The 30th Annual Meeting of the Canadian College of Neuropsychopharmacology

Banff, Alberta, June 15 to June 19, 2007

Kevin F. Casey, MSc, Richard J. Beninger, PhD, Usoa Busto, MD, Ralph E. Tarter, PhD, Marco Leyton, PhD

Casey, Leyton — Department of Neurology & Neurosurgery; Leyton — Departments of Psychiatry and Psychology, McGill University, Montréal, Que.; Beninger — Departments of Psychology and Psychiatry, Queen's University, Kingston, Ont.; Busto — Center for Addiction and Mental Health, University of Toronto, Toronto, Ont.; Tarter — Center for Education and Drug Abuse Research, University of Pittsburgh, Pittsburgh, Pa.

The 30th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) was held in Banff, Alberta, June 15 to June 19, 2007. This report summarizes the 3 CCNP award lectures and 10 symposia.

CCNP Heinz Lehmann Award lecture

Dr. Hymie Anisman (Carleton University, Ottawa) was the recipient of this year's Heinz Lehmann award, and his talk was entitled "Stress, cytokines and depressive illness." As Dr. Anisman noted, in recent years it has become clear that stressors can affect the immune system. This led to the converse question: can the immune system affect psychological states? Investigations of these associations have benefited from distinguishing between different types of stressors: predictable versus unpredictable, chronic versus intermittent, and processive (e.g., cognitive) versus systemic (e.g., disease activated). Depending on these stressor features, along with intensity and duration, the elicited response can facilitate coping, or it can lead to dysfunction and disease. For example, mild, controllable stressors activate monoamine release and lead to increased synthesis plus an enhanced coping response on subsequent re-exposure. In comparison, severe, uncontrollable stressors deplete monoamine stores, and synthesis rates are unable to compensate adequately. Similarly, monoamine sensitization might simultaneously enhance short-term coping but, in the absence of adequate increases in synthesis, increase vulnerability to the effects of prolonged stressors. The latter change might be related to the progressive acceleration of relapse rates in patients with recurrent major depression. Marked individual and rodent strain differences in these responses are also evident.

Recent work by Dr. Anisman's group has identified a neurobiological pathway that could mediate many of these effects: stress-induced activation of immune signalling cytokines. Inflammatory cytokines such as interleukin-1 (IL-1) and interferon-γ (IFN-γ) are present in the brain, and their activation can affect cell death, neurogenesis, and cell metabolism. Patients suffering from severe stress and depression exhibit increased cytokine activity, whereas cytokine immunotherapy (e.g., interferon-α, tumour necrosis factor-α [TNF-α]) can induce antidepressant-reversible depressions.

In Dr. Anisman's studies, administration of IL-1, like stress, increases norepinephrine (NE) metabolism and serotonin (5-HT) release. The bacterial endotoxin (LPS) increases dopamine (DA) release in the nucleus accumbens (NAc), whereas chronic stressor regimens can decrease responding for electrical brain stimulation (EBS) reward. Following exposure to a cytokine such as TNF-α, there is an increase in sickness-like behavioural responses (e.g., ptosis, ruffled fur, altered body posture), corticosterone release and NE metabolism, and this response becomes greater after repeated exposures followed by extended intertest intervals.

These associations have recently been followed up in studies

Correspondence to: Dr. Marco Leyton, Department of Psychiatry, McGill University, 1033 Pine Ave. W., Montréal QC H3A 1A1; marco.leyton@mcgill.ca

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using brain tissue collected rapidly from antidepressant-free suicide victims (on average, 3.5 h post mortem). In both patients and matched control subjects, cytokine messenger ribonucleic acid (mRNA) levels increase with age. As hypothesized, cytokine mRNA expression in the orbitofrontal cortex (Brodmann's areas 11 and 12) was altered in the suicide victims relative to control subjects, but the direction of effect was the opposite of what was predicted and was possibly related to a modulating influence of social isolation. Overall, these studies provide compelling, innovative evidence that immune system activation influences behaviour and psychological states, including states that are relevant to depression and other neuropsychiatric disorders.

CCNP Innovations in Neuropsychopharmacology Award lecture

Dr. Nicholas Barden (CHUL Research Centre, University of Laval, Québec) was the recipient of this year's Innovations award, and his presentation was entitled, "Pathways out of darkness: identification of mood disorder genes and their interactions." As discussed by Dr. Barden, family, twin and adoption studies have shown that bipolar disorder (BD) and major depressive disorder (MDD) have a strong genetic component. To search for specific genes, Dr. Barden performed a genome-wide search for linkage of BD in a very large pedigree derived from a homogeneous population in the Saguenay–Lac-St-Jean area of Quebec. The genetic homogeneity of this population stems from the migration of founding families combined with a prevalence of large families and the availability of excellent genealogical data. Probands with a DSM-III diagnosis of BD (n = 813 between 1973 and 1986) showed that chromosome 12 was the most probable region to contain a susceptibility gene for affective disorders. Significant allelic associations between the BD phenotype and markers *NBG6* and *NBG12* were found. Later, allelic, genotypic or family association studies suggested the presence of 2 susceptibility loci — the *P2RX7* and *CAMKK2* genes. The *P2RX7* gene within a region of chromosome 12q24.31 is a purinergic adenosine triphosphate (ATP)–binding calcium channel expressed in neurons as well as in microglial cells in various brain regions. The strongest association was observed in BD families at single nucleotide polymorphism (SNP) P2RX7-E13A which results from an overtransmission of the mutant G-allele to affected individuals. This Gln460Arg polymorphism occurs at an amino acid that is conserved between human and rodents, and it is located in the C-terminal domain of the *P2X7* receptor that is known to be essential for normal *P2RX7* function. A subsequent study performed in the Max Plank Institute in Germany investigated 29 SNPs within the *P2RX7* gene and adjacent genes in a sample of 1000 German Caucasian patients who were compared with 1029 control subjects in the same population and found that the *P2RX7* gene (rs2230912) was also significantly associated with MDD, confirming the role of this gene in affective disorders.

Since then, Dr. Barden and his group have used prospective analysis of gene–gene interactions in chromosomal regions genetically linked with mood disorders to identify 2 gene clusters, one involved in neuronal survival pathways and the other comprising members of the chemokine family that play a key role in innate immunity. Brain homeostasis and the immune response are 2 intimately linked systems, and cytokines, immune cells and growth factors work together to restore neuronal homeostasis. Cytokines, whose primary function is to act as immune system signalling molecules, have been implicated in the provocation or exacerbation of mood disorders. Indeed, depression and chronic stressor exposure typically reduce levels of growth factors, including brain-derived neurotrophic factor (BDNF) and antiapoptotic factors, and also impair processes of neuronal branching and neurogenesis. In fact, several proinflammatory cytokines, such as IL-1, TNF-α and interferon-γ, influence neuronal functioning through processes involving apoptosis, excitotoxicity, oxidative stress and metabolic derangement. Support for the involvement of cytokines in depression comes from studies showing their elevation in severe depressive illness and following stressor exposure and that cytokine immunotherapy elicited depressive symptoms amenable to antidepressant treatment. Stressors and cytokines may share a common ability to impair neuronal plasticity and, at the same time, alter neurotransmission, ultimately contributing to depression.

Glucocorticoids also play an essential role in the response to environmental stressors, serving initially to mobilize bodily responses to challenges and ultimately to restrain neuroendocrine and immune reactions. Several diseases, including autoimmune, infectious and inflammatory disorders, and certain neuropsychiatric disorders such as MDD have been associated with decreased responsiveness to glucocorticoids (glucocorticoid resistance). *P2RX7* expression is diminished by glucocorticoids and modified by antidepressant medications and mood stabilizers. Recent studies have linked the above observations, indicating that the *P2X7* gene is associated with immune responses; however, the relation of this to BD and MDD is still unclear.

