the CNS and may provide new avenues for therapeutic development.

Discovery of novel allosteric modulators muscarinic receptors for treatment of CNS disorder

Xanomeline, an acetylcholinesterase inhibitor, has antipsychotic effect in both Alzheimer´s disease and schizophrenia. New highly selective antagonists and activators of the M_1, M_4, and M_5 muscarinic acetylcholine receptors were developed. Both M_1 a M_4 positive allosteric modulators have efficacy in animal models that predict both antipsychotic and cognition-enhancing efficacy and may provide a novel approach to treatment of schizophrenia and other neuropsychiatric disorders.

New molecular targets for neuropsychiatric drug discovery

The druggable genome, defined as the genes in the human genome that express proteins able to bind drug –like molecules is thought to contain 2 000–3 000 molecular targets. At most 5% of the druggable genome has been explored for the purposes of psychiatric drug discovery. Newly created technologies suitable for screening approaches to identify drug targets on a druggable genome-wide fashion may identify new molecular targets for neuropsychiatric drug discovery.

3. Neuregulin in neuropsychiatry 2010: Genetics, neurobiology and therapeutic response

The neuregulin (NRG) ligand family interacts with four transmembrane tyrosine kinase receptors of the epidermal growth receptor ($ErbB_{1-4}$) family. This NRG-ErbB signalling cascade regulates or modulates neuronal development and migration, synaptogenesis, gliogenesis, myelination, and neuron-neuron/neuron-glia communication. NRG_1 and its $ErbB_2/B_4$ receptors are encoded by candidate susceptibility genes for schizophrenia. Genetic variation in the $ErbB_4$ gene has been previously reported to affect treatment response to paliperidone. Since individualization by genetic profiling might maximize benefits for patients, candidate gene and genome wide association studies (GWAS) approaches may be utilized to indentify combinations of genetic factors that may contribute to variations in treatment response to antipsychotics.

David Braff interrogated 94 functionally relevant candidate genes for schizophrenia to identify associations with 12 heritable neurophysiological and neurocognitive endophenotypes collected as part of the Consortium on the Genetics of Schizophrenia. NRG_{-1} and its $ErbB_4$ receptor single nucleotide polymorphisms were selected for interrogation because of their a priori relevance in glutamate modulation in schizophrenia. The authors have confirmed the importance of NRG_{-1} and other glutamate related genes in the identification of genetic variation underlying the etiology of endophenotypes in schizophrenia.

4. Drug development – emerging nanotechnology-based drug delivery methods

Nanometer is one billionth of the meter. Nano size ranges 20–100nm. Aerosol was the first nanoformulation, i.v. 100 nm – tablet 10mm. Nanoparticle manufacturing is possible by size reduction (top-down method) and nanoprecipitation (bottom-up method). The absorption of nanoparticles from the gastrointestinal tract to improve the absorption rate and/or bioavailability has great potential for almost all classes of pharmaceuticals. There is an increasing need to develop delivery systems for drugs with low solubility and/or permeability to obtain the desired pharmacological effect. Nanoparticle delivery involves several crucial parameters that influence uptake (such as particle diameter, the nature of the particle and surface characteristics that effect targeting to and uptake into cells). Many insoluble compounds are dry or wet milled in an order to increase the dissolution properties, which results in an increased absorption after oral administration. Particulate delivery systems, in the form of nanoparticles, microparticles, and microencapsulated particles, are usually formed ether by size reduction (dry or wet milling), spray drying, precipitation or complexing a drug with a polymer of an opposite charge.

Addiction treatment if one of the most difficult health care challenges due to the mixture of complex changing neurochemical pathways and psychological behaviour. For large population addiction, such as nicotine, a promising system is where dosing regimen can be remotely programmed to account for daily environmental factors. Voltage gated carbon nanotubes membranes have attributes that make them of great interest for novel applications such as programmed transdermal delivery of addictive substances.

Gold nanoparticles, are useful for a range of biomedical applications due to their biocompatibility and their ability to bind and deliver many biomolecules. Their surfaces can be modified and can form stable electrostatic complexes with anionic nucleic acids such as small interfering RNA for the purpose of targeted gene silencing. The effects of silencing adenosine 3,5-monophosphate-regulated phosphoprotein ($DARPP_{-32}$) expression using nanotechnology on the pathogenesis of HIV-1 infections was investigated.

In the symposium entitled Dissecting the heterogeneity of treatment response in first episode schizophrenia

Stephan Leucht dealt with meta-analyses of randomized controlled studies, that compared second-generation antipsychotic (SGA) drugs with placebo, SGAs with first-generation antipsychotic (FGA) drugs or head-to-head comparisons of SGAs in first-episode schizophrenia.

Wolfgang Fleischhacker summarized results form European First Episode in Schizophrenia Trial (EUFEST) and focused on clinical predictors of response/remission in antipsychotic-naïve first episode patients. Close to 500 patients with a first episode of schizophrenia, schizophreniform, or schizoaffective disorder were included in the EUFEST. All cause discontinuation, defined as loss of retention on treatment, was the primary outcome variable of this clinical trial, in which the effectiveness of 4 new generation antipsychotics (amisulpride, quetiapine, olanzapine, ziprasidone) was compared to that of a low dose of haloperidol over a one year period. Treatment adherence and higher PANSS total scores at baseline were positive predictors of response and remission, while akathisia, male gender and concurrent substance abuse proved to be negative predictors. In addition, a positive attitude towards treatment, as measured with the Drug Attitude Inventory, predicted retention in the study.

