Worldview of Psychiatry

CINP 2004 Congress Preview

The Collegium Internationale Neuropsychopharmacologicum (CINP), the oldest international group dedicated to the advancement of psychopharmacology, will hold its 24th Congress from June 20–24, 2004, in Paris, France.

In this column, we provide program highlights. The Congress will emphasize materials relevant to the concerns of both clinicians who treat patients and basic research scientists who have an interest in neuropsychopharmacology. All major psychiatric disorders, neurotransmitters, receptors, and relevant areas such as clinical treatment and clinical trials, side effect management, biological markers, genetics, and brain imaging will be covered. There will be particular emphasis on new treatments for mental illness and understanding the mechanism of action of psychotropic drugs.

We urge you to attend. Information is readily available at http://cinp2004.com/.

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Neurodegeneration in Stress and Anxiety Disorders: Mechanisms and Implications

Bruce S. McEwen, Ph.D., and Dennis Charney, M.D., Chairs

Growing evidence from neuroimaging and postmortem studies shows that severe mood and anxiety disorders, which have traditionally been conceptualized as neurochemical disorders, are associated with impairments of structural plasticity and cellular resilience. In the human brain, structural magnetic resonance imaging (MRI) has shown amygdala enlargement and hippocampal shrinkage in a number of mood and anxiety disorders, which accompany altered patterns of neural activity as demonstrated by positron emission tomography (PET). For example, hippocampal atrophy is reported in Cushing's disease, posttraumatic stress disorder (PTSD), recurrent depressive illness, bipolar disorder, and borderline personality disorder. There are also reports of atrophy of the prefrontal cortex in major depression and enlargement of the amygdala in the first episode of major depression. For recurrent major depression, autopsy studies reveal evidence of glial cell loss and reduced neuron cell body size in prefrontal cortex, amygdala, and hippocampus without clear evidence of outright neuron loss. Structural changes of this type imply changes in neuronal circuitry that can influence how the brain processes emotions and memory. Prof. Patrice Boyer (*University of Paris, France*) will discuss how our views of structural plasticity have changed how we conceptualize the pathophysiology and treatment of mood and anxiety disorders. Knowledge of underlying anatomical changes and the mechanism of brain structural changes may help in developing treatment strategies to either reverse or prevent these disorders.

Plasticity-Enhancing Treatment Strategies

Complex mechanisms underlie altered brain structure in mood and anxiety disorders. Dr. Dennis Charney (*National Institutes of Health, USA*) will summarize preclinical studies showing that critical molecules in neurotrophic signaling cascades (e.g., cyclic adenosine monophospate [cAMP] response element-binding protein [CREB], brain-derived neurotrophic factor [BDNF], bcl-2, and mitogen-activated protein [MAP] kinases) are long-term targets for antidepressant treatments. These findings suggest that effective treatments provide both trophic and neurochemical support, which serves to enhance and maintain normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning. For many treatment-refractory patients, drugs mimicking "traditional" strategies, which directly or indirectly alter monoaminergic levels, may have limited benefit. Newer "plasticity enhancing" strategies that may be more effective in the treatment of refractory depression include *N*-methyl-D-aspartate antagonists, alpha-amino-3-hydroxy-5 methylisoxazole propionate (AMPA) potentiators, cAMP phosphodiesterase inhibitors, and glucocorticoid receptor antagonists. Small-molecule agents that regulate the activity of growth factor, MAP kinases cascades, and the bcl-2 family of proteins are also promising future avenues. The development of novel nonaminergic-based therapeutics holds much promise for improved treatment of severe, refractory mood disorders.