Finally, gene protein receptor kinase 3 (*GRK3*) has also been shown as a gene that may contain a susceptibly locus for BD, and it is positive in the Quebec population studied by Dr. Barden and his group. This gene also has interactions with *P2RX7*. A second study, though, was not able to confirm that dysregulation of this gene predisposes to the disease. However, recent studies have demonstrated an interaction between *GRK3* and another susceptibility gene for BD. *P2RX7* is decreased after stress, and *Q460R* also decreases activity of this SNP; thus, the combination of these 2 factors may cause MDD. *GRK3* phosphorylates the intracellular domain of *P2X7* receptors recruiting β-arrestins and dynamin and initiates receptor endocytosis and degradation or redistribution. It is possible that the interaction between *GRK3* and *P2RX7* is also important for the development of BD.

The finding that *P2RX7* is implicated in the etiology of mood disorders has important therapeutic implications. Drug development is currently underway, and small activations of *P2RX7* given orally have been shown to have antidepressant-like effects in mice.

CCNP Young Investigator Award

Dr. Martin Lepage (McGill University, Montréal) was the recipient of this year's Young Investigator Award. His award lecture was entitled "Memory and schizophrenia: behavioral and functional neuroimaging findings." Dr. Lepage has developed a research program investigating cognitive deficits in schizophrenia. His work is part of the larger Prevention and Early Intervention Program for Psychosis (PEPP-Montréal). In this program, patients experiencing a first episode of psychosis are evaluated on psychotic symptom severity (assessed with the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms) and undergo a cognitive battery. Symptom severity at intake was not predictive of response to treatment, but severity of neurocognitive deficits was. Patients with relatively preserved verbal and working memory were much more likely to respond to treatment. In the broader literature, patients who retained performance on tests of recognition memory were more likely to respond to treatment. Dr. Lepage then described functional magnetic resonance imaging (fMRI) studies of facets of recognition memory in populations with schizophrenia. A meta-analysis of 18 studies suggested that schizophrenia patients show prefrontal and temporal lobe hypoactivations during memory encoding and retrieval. Many of these studies are marred by group differences in performance and focus only on group differences, ignoring potentially important similarities. Dr. Lepage conducted similar fMRI studies that sought to address these weaknesses. In a first study of item and association recognition memory, Dr. Lepage was able to design a task in which control subjects and schizophrenia patients performed similarly on item recognition and only differed slightly on associative recognition. He reported finding broad areas of conjunction between the groups, as well as some areas of difference. This suggests that populations with schizophrenia are engaging similar brain regions to complete the tasks, with relatively small differences in the overall pattern of activation. Dr. Lepage then described a study of associative memory encoding in first-episode psychosis (FEP) patients from the PEPP-Montréal population. The FEP group showed similar activations to control subjects in comparisons of remembered versus forgotten item pairs and in associative versus item-oriented encoding. In a contrast of arbitrary versus related pairs, control subjects showed much more hippocampal activation than FEP patients. This effect does not appear to have been due to differences in hippocampal volume.

Dr. Lepage then turned his attention to studies of emotional processing and memory in both healthy populations and populations suffering from schizophrenia. Previous work suggested reduced activation of the amygdala and hippocampus during discrimination of emotional valence tasks. In healthy subjects, Dr. Lepage was able to demonstrate that fearful expressions are preferentially remembered. The encoding of this memory appears to depend on the right amygdala, whereas recognition recruited the left amygdala. Using similar methods, Dr. Lepage demonstrated that people are poor at recognizing sad faces but that they are more likely to find them familiar. The left amygdala appears to be activated when a face is perceived as being novel, even if it has been presented before. Unlike healthy subjects, subjects with schizophrenia showed selective memory for happy faces in comparison with neutral or sad faces. However, they showed the same propensity to mistakenly view sad faces as familiar. In contrast to control subjects, the right, and not the left, amygdala was activated when novel faces were perceived as familiar. Dr. Lepage concluded by suggesting that, although functional imaging is often used as a tool to identify pathophysiology in psychiatric disease, it can be profitably used to inform models of both cognitive function and dysfunction. Overall, his results suggest that associative memory formation and retrieval are selectively impaired in schizophrenia but that processing of emotional information appears to be relatively normal.

Symposia

Presidential Symposium: Psychiatry, neurology and neuroscience in the 21st century: where do we go from here? (Chair: Dr. Harold Robertson, Dalhousie University, Halifax. Speakers: Dr. Tom Insel, Director of the National Institute of Mental Health, Bethesda, Md.; Dr. Remi Quirion, Director of the Institute of Neuroscience, Mental Health and Addiction of the Canadian Institutes of Health Research, Ottawa; Dr. H. Christian Fibiger, Amgen Inc., Thousand Oaks, Calif.; Dr. Harold Robertson, Dalhousie University, Halifax)

When abnormalities of behaviour can be linked to a specific brain lesion, that syndrome moves into the realm of neurology. For example, neurologists treat patients with epilepsy and Parkinson's disease. When behavioural abnormalities have no apparent brain lesion associated with them, they generally are treated by psychiatry. Neurology and psychiatry have coexisted for many years, both witnessing the meteoric rise of neuroscience. The rapid growth of this relatively new discipline can be appreciated with reference to attendance figures from the meeting of the Society for Neuroscience. The inaugural meeting of the Society took place in 1971 in Washington, with about 1400 people attending; 34 years later, the same meeting took place in the same location with an attendance of nearly 35 000! The content of neuroscience, being dedicated as it is to the advancement of knowledge about the structure and function of the nervous system, is directly relevant to neurology and psychiatry (as well as other disciplines), and there is a need to reassess the interrelation of psychiatry, neurology and neuroscience. The Presidential Symposium took up this task. The audience was treated to thoughtful, critical and forward-looking perspectives taken by the 4 participants.

Referring to the success of medicine in reducing mortality from heart disease, stroke and cancer over the past 50 years, Dr. Insel, Director of the National Institute of Mental Health in Bethesda, Md., pointed out the relative failure of psychiatry during the same period. Psychiatry is still plagued by a

poor ability to predict who will become mentally ill, little understanding of the etiology of many psychiatric disorders and no cures. To move forward, there is a need to identify the pathophysiology of psychiatric disorders. Insel argued that success at this enterprise will require an integrated approach across different levels of analyses ranging through genetic, cellular, systems, individual and social levels.

At the genetic level, we now know that we have about 23 000 genes consisting of 3 billion base pairs making up 46 chromosomes. Estimating an average of 1 SNP for every 1000 base pairs provides about 3 million SNPs that form the basis of variation among individuals; understanding that variation is the key to understanding the genes that may be responsible for psychiatric diseases. The HapMap project further narrowed the search, revealing that about 300 000 SNPs account for human variability around the globe. This project already has led to success in identifying the genes responsible for some nonpsychiatric diseases, and a gene associated with BD was recently identified through the whole genome association approach. The Allen Brain Atlas (www.brain-map.org) has made it possible to localize gene expression to specific brain regions, providing a further tool for researchers to unravel the sites of action of disease-associated proteins.

Achieving the goal of finding reliable biomarkers for psychiatric diseases will require a change in the culture of science. One key is to work in teams made up of individuals with different expertise and techniques who can work together taking a multidisciplinary approach that cuts across levels of analyses, species, sites and databases. We need a culture of data sharing and a focus on translation that includes networks of clinical sites. Dr. Quirion, Director of the Institute of Neuroscience, Mental Health and Addiction of the Canadian Institutes of Health Research in Ottawa took up Dr. Insel's theme. He emphasized the need to re-evaluate how we train medical doctors and psychiatrists. A greater emphasis should be placed on training in basic and systems neuroscience and in neuroethics. It is only through transforming the current disciplines of psychiatry and neurology into a clinical neuroscience discipline that the goal of identifying the pathophysiology of brain disorders will be achieved.

