The 28th Annual Meeting of the Canadian College of Neuropsychopharmacology

St. John's, Newfoundland, Canada, July 2–5, 2005

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The 28th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) was held in St. John's, Newfoundland, July 2–5, 2005. This report summarizes the plenary lecture, the plenary Collegium Internationale Neuro-Psychopharmacologicum (CINP) symposium, 2 award lectures and 8 additional symposia, including the annual CCNP Next Generation session. Unusual weather conditions along the east coast prevented some participants from attending the meeting, and only those talks that were presented are discussed below.

Plenary lecture

This year's plenary lecture was given by Dr. Anthony Grace (University of Pittsburgh, Pa.). Dr. Grace spoke about "Prefrontal cortical interactions with the limbic system and its relationship to the pathophysiology of schizophrenia." His laboratory has conducted a series of electrophysiological studies of the amygdala and its interconnections with other brain regions. He began with an overview of the connections between the basolateral amygdala (BLA), the prefrontal cortex (PFC) and sensory association cortices. He highlighted the inhibitory effect that PFC activity has on BLA activation and the anxiety and changes in affect seen in patients with prefrontal damage. He then reported evidence that the PFC suppression of BLA activity is mediated through dopamine D_1 receptors, whereas association cortex stimulation of BLA activity is mediated through activation of D_2 receptors. He then discussed fear conditioning in the BLA and the suppression of long-term potentiation (LTP) by PFC activation. Dr. Grace examined the role the amygdala plays in emotional learning in the medial PFC. He demonstrated that mPFC neurons encode emotional learning, that BLA activation facilitates this learning, and that inactivation of the BLA prevents it. He went on to show that D_4 receptors are required for mPFC emotional learning. Dr. Grace then turned his attention to the interaction of the PFC and amygdala during chronic stress. Chronic stress increases BLA firing rates both at rest and in response to acute foot-shock stress. In the medial sector of the central amygdala (CeM), however, baseline activity is decreased, and the foot-shock response increased without habituating. This suggests that chronic stress increases the signal/noise output of the amygdala. Lesions of the PFC seem to induce a pattern of firing in the CeM similar to that seen in chronic stress. In an animal model of schizophrenia, where the PFC function has been compromised, stress appears to inhibit LTP. Patients with schizophrenia are also more stress responsive than healthy controls. Dr. Grace hypothesized that PFC deficits in people who go on to develop schizophrenia lead to a cascade of inappropriate stress responses that damage the hippocampus and lead to the pathology seen in patients with schizophrenia.

Special plenary symposium

Current issues in psychopharmacology, a CINP executive perspective (Co-chairs: Drs. Shigeto Yamawaki and Phillipe Robert)

Dr. Herbert Meltzer (Vanderbilt University, Nashville) opened the session with a talk entitled "Targeting cognitive dysfunction in schizophrenia with atypical antipsychotic drugs." As he

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Medical subject headings: alcohols; Alzheimer disease; antidepressive agents; antipsychotic agents; behavioral change; cholesterol; cocaine; cytokines; depression; developmental disabilities; growth and development; idazoxan; limbic system; mice; models, animal; mood disorders; Parkinson disease; prefrontal cortex; rats; schizophrenia; serotonin.

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noted, there are marked deficits in a number of cognitive domains in individuals with schizophrenia that have a greater impact on functional outcome than either positive or negative symptoms. Both typical and atypical antipsychotic drugs have been reported to have modest and variable effects on specific components of cognition; however, as a class atypical drugs are more effective than typical antipsychotics. In support of this proposition, he presented data from a new meta-analysis of 42 studies of the effects of clozapine, olanzapine, quetiapine and risperidone compared with typical antipsychotic drugs or prior treatments. The largest effect of these agents is on verbal fluency and long-term memory, while the smallest effects are on executive function and working memory. Finally, potentially effective new pharmacological strategies for improving cognitive function were briefly reviewed, including serotonin (5-HT)-1A agonists, 5-HT_6 antagonists, and cholinergic and glutamatergic agents. Cognitive retraining, it was noted, might augment the effect of these agents.