Models of Stress Effects

Much of our knowledge of structural plasticity in brain regions comes from studies of stress effects on animal models. Dr. Bruce S. McEwen (*Rockefeller University, USA*) will summarize knowledge showing that the hippocampal formation expresses high levels of adrenal steroid receptors and is a malleable brain structure that is important for certain types of learning and memory. The hippocampus is vulnerable to the effects of stress hormones during development and adult life. The amygdala is an important target of stress and is important in fear and strong emotions. The hippocampus and amygdala show opposite response to repeated stress, involving remodeling of dendrites. Hippocampal neurons become shorter and less branched and dentate gyrus neurogenesis is suppressed by repeated stress, whereas amygdala neurons show signs of hypertrophy after repeated stress. Repeated stress promotes impairment of

hippocampal-dependent memory and enhances fear and aggression, which are likely to reflect amygdala function. New evidence shows that acute stress causes a neuronal growth response in amygdala along with increasing anxiety.

One of the brain structures that have been the most extensively studied with regard to the actions of stress, depression, and antidepressants is the hippocampal formation. Within the hippocampal formation, the dentate gyrus is one of the few brain structures in which production of new neurons occurs even in the adult mammalian brain. Stress was identified as one factor that suppresses the formation of new cells. Dr. Eberhard Fuchs (*German Primate Center, Germany*) will summarize studies using the chronic psychosocial stress paradigm in male tree shrews, an animal model that has a high validity in the investigation of pathophysiology of depressive disorders. Chronic psychosocial stress decreased in vivo concentrations of the neuronal marker *N*-acetyl-aspartate, decreased the proliferation rate of the granule precursor cells in the dentate gyrus, and reduced the hippocampal volume. These stress effects were prevented by the simultaneous administration of 3 different antidepressant drugs, yielding normal values for all 3 parameters. The 3 drugs are a classic tricyclic antidepressant (clomipramine), a modified tricyclic antidepressant (tianeptine), and a potential antidepressant agent, the neurokinin-1 receptor antagonist L-760,735. These findings provide a cellular and neurochemical basis for evaluating antidepressant treatments with regard to possible reversal of structural changes in brain that have been reported in depressive disorders.

Neuroimaging Findings

Much of the future work on the pathophysiology and treatment of mood and anxiety disorders will increasingly rely upon neuroimaging techniques. Dr. Israel Liberzon (*University of Michigan, USA*) will provide a critical overview of successes and problems with the use of neuroimaging techniques in elucidating the pathophysiology of psychiatric disorders and guiding the search for therapeutic agents. In his view, this is particularly true for mood and anxiety disorders, where the link between the neuroanatomical "abnormalities" (prefrontal and limbic regions) and the mechanism of action of therapeutic agents is largely unknown. The majority of the neuroimaging research in mood and anxiety has focused on major depressive disorder (MDD) and PTSD, with some findings also reported in bipolar disorder, panic disorder, specific phobia and social phobia. Interestingly, in both PTSD and MDD, similar structural findings of smaller hippocampal volumes have been reported, whereas the HPA axis profiles appear abnormal in opposing directions. The possibility of a link between lower hippocampal volumes and abnormal HPA axis function suggests specific pathophysiologic mechanisms and a possible causal relationship, but the discrepancy in PTSD versus MDD forces a more careful examination of underlying mechanisms from the animal model studies and a more careful evaluation of the human clinical data. Recent functional neuroimaging studies may shed new light on some of these issues and focus attention on other brain regions such as anterior cingulate, medial prefrontal areas, and amygdala. These regions have been identified as key components of emotional circuitry, but volumetric analysis of them is technically difficult and is seldom reported. Furthermore, a better understanding of neuroanatomical or neurochemical underpinning of enhanced or attenuated activity patterns is needed to make these findings relevant to pathophysiology or therapeutics. The use of PET ligand binding and MRS techniques, in conjunction with rCBF and fMRI, offers greater promise in this respect, but these studies remain technically complex and only a small number of appropriate ligands are currently available. Dr. Liberzon concludes that neuroimaging studies will play a key role in elucidating normal physiology of mood and affect regulation, but there is also a need to integrate them with careful cellular, neuroendocrine, and neurophysiologic investigations.