Dr. Fibiger of Amgen Inc., Thousand Oaks, Calif., agreed with Dr. Insel's evaluation of the general failure of psychiatry to provide improved treatment to its patients. For over 20 years, the pharmaceutical industry has similarly failed to deliver new perspectives on treatment. The failure cannot be attributed to a shortage of funds because massive budgets (industry-wide, perhaps US$30 billion yearly) have been available for research and development (R&D). During the same period, there have been major advances in neuroscience research. Dr. Fibiger referred to the negative influence of the regulatory environment and the ever-increasing demand for better drugs as factors that are constantly raising the bar for successful development of new drugs. Another factor is the mismanagement of R&D by industry. For example, managers frequently have little scientific training and, as a result, do not understand how science progresses and cannot lead effectively. The situation is further exacerbated by pressures from shareholders for quick, spectacular results and by pressures from marketing that often influence the direction of R&D without an appreciation of the implications of these pressures for research. There is an urgent need to restructure industry so that it can more effectively respond to advances in academic research within a practicable time frame.

Some solutions to the problems in "big pharma" include the development of compounds that can serve as research tools that will make it possible to study new targets, the development of better animal models, the development of ligands for positron emission tomography studies, the redeployment of high throughput behavioural screens and an expansion of academic–industry collaboration. With reference to this last point, legal paperwork often creates such long delays that the collaborating parties lose interest in the project before it gets approved. A solution would be to put master research agreements into place, making it possible to respond more quickly to potential collaborative projects.

Dr. Robertson of Dalhousie University in Halifax provided a look into the possible future of treatments for psychiatric disorders, including schizophrenia. He drew on successes in the use of brain repair techniques in the treatment of Parkinson's disease as an example of what might be possible. These techniques include neuroreplacement and functional restoration with deep brain stimulation. Stem cell therapies, possibly including recruitment of endogenous stem cells, provide another replacement technique. He pointed out, for example, that there are stem cells in the substantia nigra that could be targeted. Achieving the goal of identifying biomarkers for psychiatric diseases may provide the basis for developing brain repair techniques. Collectively, the speakers in this symposium provided a frank and critical assessment of the current state of psychiatric understanding of etiology and pathophysiology and of "big pharma" brain research. They identified how historical trends have led to the separation of psychiatry from neurology and emphasized the need for both disciplines to begin a rapprochement built on the extensive success of basic neuroscience over the past 35 years.

The Next Generation (Chair, Dr. Meir Steiner, McMaster University, Hamilton)

The first speaker in the CCNP Next Generation session was Laura Tan (University of Toronto, Toronto), and her talk was entitled, "Identification of teneurin C-terminus associated peptide (TCAP)-1 responsive regions of the brain as determined by immunoreactive c-*fos* induction." TCAPs are a newly identified family of bioactive peptides. They share about 20% amino acid identity overlap with corticotrophin-releasing hormone (CRH). In the embryonic mouse brain, they are spread widely, raising the possibility that they play a role in neurodevelopment. In comparison, in the adult brain, they are primarily localized in limbic brain regions associated with stress and anxiety. TCAP-1 injections increase and decrease cyclic adenosine monophosphate (cAMP) accumulation at low versus high dosages, respectively, and modulate behaviour in rodent models of anxiety. Intracerebroventricular injections of TCAP-1 do not affect c-*fos* induction, but they do block the effects of CRH in the amygdala and

hippocampus. Together, the results suggest that TCAPs may play an important role in modulating neurobiological and behavioural responses to stress.

The second speaker was Aaron Lai (University of Alberta, Edmonton), who gave a talk entitled, "Transformation of microglia between toxic and trophic phenotypes: role of extracellular adenosine 5′-triphosphate and its metabolite adenosine." Microglia are immune cells in the central nervous system. Some evidence, though, suggests that their actions can be either neurotrophic or neurotoxic. It was proposed that the differential effects are modulated by adenosine 5′-triphosphate (ATP), which is released by injured neurons. Mr. Lai's experiments indicate that low concentrations of ATP induce neurotrophic effects, whereas high concentrations have neurotoxic effects. These opposite effects were antagonized by the blockade of *P2XA* microglial ATP receptors and *P2X4 / P2X7 / P2Y12* receptors, respectively. It was proposed that, in vivo, microglia regulate ATP concentrations by metabolizing ATP to adenosine 5′-monophosphate (AMP) and then adenosine. Together, the results suggest that ATP provides a signal between injured neurons and microglia that helps regulate cell survival and death.

The third speaker was Jessica Castellano (McMaster University, Hamilton), and her talk was entitled "Atypical antipsychotic drugs downregulate insulin receptor substrate-2 in the liver: implications for drug-induced metabolic side effects in humans." As Ms. Castellano noted, atypical antipsychotic drugs commonly induce weight gain, glucose dysregulation, increased insulin release coupled with decreased insulin efficacy, and type II diabetes. Although the mechanism by which this occurs remains unclear, her studies indicate that atypical antipsychotics increase levels of glucose-dependent insulinotropic peptide (GIP), a protein that interacts with insulin. Subsequent studies have indicated that administration of olanzapine also has the same effects on plasma glucose, insulin and GIP levels, as well as decreasing mRNA expression of insulin receptor substrate-2. It was proposed that, together, these effects might account for the increased susceptibility to diabetes and associated metabolic disturbances seen in patients treated with atypical antipsychotics.

The fourth speaker was Laurie Jantzie (University of Alberta, Edmonton), and her talk was entitled, "Avenues for intervention for perinatal hypoxic-ischemic brain injury." As the speaker noted, 16% of deaths in Canadian neonatal intensive care units are related to hypoxia-ischemia (HI) that is most commonly due to the umbilical cord becoming wrapped around the neck. Among those babies who survive HI, 20% to 30% develop behavioural disorders or other permanent disabilities. Some of these adverse effects might be attributable to HI-induced neurotoxic effects of intense microglia activation. Recent evidence suggests that the second-generation tetracycline derivative, doxycycline, reduces microglia activation and improves neuronal survival. In further support of this model, Ms. Jantzie reported that doxycycline administration increases neurogenesis and decreases HI-induced decreases in neurogenesis, as indexed by changes in the number of BrdU-positive cells in the hippocampus as well as HI-induced increases in various amino acids. Together, the results suggest that doxycycline, by altering neurogenesis, might be an effective neuroprotective agent in HI.

Symposium 3: Recent developments in Alzheimer's disease pathology: basic and clinical advances. (Co-chairs: Drs. Darrell Mousseau and Satyabrata Kar, University of Saskatchewan, Saskatoon, and University of Alberta, Edmonton)

Dr. Joanne McLaurin (University of Toronto, Toronto) gave a talk entitled "Cyclohexanehexol inhibitors of amyloid beta-aggregation prevent and reverse Alzheimer phenotype in the TgCRND8 mouse model." Dr. McLaurin discussed a family of cyclohexanehexol stereoisomers that may be effective in preventing the β-amyloid (Aβ) peptide aggregation thought to be involved in the pathogenesis of Alzheimer's disease. She described experiments in TgCRND8 mice, a transgenic model of Alzheimer's disease, that showed dose-dependent cognitive improvements in response to prophylactic administration of the stereoisomers. The treated animals had reduced Aβ levels, amyloid pathology, synaptic loss, glial inflammatory reactions and mortality. The scyllo-cyclohexanehexol steroisomer appears to be more effective than the epi-stereoisomer. When administered to older animals with significant behavioural disturbance, the scyllo, but not the epi-stereoisomer, improved performance on a test of spatial reference memory to control levels. These animals showed reductions in Aβ40 and Aβ42 accumulations, fewer plaques were detected, and those plaques that were detected were smaller and covered less of the brain than in untreated animals. Dr. McLaurin then suggested that the cyclohexanehexol stereoisomers may in part produce these effects by interfering with phosphatidylinositol binding to Aβ and preventing fibril assembly. Absolute Aβ concentrations do not appear to be affected, but the concentration of the high-molecular-weight Aβ oligomers thought to be neurotoxic was reduced. Finally, Dr. McLaurin noted that these cyclohexanehexol stereoisomers appear to be well tolerated and effective in treating the Alzheimer's-like symptoms of TgCRND8 mice.