According to René Khan a subgroup of patients closely resembling the original depiction of schizophrenia by Kraepelin and characterized by psychotic, disorganized

and negative symptoms had significantly lower IQ and showed the largest decline in brain volume over time.

Candidate gene analysis of the first episode cohort revealed that dopamine receptor type D2 polymorphism predicted antipsychotic response to olanzapine and risperidone, moreover, the same polymorphism was associated with weight gain in the first episode cohort.

A symposium on kynurenine and its metabolites offered emerging targets for new neuropsychiatric disease intervention

The kynurenine pathway of tryptophan metabolism contains three neuroactive metabolites with purported links to neuropsychiatric diseases: kynurenic acid, 3-hydroxykynurenine and quinolinic acid. The astrocyte-derived compound kynurenic acid antagonizes the alfa$_2$ nicotinic acetylcholine receptor and, possibly, the glycine co-agonist site of the NMDA receptor. These effects are especially interesting in view of the fact that schizophrenia patients present with increased kynurenic acid levels in brain and cerebrospinal fluid. Conversely, cognitive processes may be enhanced by reductions in brain kynurenic acid. Interventions aimed specifically at reducing kynurenic acid formation in the brain may constitute a promising molecular strategy for cognitive improvement in health and disease.

The concept of inflammation-associated depression was initially developed in the context of psychiatric side effects of cytokine immunotherapy in patients with viral infections or chemotherapy and radiotherapy-resistant malignancies. The mechanisms of inflammation –associated depression represent potential targets for the development of new antidepressants. Clinically, reduced circulating tryptophan and increased kynurenine levels are correlated with increased depression scores of patients undergoing cytokine immunotherapy, and with various chronic inflammatory disorders. These biochemical alterations point to a possible role of activation of the tryptophan degrading enzyme indoleamine$_{2,3}$ dioxygenase (IDO) in the pathophysiology of inflammation-associated depression. Inhibition of proinflammatory cytokine production abrogates the increased expression of proinflammatory cytokines and the subsequent activation of IDO, resulting in inhibition of both inflammation-induced sickness and depressive-like behaviour.

Peripheral activation of the kynurenine pathway by interferon alpha leads to altered CSF concentrations of kynurenine and its metabolites which correlate with depression. In patients with hepatitis C interferon alfa significantly increased peripheral blood L-kynurenine, which was accompanied by marked increase in CSF L-kynurenine. Increased CSF L-kynurenine was in turn associated with significant increases in CSF quinolinic acid, kynurenic acid and ultimately depressive symptoms.

The excitoxic quinolinic acid is likely to play a role in the pathogenesis of Alzheimer´s disease. It was shown that the kynurenine pathway is overactivated and that quinolinic acid accumulates in amyloid plaques and within dystrophic neurons. Gilles Guillemin hypothesized that quinolinic acid in pathophysiological concentrations affects tau phosphorylation. Quinolinic acid significantly induces 10 genes in human neurons all known to be associated with Alzheimer disease pathology. Of these 10 genes, 6 belong to pathways involved in tau phosphorylation and 4 of them in neuroprotection.

The symposium called Cannabinoids: Is there a future? was a very interesting event

Quantitative positron emission tomography (PET) imaging of cannabinoid (CB) receptors subtype $_1$ and $_2$ in animal and humans has been limited by the drawbacks of the available radioligands. The latest research has revealed several radioligands with improved imaging properties. Molecular imaging of the CB receptors in human brain with these radioligands has now become possible. There are multiple lines of evidence that CB_2 is upregulated under many pathological conditions including neuroinflammation, Alzheimer´s disease, multiple sclerosis and cancer.

Several studies have examined the link between the cannabinoid CB_1 receptor and several neuropsychiatric illnesses including schizophrenia. David Wong studied a total of 10 healthy control patients and 10 patients with schizophrenia using a high specific activity novel PET tracer. He observed elevated mean binding in patients with schizophrenia across all regions studied and an association of elevating binding specific brain regions and symptoms of the disease.

From the clinical point of view, a relatively new domain of cognition, i.e.. social cognition, was discussed, especially in schizophrenia

Social cognitive impairments in chronic schizophrenia are large in magnitude and are associated with poor outcome. Three different aspects of social cognition required for meaningful social interaction were studied. Each social cognitive measure revealed clear cross-sectional impairments in prodromal, first-episode, and chronic patients compared to their corresponding control groups. The magnitude of impairments on the

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social cognitive tasks was medium to large and there was no evidence of progression or improvement across the three patient cohorts. Among first-episode patients, each social cognitive test demonstrated good 12-month longitudinal stability. Social cognitive impairments also robustly predict real-world functional outcome during the early course of schizophrenia.

Social information processing is impaired in schizophrenia in a variety of domains, including the tendency to appraise individuals as threatening or persecutory. Twenty-one stable outpatients with chronic psychotic disorders and 21 matched, healthy subjects underwent functional magnetic resonance imaging (fMRI). Subjects performed an explicit social appraisal task, in which subjects judged whether or not they liked face stimuli (negative, neutral and positive expressions). For social appraisal, patients were slower to respond, but particularly slow when they judged negatively-valenced faces, compared with the control subjects. This slowness correlated positively with the amount of negative emotion reported by the patients. Appraisal activated the mPFC across all face valences.

Rachel Gur studied facial and vocal affect stimuli using fMRI. She found, that the deficits in facial affect processing seem to parallel those in vocal affect identification, although the later are relatively more severe. Both deficits are associated with more sever neurocognitive impairment.

Traditionally no pharmaceutical companies were present. The quality of the scientific program was absolutely excellent and there has been a growing interest in this meeting every year.