Dr. Gabrielle L. Boulianne (University of Toronto, Toronto) gave a talk entitled "The FK506-binding protein FKBP13 stabilizes presenilin and is required for gamma-secretase activity." Dr. Boulianne discussed studies of Alzheimer's disease in a drosophila model and the challenges of studying cognitive impairment in flies. She presented evidence that presenilins are conserved between drosophila and humans, where they are known to be involved in familial Alzheimer's disease. They are part of the γ-secretase complex involved in cleavage of transmembrane proteins including notch and amyloid precursor protein. She showed evidence that loss of function mutations in the *FKBP13* gene result in animals being impaired on tests of paired-pulse synaptic plasticity and posttetanic potentiation indicative of disturbed learning. She then presented data suggesting that FKBP13 binds to presenilin, and that FKBP13 null mutants have reduced presenilin protein levels. The drug FK506, which binds and inactivates

FKBP13, induced behavioural deficits similar to those seen in the null mutants, reduced presenilin and presenilin enhancer 2 (PEN2) levels and reduced the rate of assembly and activity of the γ-secretase complex. She concluded by suggesting that FKBP13 is necessary for normal presenilin function, which is in turn critical to maintaining γ-secretase activity. She concluded with the suggestion that FKBP13 could be an important target in studies of familial Alzheimer's disease.

Dr. Darrel D. Mousseau (University of Saskatchewan, Saskatoon) gave a talk entitled "The contribution of a direct interaction between monoamine oxidase (MAO) and Ca^{2+} to the etiology of familial Alzheimer's disease." Dr. Mousseau began by reviewing evidence of the neuroprotective effects of MAO-A inhibition. Mitochondrial Ca^{2+} is known to enhance the activity of MAO-A but not MAO-B. Reducing Ca^{2+} availability with the Ca^{2+}–binding protein CB-28K decreases levels of reactive oxygen species (ROS) and basal MAO-A activity in cell cultures. Increasing Ca^{2+} availability with the Ca^{2+} ionophore A231187 has the opposite effects. Because presenilin-1 (PS1) activity affects Ca^{2+} homeostasis, Dr. Mousseau began searching for interactions between proteins implicated in Alzheimer's disease, Ca^{2+} and MAO. He presented evidence that the increase in ROS induced by Aβ in cell culture can be partially prevented by inhibiting MAO-A with clorgyline. Further experiments suggested that exposure to Ca^{2+} increased MAO-A activity in a *PS1* mutant mouse (Tg-PS-1), but not in wild-type animals. Several mutations in the *PS1* gene (*D267A*, *Y115H*, *EX10* del) implicated in Alzheimer's disease affect MAO sensitivity to Ca^{2+}. PS1 could interact with MAO in the mitochondria, a notion supported by the observation that *PS1* mutants are more sensitive to DAPT, a mitochondrial toxin. Dr. Mousseau suggested that the interaction between MAO-A and Ca^{2+} contributes to the development of Alzheimer's disease and that these interactions might influence the age of onset or the course of the disease.

Dr. Satyabrata Kar (University of Alberta, Edmonton) concluded the session with a talk entitled "Amyloid beta peptides and glutamatergic neurons: functional interrelationship and relevance to Alzheimer's disease pathology." Loss of neurons is a hallmark of the Alzheimer's brain, and it has been suggested that an excess of extracellular glutamate may be involved. Dr. Kar reviewed evidence that Aβ peptides can enhance excitotoxicity. He then described studies suggesting that, when given acutely, nanomolar concentrations of Aβ peptides can potentiate glutamate release in the hippocampus and cortex of adult rats. These Aβ-related peptides appear to exert their neuromodulatory effects through direct interaction with glutamatergic terminals. He went on to describe studies of chronic administration of Aβ peptide in micromolar concentrations. This regimen can induce toxicity in rat cortical cultured neurons by increased tau protein phosphorylation and activation of the associated signalling pathways. The noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist memantine can prevent this toxicity. Memantine may exert this effect by attenuating phosophorylation of tau protein and associated intracellular signalling molecules. This effect does not appear to be mediated by internalization or conformational changes in the Aβ peptide. Memantine has beneficial effects in Alzheimer's patients, which may be due in part to the drug's inhibition of tau protein phosphorylation and a reduction in Aβ-induced neurotoxicity.

Symposium 4: Identification and treatment of the first-episode psychosis prodrome: overview and update (Chair: Dr. Keith Hawkins, Yale University, New Haven, Conn.)

Dr. Daniel H. Mathalon (Yale University, New Haven, Conn.) gave a talk entitled "Functional brain abnormalities in the psychosis prodrome." He described work in prodromal patients who have begun to exhibit schizophrenia-type symptoms but have not developed frank psychosis. Neurodevelopmental and high genetic risk theories of schizophrenia suggest that brain abnormalities should exist during the prodromal phase. Prodromal subjects performed similarly to recently diagnosed schizophrenia patients on electroencephalograph (EEG) measurements of event-related potentials (ERP) on tests of mismatch negativity (MMN) and both auditory and visual novelty, measured with the characteristic P300a wave. Response to the tests of auditory target P300 and MMN were predictive of prodromal patients' risk of converting to psychosis within 12 months. Dr. Mathalon conducted functional magnetic resonance imaging (fMRI) studies of patients very recently diagnosed with schizophrenia that suggest deficits in tests of attention to target stimuli (overactivations in the parahippocampal gyrus, cerebellum, occipital lobe, Brodmann's area 6 and basal ganglia and underactivation in the prefrontal cortex, superior temporal gyrus and anterior cingulate cortex). In tests of working memory, these patients showed overactivations of prefrontal and parietal cortices across all task loads, which may represent inefficient use of resources. These patients did not show the prominent linear increase in activity with task load exhibited in prefrontal regions by control subjects. Dr. Mathalon is beginning a series of fMRI investigations in prodromal patients to see whether the deficits seen in early-stage schizophrenia patients are present in prodromal patients and whether these deficits are predictive of conversion to psychosis.

Dr. Keith Hawkins (Yale University, New Haven, Conn.) gave a talk entitled "Identification and treatment of first episode psychotic episode prodrome: neuropsychological findings." Dr. Hawkins discussed the neuropsychological deficits present during the schizophrenia prodrome. He reviewed evidence that neurocognitive deficits are present in asymptomatic high-risk children and in family members of schizophrenia sufferers. The aggravation of these neurocognitive problems is a hallmark of the prodrome, but they do not necessarily predict the development of psychosis. These deficits do not appear to become more severe as a first episode of psychosis becomes chronic schizophrenia. It is unclear how the deficits develop from the premorbid phase through the prodrome and first episode of psychosis. Dr. Hawkins went on to describe as-yet unpublished results of a double-blind treatment trial during the prodrome. Neurocognitive batteries were conducted at intake and after treatment. The study focused on the ability of neurocognitive deficits to

predict treatment outcome and on changes in test performance as a function of treatment.

Dr. Jean Addington (University of Toronto, Toronto) gave a talk entitled "Social functioning and social cognition in the prodrome and beyond." She discussed the importance of impairments in social functioning and social cognition in schizophrenia. Schizophrenia patients are more severely affected by social deficits than are other psychiatric patients. These deficits in social function are often present from an early age. Although these deficits are partially attributable to decreased cognitive function, disturbed social cognition (perception of facial affect, social perception and judgment) may be equally important. Dr. Addington then described the results of the PREDICT study and the North American Prodrome Longitudinal Study (NAPLS). The PREDICT study suggested that a clinical high-risk (CHR) population shows the same deficits in social functioning (both in social and in role functioning) as populations with first-episode and multiple-episode schizophrenia. The NAPLS study also demonstrated deficits in both social and role functioning in a CHR population. Further, the differences between CHR and control populations were larger at 1- year follow-up, suggesting decline during the prodromal phase. Only 35% of the CHR population converted to psychosis at 30-month follow-up; however, converters did not differ from nonconverters at baseline or in change in social or role functioning. An emerging body of literature suggests that cognitive-behavioural therapy used to address the misinterpretations and maladaptive schema central to these cognitive deficits may be effective in prodromal subjects.

Dr. Scott W. Woods (Yale University, New Haven, Conn.) gave a talk entitled "The psychosis prodrome: update on prediction and treatment." Dr. Woods reviewed evidence that prodromal subjects are functionally and cognitively impaired, with a distinct set of diagnosable symptoms. Prodromal subjects have up to 400 times the risk of converting to psychosis, compared with members of the general population. Dr. Woods then discussed the symptoms present during the prodrome that might predict the development of psychosis or schizotypy, as well as those that are predictive of remission to normal levels of functioning. He examined the interactions between prodromal symptoms of genetic risk, decreased function, unusual thought content, suspicion and paranoia, social functioning and drug abuse. His analysis suggests that complex interactions exist between these factors but that, in general, having more symptoms during the prodrome is predictive of a worse outcome. Dr. Woods then turned his attention to the neural underpinnings of the prodrome. He proposed that the reduction in cortical synapses characteristic of schizophrenia might be in part regulated by polymorphisms of the neuregulin gene. Neuregulin is involved in cellular learning processes as well as neuronal and glial growth and development. Subjects with the T/T type polymorphism *SNP8NRG243177* in the neuregulin gene had more psychotic symptoms and were at increased risk of developing schizophrenia. Dr. Woods then suggested that treatment with novel agents such as glycine might be more effective than treatment with antipsychotics during the prodrome. Glycine was more effective than olanzapine or placebo in managing psychotic symptoms in this population. He suggested that glycine might exert its effects by supporting long-term potential (LTP), which is thought to be suppressed during the prodrome. Dr. Woods intends to continue this work by examining the efficacy of D-serine, which acts at the *N*-methyl-D-aspartate (NMDA) glycine binding site and might be clinically effective in prodromal patients at much lower concentrations.

Symposium 5: ΔFosB: a molecular mediator of synaptic plasticity in the mesotelencephalic dopamine system — friend or foe? (Chair: Dr. George Robertson, Dalhousie University, Halifax)

The fos family of transcription factors includes Fra1, Fra2, c-Fos, FosB and ΔFosB; ΔFosB is a truncated form (splice variant) of FosB. This symposium, organized by Dr. George Robertson of Dalhousie University in Halifax featured 4 speakers who provided up-to-date results on a range of studies that related well to the theme and collectively provided new insights into the function of this molecule. In the end, the answer to the "friend or foe?" question depended on what was measured.

Dr. Yusaku Nakabeppu of Kyushu University, Japan, originally described ΔFosB in 1991. Appropriately, he was the first speaker, and his talk was entitled "Mice that express only ΔFosB display a hyperactive phenotype accompanied by increased neurogenesis and resistance to excitotoxicity." He reported results of behavioural phenotyping of genetically modified mice that expressed only the ΔFosB form of FosB. These mice showed elevated levels of ΔFosB in several brain regions, including the striatum and hippocampus. Behavioural differences included increased activity in their home cage and in a novel environment and spending more time in the open arms of the elevated plus maze; this latter observation is often interpreted as evidence for decreased anxiety but in this case could have reflected the general elevation in activity.

The second presentation was by Dr. Catharine Winstanley (University of British Colombia, Vancouver) and was entitled, "ΔFosB: a molecular switch for addiction." The speaker reported that ΔFosB in the orbitofrontal cortex (OFC) was linked to impulsivity. Impulsivity can be measured by the ability to withhold premature responses in the 5-choice serial reaction time task (FCSRT) or by the ability to change response options with increasing delays in the delay-discounting task. Animals with damage to the OFC made more premature responses in the FCSRT but endured greater delays to receive the large reward in the delay-discounting task, implicating the OFC in impulsivity. In both tasks, OFC lesion rats appeared to be less able than controls to adjust their responding to the changing values of reward. From the observation that rats that chronically self-administer cocaine show elevated levels of ΔFosB in the OFC, Winstanley hypothesized that these rats would show increased impulsivity. She employed adeno-associated viral-mediated gene transfer techniques to overexpress ΔFosB in the OFC. These rats behaved like rats that were tolerant to detrimental effects of cocaine in the FCSRT and in the delay discounting task but

showed impaired responding following withdrawal, suggesting increased impulsivity. Together, the results suggest that ΔFosB elevations in animals chronically exposed to cocaine serve to protect the function of the OFC but that these same elevations lead to impaired function during drug withdrawal.

The third presentation, entitled "ΔFosB: a molecular marker of L-DOPA-induced dyskinesia in rodent models of Parkinson's disease," was by Dr. Angela Cenci (Wallenberg Neuroscience Centre, Lund, Sweden). She reported that chronic treatment with L-3,4-dihydroxyphenylalanine (L-dopa) in rats that had undergone a unilateral 6-OHDA lesion of the nigrostriatal pathway led to elevated ΔFosB expression in the lateral striatum. These rats also showed L-dopa–induced dyskinesias that could be blocked by treatment with an antisense oligonucleotide against FosB or ΔFosB mRNA. The increase in ΔFosB that followed chronic L-dopa treatment in the unilateral lesion rats was blocked by inhibition of extracellular signal-regulated kinase (ERK1/2) phosphorylation or by a dopamine D_1-like receptor antagonist. Human postmortem studies of Parkinson's disease patients showed elevated levels of ΔFosB in the lateral septum, and this was apparent only in those individuals who had shown L-dopa–induced dyskinesias. Together, the results implicate ΔFosB in the lateral striatum in L-dopa–induced dyskinesias and suggest novel approaches to therapeutics for these undesirable side effects of treating Parkinson's disease.

The concluding talk of the session was given by Dr. George Robertson (Dalhousie University, Halifax) and was entitled "Aberrant ΔFosB expression and cognition in a rat model of schizophrenia: reversal of cognitive deficits by darbepoietin alfa but not clozapine." The described studies used rats with neonatal ventral hippocampal lesions (nVHL), a widely used animal model thought to be related to aspects of schizophrenia. As discussed by Dr. Robertson, when the lesions are made at postnatal day 7 (P7), ΔFosB expression remains normal at P14, P21 and P35, but then it increases significantly in cortex at P56. At P70, ΔFosB levels dropped in controls but remained elevated in nVHL rats. Moreover, lesioned rats were impaired in a novel object recognition working memory task, consistent with working memory impairment observed in schizophrenia. Treatment with an erythropoiten, darbepoetin alfa, reversed this deficit. Erythropoitens are molecules that promote neuronal survival, synaptic plasticity and increased cognitive function by working through classic signalling cascades. These compounds may be novel cognitive enhancers. Overall, the papers presented in this symposium provided a review of current knowledge about the function of ΔFosB and pointed to novel directions for the development of therapeutics for the treatment of drug abuse, impulsivity, drug-induced dyskinesias and cognitive impairments.

Symposium 6: Neuropeptide modulation of motivation and emotion: emerging ideas. (Cochairs: Dr. Susan Rotzinger and Franco Vaccarino, University of Toronto, Toronto)

The session's opening presentation was by Dr. Xia Zhang and was entitled "Tat-3L4F, a novel peptide for the treatment of drug addiction." As reviewed by Dr. Zhang, the ventral tegmental area (VTA) is a brain region activated by virtually all drugs of abuse, producing rewarding effects due to the release of dopamine (DA) in limbic projection sites. Serotonin 2C (5-HT_{2C}) receptors appear to exert inhibitory influence over VTA DA cell firing. Current literature suggests that this inhibitory influence of 5-HT_{2C} receptors on DA neurotransmission occurs via indirect activation of γ-aminobutyric acid (GABA) inhibitory neurons rather than by direct action of 5-HT_{2C} receptors on DA neurons. Moreover, the phosphatase and tensin homologue (PTEN) tumour suppressor enzyme appears to play an intriguing role by limiting agonist-induced 5-HT_{2C} receptor phosphorylation via its protein phosphatase activity. Recent work by Dr. Zhang and his group suggests that this interaction likely reflects the existence of PTEN–5-HT_{2C} receptor complexes in putative VTA DA neurons. This PTEN–5HT_{2C} receptor coupling is disrupted by the interfering peptide, Tat-3L4F, and systemic application of Tat-3L4F or the 5HT_{2C} receptor agonist Ro600175 suppresses the increased firing rate of VTA DA neurons induced by Δ-9-tetrahydrocannabinol (THC). Moreover, Tat-3L4F also blocks THC- and nicotine-induced conditioned place preference (CPP), effects that are not due to altered learning or memory. Together, the results suggest that Tat-3L4F may suppress the rewarding effects produced by drugs of abuse.

The session's second presentation was by Dr. Kathleen Bailey (Laboratory of Behavioural Neuroscience, National Institute of Mental Health, Bethesda, Md.), and her talk was entitled, "Galanin and galanin receptor subtypes in anxiety-like and depression-related behaviours in rodents." Galanin is a neuropeptide that coexists with norepinephrine and serotonin in neural systems that regulate emotions. It has also been implicated in various physiologic actions such as feeding, sexual behaviour, affective states and cognition. Neuromodulatory actions of galanin are mediated by 3 G protein-coupled receptors galanin receptor subtypes that have been identified and cloned: GalR1, GalR2 and GalR3. Understanding their functions, however, has been limited by the lack of galanin receptor subtype–selective ligands. Differences in receptor expression levels as well as diverse intracellular signalling pathways suggest unique contributions of these receptors to the modulatory effects of galanin in anxiety and depression. Two independent cohorts of GalR2 knockout null mutant mice have demonstrated an anxiogenic-like phenotype in the elevated plus maze, but no genotypic differences were found in several other measures of anxiety-like behaviour. This anxiogenic phenotype was also discovered in GalR1 null mutants, and a GalR3 receptor–specific antagonist produced anxiolytic and antidepressant-like behaviour in rodents. Together these findings support a role for galanin in mediating affective behaviours. The discovery of an anxious phenotype specific for GalR1 and GalR2 receptors highlights the potential therapeutic efficacy of targeting these receptors, and the effects of the selective GalR3 antagonist opens an avenue for the development of novel therapeutic agents for the treatment of mood and anxiety disorders.

The session's third speaker was Dr. Susan Rotzinger (University of Toronto, Toronto), and her talk was entitled,

"Anxiety-modulating effects of the novel neuropeptide teneurin C-terminal associated peptide (TCAP) in rat models." The teneurin C-terminal associated peptides (TCAPs) are a recently discovered family of bioactive peptides located on the C-terminal of the teneurin protein. Four TCAPs are highly conserved among all veterbrates, and they have structural similarities to the corticotropin-releasing factor (CRF) family of peptides. The focus of the present work was TCAP-1, which activates cyclic adenosine monophosphate (cAMP) and increases neurite outgrowth and may act to modulate CRF actions in vivo. TCAP-1 is active in the rat acoustic startle test, as well as in the elevated plus maze and open field test of anxiety. TCAP-1 alone did not affect behavioural responses significantly; however, it did significantly affect CRF-regulated behaviours, depending on how CRF was injected. TCAP-1 had anxiolytic effects on intravenous CRF responses, as evidenced by decreased stretched-attend postures in the elevated plus maze and increased centre time and centre entries in the open field. These TCAP actions were not mediated through acute changes in glucocorticoid levels and may occur via central actions in the brain. Together, the data support the role of TCAP-1 as a novel antianxiety modulatory peptide.

Symposium # 7: Addiction endophenotypes: the transition from vulnerability to disease (Chairs: Drs. Marco Leyton and Robert Pihl, McGill University, Montréal)

The session's opening speaker was Dr. Andrew Chen (State University of New York, Brooklyn), and he gave a talk entitled "Neurophysiological endophenotypes related to CNS disinhibition." As Dr. Chen noted, the concept of "endophenotype" was first proposed 40 years ago. It was considered a heritable vulnerability trait, a phenotype that endowed vulnerability to a disease. In neuropsychiatry, this would correspond to biopsychological clusters that do not necessarily mirror well our current diagnostic categories. A valid endophenotype should be heritable, related to the disorder of interest, state-independent and expressed in unaffected at-risk relatives. Dr. Chen's research suggests that individual differences in electroencephalogram (EEG) oscillations might provide sensitive markers of alcoholism-related vulnerabilities. The brain oscillations, including event-related potentials (ERPs) and event-related oscillations (EROs), can be measured at rest (eyes closed) or during sensory or cognitive tasks. These brain oscillations are under genetic control, with different frequency bands exhibiting heritabilities of 76% (delta), 86% (beta) and 89% (theta, alpha). Both abstinent alcoholics and their high-risk offspring exhibit increased resting beta power, a feature that is also predicted in linkage analyses to chromosomal regions containing genes that encode for GABA receptors (*GABRA2*, *GABRA4*, *GABRB1*, *GABAG1*). Very recently, a SNP for *GABRA2* has been identified that predicts increased EEG beta 2, drug and alcohol dependence and conduct disorder. A second potential EEG endophenotype is increased theta coherence, a feature that is also seen in people with alcoholism and their high-risk offspring. Two groups of genes have been identified that predict high theta coherences: SNPs of the genes that encode for GABA-A receptors and the muscarinic acetylcholine M2 receptor (CHRM2). The ERP and ERO P300 amplitudes have also demonstrated some predictive potential. Reduced P300 amplitude is evident in abstinent people with alcoholism and their offspring. Differences in the theta ERO have been linked to a site on chromosome 7 as well as to 27 SNPs within or close to the *CHRM2* gene. Finally, SNPs of the *GRM8* gene, which encodes for metabotropic glutamate receptor 8, also predict theta EROs and alcohol dependence. Together, these studies suggest that a cluster of GABAergic, muscarinic and glutamatergic genes contribute to an endophenotype that affects vulnerability to a range of externalizing disorders, particularly drug and alcohol dependence and antisocial behaviours.

The second talk of the symposium was given by Dr. Ralph Tarter (Center for Education and Drug Abuse Research, University of Pittsburgh, Pittsburgh) and was entitled "Longitudinal modeling of substance use disorders: linking genes, biochemistry, neurophysiology, and behavior in social context." The presentation described the results of a longitudinal research program now in its 17th year of funding by the National Institute on Drug Abuse. This research has revealed that a prominent feature of substance use disorder liability is neurobehavioural disinhibition (ND). This trait (consisting of poor emotion modulation, low executive cognitive capacity and low behavioural control) in childhood and adolescence predicts substance use disorder by young adulthood, along with correlated outcomes such as arrests, violence and concussion. ND also predicts affiliation with socially nonnormative peers, presaging substance use disorder. Children having high ND at ages 10–12 years affiliate with friends who are inclined toward deviancy and substance abuse. ND is also a predictor of low frontal cortex activation during performance of an antisaccade task and, as well, mediates the association between P300 amplitude of the ERP and substance use disorder.

Whereas ND score is predicted by both paternal and maternal substance use disorder, it is not related to parental neglect or lax discipline. However, punishment of the child by the father reciprocally interacts with the child's ND to amplify risk for substance use disorder. A child's ND at ages 10–12 years mediates the association between physical punishment received from the father and subsequent risk for substance use disorder. Notably, ND is not the result of living in an adverse neighbourhood, indicating that this phenotype is not the result of social contagion, nor is ND predicted by testosterone, although plasma levels of this hormone and ND both predict social norm–violating behaviour that in turn leads to substance use disorder.

Finally, Dr. Tarter noted the heterogeneity of the population that is at high risk for substance use disorder. Results were shown indicating that, between childhood and adulthood, most youths remain stable in their risk for substance use disorder. A significant subset, however, begin adolescence at low risk that amplifies to high risk by early adulthood. This subset is characterized by the emergence of psychosocial problems at ages 12–14 years that are posited to be the result of accelerated puberty that places the youngsters in high-risk situations, including opportunities to affiliate

with older peers in whom drug use is more prevalent. Thus individual psychological makeup in conjunction with biological maturation, including both neurologic and reproductive processes, in the context of a facilitating social environment orients the developmental trajectory to the manifestation of substance use disorder by young adulthood. Together these findings indicate that ND via interaction with the environment predisposes youths to substance use disorder and related adverse outcomes.

The third talk was given by Dr. Marco Leyton (McGill University, Montréal) and it was entitled, "The transition to addiction: from vulnerability traits to dependence." As often noted, only a subgroup who try addictive drugs develop clinically relevant problems. In part, this might reflect individual differences in the effect of abused drugs on DA limbic pathways. In Dr. Leyton's studies, individual differences in the DA response to a first dose of a psychostimulant predict differences in aspects of the reward response, the personality trait of novelty seeking and childhood family environments. With repeated stimulant drug exposure, the DA response becomes progressively greater and elicited by drug-paired cues, consistent with the development of DA sensitization and conditioning. Among individuals with a history of stimulant drug abuse, preliminary studies raise the possibility that this sensitized DA response can come under conditioned control; in the presence of drug-paired stimuli, the DA response is heightened, potentially related to the increased ability of drugs and drug-paired cues to elicit relapse. In comparison, in the absence of drug-related stimuli, the DA response is diminished, potentially related to the progressively diminishing ability of non–drug-related events to motivate those suffering from addiction. Individuals with low 5-HT function may be particularly susceptible to the rewarding effects of abused drugs. Combined molecular genetic and functional neuroimaging studies suggest that a low rate of 5-HT synthesis within the limbic cortex is a trait related to susceptibility to a wide range of impulsive and aggressive behaviours. Experimental inductions of a low 5-HT state increase impulsive behaviours and augment cocaine-induced increases in extracellular DA levels and drug craving. Finally, transiently decreasing DA transmission decreases craving and self-administration behaviour in nondependent drug users but not in nicotine-dependent smokers. Together the results raise the possibility that a gene-influenced low 5-HT trait may predispose individuals to a larger stimulated DA response and a wide range of impulsive behaviours, including substance abuse. The role of these mechanisms in maintaining established substance dependence, though, remains unclear.

The symposium's final talk was given by Dr. Robert Pihl (McGill University, Montréal) and was entitled "The high heart rate response to alcohol challenge: an endophenotypic marker of risk for addiction." A high heart rate response to alcohol predicts a wide range of alcohol-related behaviours, including subjective stimulant responses to ethanol; drug and alcohol use behaviour on the street; reward-seeking personality traits; disinhibitory behaviour, both when sober and intoxicated; and alcohol-induced DA release within the limbic striatum. Alcohol-induced heart rate responses are particularly high in aggressive sons of male alcoholics and predict susceptibility to delinquency, aggressive responding when intoxicated, risk taking, reward sensitivity and gambling. Experimentally decreasing DA function by means of the acute phenylalanine/tyrosine depletion method decreases alcohol self-administration progressive ratio breaking points in social drinkers, and the magnitude of this effect is predicted by the ethanol-induced cardiac response: the greater the heart rate response, the greater the effect of DA depletion. Finally, the heart rate response to alcohol can be modulated by endogenous opioids and environmental cues. The long-lasting opiate receptor antagonist naltrexone decreases the ethanol-induced cardiac response, as do conditioned cues that have been paired with the absence of reward. Together the results indicate that there are individual differences in the stimulant response to alcohol and that a high heart rate response may provide an endophenotypic marker of one pathway to alcohol abuse, a pathway characterized by behavioural disinhibition and a wide range of impulsive and aggressive behaviours. Environmental cues that predict the absence of reward might "soothe" some of these responses, potentially via endogenous opioid and DA-related mechanisms.

Symposium # 8: From molecules to cognition: regulation of synaptic plasticity and memory by cAMP and PKA (Chair: Dr. Peter Nguyen, University of Alberta, Edmonton)

The session's first presentation was by Dr. Ted Abel (University of Pennsylvania, Philadelphia) and was entitled "The role of PKA anchoring in synaptic plasticity and memory." As discussed by the speaker, cAMP-dependent protein kinase A (PKA) has been implicated in late-phase long-term potentiation (L-LTP) in the hippocampal CA1 region. L-LTP is a form of synaptic plasticity elicited by four 100-Hz trains of stimulation of the Schaffer collaterals in the CA3 region of the hippocampus. Transgenic mice that express an inhibitor of PKA showed impaired L-LTP; these mice also were impaired in spatial memory in the water maze and electrophysiological recordings of hippocampal place cells revealed decreased place field stability. Results suggest that L-LTP and spatial memory require intact PKA function. The regulatory subunits of PKAs are anchored within cells by A-kinase anchoring proteins (AKAPs). Over 50 AKAPs are known, and they anchor PKA within dendrites, mitochondria or the cell membrane. Some examples of AKAPs include AKAP79, AKAP12, yotiao and gravin. Dr. Abel's studies indicate that L-LTP is impaired in genetically modified mice with an inducible peptide, Ht31, that competes with AKAPs. He reported on 2 types of mice in which AKAP anchoring could be blocked by induction of Ht31 in both the CA1 and CA3 regions of the hippocampus [Ht31(1)] or only in CA1 [Ht31(6)] . Results showed that Ht31(1) but not Ht31(6) mice were impaired in water maze learning and that L-LTP was reduced, implicating AKAPs in synaptic plasticity in the CA3 region of the hippocampus. Further study of AKAPs are expected to provide new insights into how neurons successfully modify only those synapses that have been active while a particular task was being performed.

The session's second speaker was Dr. Suzanne Zukin (Albert Einstein College of Medicine, New York), and the title of her talk was "Modulation of NMDA-receptor calcium permeability by PKA: potential new targets for schizophrenia." The critical role played by calcium ions in LTP and other forms of synaptic plasticity is well known. One of the ways that calcium enters cells is through glutamatergic (NMDA) receptors. In the postsynaptic density, the AKAP yotiao links NMDA receptors to PKA. Dr. Zukin reported that inhibition of PKA reduced NMDA calcium currents and used calcium imaging to show that this effect took place at synapses on dendritic spines. PKA blockers depress the early phase of NMDA receptor–dependent LTP in the CA1 region of the hippocampus. Results suggested a novel mechanism by which PKA may regulate the induction of LTP.

The session's third presentation was by Dr. Peter Nguyen (University of Alberta, Edmonton) and was entitled "A requirement for PKA in synaptic tagging during long-term potentiation." A central question to understanding the signalling mechanism underlying L-LTP and learning concerns synaptic tagging. It is now well known that some of the signalling molecules involved in long-term changes at synapses travel to the nucleus, where they influence transcription. Many questions remain, though. How do the gene products know where to go? Which of the thousands of synapses on that neuron was responsible in the first place for the message and protein production, and how do these newly synthesized molecules find their way specifically to those synapses? Dr. Nguyen showed that, if a synapse on a cell is mildly stimulated just before another synapse is tetanized, then that synapse will also undergo LTP. Presumably, it is somehow tagged on stimulation and as a result can capture the molecules produced in the nucleus that contribute to plastic changes, leading to strengthening of the synapse. He showed that PKA played a critical role in this synaptic tagging process. Thus transgenic mice that could not activate PKA failed to show synaptic capture by a synapse that was mildly stimulated before application of a tetanus to another synapse on the same cell. Alternatively, chemical activation of the cAMP-PKA pathway was sufficient to produce a tag that could capture L-LTP expression. Thus PKA plays a critical role in the signalling that takes place when specific synapses are tagged for modification.

The session's closing presentation was by Dr. John McLean (Memorial University of Newfoundland, St. John's), and his talk was entitled "The long and short of cAMP in early olfactory learning." He reported on a form of olfactory learning in 6-day-old rat pups. In this model, cAMP expression shortly after training was critical for learning, and prevention of cAMP breakdown by using a phosphodiesterase inhibitor prolonged memory. The norepinehrine β-receptor agonist isoproterenol produced olfactory learning in rat pups, and the combination of subthreshold doses of isoproterenol plus the phosphodiesterase inhibitor cilomilast synergized to produce a learning effect. Synergy was also seen with subthreshold doses of isoproterenol and the calcineurin inhibitor tacrolimus. Taken together, the papers of this symposium provided new insights into the molecules of cognition. The important role of the cAMP-PKA pathway in several aspects of LTP and memory was shown clearly. Continued study of the signalling mechanisms underlying learning and memory is sure to point the way to new avenues for the development of novel pharmacotherapeutics for the treatment of neuropsychiatric disorders such as schizophrenia and Alzheimer's disease.

Symposium # 9: The European College of Neuropsychopharmacology (ECNP) symposium: future targets for antidepressant treatments (Chairs: Drs. Peter Lesch and Michel Hamon, University of Würzburg, Germany, and INSERM, France)

Dr. Trevor Sharp (University Department of Pharmacology, Oxford, United Kingdom) opened the session with a talk entitled "Studies on molecular adaptations to antidepressant treatment: a source of new treatment strategies." Dr. Sharp proposed that antidepressant-induced increases in monoamine function trigger a series of molecular events that ultimately account for their clinical efficacy. Ongoing monoamine transmission acting on these altered circuits might then be required to sustain the clinical response. In some individuals, though, the relevant molecular events might not occur, which would account for the lack of clinical response. One implication is that directly targeting these molecular events might lead to a clinical response in otherwise treatment-resistant patients as well as enhancing treatment efficacy in those who have not achieved full remission. The relevant mechanisms could include antidepressant-induced, 5-HT–regulated changes to BDNF, activity-related cytoskeletal protein (Arc) and the vesicular glutamate transporter (VGLUT1). For example, BDNF induces changes in neural proliferation and survival and is increased by antidepressants and inhibited by environmental stressors. 5-HT agonists also increase Arc gene expression and protein levels in the frontal cortex, orbitofrontal cortex and cingulate, and the Arc protein plays a central role in AMPA receptor trafficking. Finally, antidepressants increase in VGLUT1 mRNA and protein levels within the limbic cortex, while *VGLUT1* knockout mice exhibit depression-like behaviours. Together, these findings have supported a neural plasticity hypothesis of depression and antidepressant efficacy. Further identification of the relevant mechanisms might provide multiple new targets for treatment.

The session's second presentation, given by Dr. Klaus-Peter Lesch (University of Würzburg, Würzburg, Germany), was entitled "Long story short: serotonin transporter in emotion, cognition, and depression." The gene that encodes for the 5-HT transporter (SERT) was first cloned by Dr. Lesch in 1993. Polymorphic variants of the gene were then found to predict susceptibility to mood, anxiety and alcohol abuse disorders. Although these associations were of modest strength, more robust associations have since been consistently identified by multiple groups to predict individual differences in amygdalar and limbic prefrontal cortex responses to threatening stimuli as well as their coordinated activity. Moreover, the direction of these effects appears to be related to the pres-

ence or absence of stressful life events. In subjects with the s allele, increased numbers of stressful life events predict a progressively smaller amygdalar response to emotional faces, whereas the l allele predicts the converse. In various animal models, the SERT knockout mouse exhibits evidence of anxiety and depression (e.g., assessed in open field exploration, elevated plus maze, forced swim test). Neurobiologically, the SERT knockout mouse has increased extracellular 5-HT levels but decreased cellular 5-HT stores, raising the possibility that these mice might be susceptible to 5-HT depletion under challenge conditions. Moreover, in BALB/c mice, which provide relatively impoverished maternal care to their pups (low licking and grooming), SERT knockout heterozygotes exhibit more anxiety in the elevated plus maze. In comparison, in C57BL/6 mice, which provide greater maternal care, plus maze behaviour is unaltered in the SERT heterozygotes. SERT knockout mice also demonstrate increased dendritic branching in the infralimbic region (cingulate–medial prefrontal cortex) and decreased dendritic material plus increased spine density in pyramidal neurons of the basolateral nucleus of the amygdala

The session's concluding speaker was Dr. Per Svenningsson (Karolinska Institute, Stockholm, Sweden), who gave a talk entitled "Alterations in 5-HT1B receptor function by p11 in depression-like states." P11 is an inducible adaptor protein of the S100 protein family. It occurs densely in neuronal cell membranes, overlapping with serotonin 5-HT_{1B} receptors. P11 mRNA levels are increased by electroconvulsive shock treatments (ECT) and 2 weeks' administration of the tricyclic antidepressant imipramine. In comparison, p11 levels are decreased in a mouse model of depression (susceptibility to helplessness in tail-suspension immobility test) and in postmortem tissue from depression patients. The relevant mechanism might include p11-regulated changes to $5HT_{1B}$ function. Transgenic mice that overexpress p11 have increased cell surface $5HT_{1B}$ receptor levels, and p11 stimulates $5HT_{1B}$ receptor signalling, as measured by cAMP. In comparison, p11 knockout mice exhibit reduced 5-HT_{1B} receptor binding levels, even as 5-HT_{1A}, and dopamine D_1 and D_2 receptor levels remain normal. The knockout mice also exhibit reduced negative feedback to the presynaptic cell plus decreased postsynaptic 5-HT_{1B} function. For example, 5-HT turnover is increased, yet various indices of postsynaptic function are decreased; these include diminished 5-HT_{1B}–mediated ERK1/2 activation and inhibition of synapsin phosphorylation as well as decreased 5-HT_{1B}–mediated inhibition of postsynaptic cell firing. Finally, the p11 knockout mice exhibit more behavioural immobility in the tail-suspension test, suggestive of behavioural despair; lower sucrose consumption, suggestive of anhedonia; and reduced beneficial effects from imipramine. Together the results suggest that 5-HT_{1B} receptor function is regulated by p11 and that these molecular pathways play an important role in the pathogenesis of depression and recovery.

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