Dr. Brian Leonard (National University of Ireland, Galway) gave a talk entitled "Depression as an immunological disorder: if so, do antidepressants act as anti-inflammatory drugs?" He presented the hypothesis that central inflammatory changes form the pathological basis for depression and that antidepressants act by reversing these inflammatory changes. He noted, however, that although some aspects of the immune system are inhibited in depressed patients, other aspects are enhanced. There is evidence of the release of pro-inflammatory cytokines, such as interleukins-1 and -6, and tumour necrosis factor-α, from activated macrophages and monocytes in the blood and microglia and astrocytes in the brain. Furthermore, the activation of cyclo-oxygenase 2 and nitric oxide synthase add to the central inflammatory changes. The pro-inflammatory cytokines contribute to neurotoxicity and neurodegeneration, effects that are reversed following treatment with antidepressants. The time course of these changes in immune and endocrine functions caused by antidepressant drugs parallels the onset of remission.

Dr. Torgny H. Svensson (Karolinska Institute, Stockholm) gave a talk entitled "Role of alpha2 adrenoceptor blockage in the treatment of schizophrenia." He discussed evidence that adjunctive treatment with a selective α2 adrenoceptor antagonist, idazoxan, significantly augmented the effect of classic antipsychotic drugs in treatment-resistant schizophrenia. Adding IDA to very low doses of a selective D_2 antagonist, raclopride, markedly enhanced raclopride-induced suppression of conditioned avoidance response, a preclinical screen for antipsychotic efficacy, as well as increased prefrontal dopamine efflux, an effect that is thought to improve negative and cognitive symptoms. He also showed that the combination of idazoxan with raclopride generated a clozapine-like facilitation of prefrontal glutamatergic transmission, an effect that appears to be mediated by dopamine D_1 receptors. His data indicate that adjunctive treatment with idazoxan might augment the clinical efficacy of both typical and atypical antipsychotic drugs lacking appreciable α2 antagonistic action, and that the unique efficacy of clozapine may reside in its potent α2 antagonistic activity. In support of this proposition, the combination of idazoxan and raclopride also reversed the working memory impairment in rats induced by the selective *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801. Based on these findings, Svensson proposed that the pro-cognitive effect of adjunctive idazoxan treatment may be executed at presynaptic, and not postsynaptic, α2 adrenoceptors in the medial prefrontal cortex.

Dr. Roger M. Pinder (pharmaceutical consultant, 's-Hertogenbosch, The Netherlands) in his talk "Treatment of depression: present and future" noted that existing treatments for depression that are effective and have been used for almost half a century are largely symptomatic with varying responses in individual patients. Many of the newer agents — selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenaline and serotonin specific antidepressants (NaSSAS) and others — lack the side-effect burden and lethality in overdose, but they have not, in general, improved on efficacy. However, there is emerging evidence that dual action SNRIs and NaSSAs, particularly venlafaxine and mirtazapine, offer advantages over SSRIs in terms of faster onset of action and greater rates of response and remission. He underlined the need for new antidepressant drugs, and discussed newer targets other than monoamines, for example, neurokinin and melatonin receptors, glutamate systems especially NMDA, sigma receptors and various hormones. A melatonin agonist with 5-HT_{2C} antagonist properties, agomelatine, is probably the agent nearest to regulatory approval. Another agent, the glucocorticoid receptor antagonist, mifepristone, is in final development for blocking hypothalamic–pituitary–adrenal axis hyperactivity in individuals with depression. Brain-derived neurotrophic factor, which plays a vital role in maintaining neural plasticity and is lowered by stressors and in patients with mood disorders, could be another such target.

Award lectures

CCNP Heinz Lehmann Award lecture

Dr. Michael J. Meaney (McGill University, Montréal) gave the 2005 Heinz Lehmann award lecture entitled "Maternal programming of individual differences in defensive behaviours through alterations in DNA methylation and chromatin structure." As Dr. Meaney described, early maternal care alters the development of emotional, cognitive and endocrine responses to stress in the rat. The mechanisms mediating these effects include changes in the expression of genes in brain regions that regulate central corticotrophin-releasing factor synthesis and release from hypothalamic and amygdaloid nuclei. The adult offspring of mothers that exhibit increased pup licking/grooming and arched-back nursing show increased glucocorticoid receptor expression in the hippocampus. He presented data that maternal behaviour affects DNA methylation within the promoter regions of the rat glucocorticoid receptor gene. These studies reveal sustained effects of maternal behaviour on the cytosine methylation of the consensus binding sequences for specific transcription factors associated with chromatin remodelling and transcription factor binding. Studies targeting histone deacetylation

confirm that methylation is indeed the mechanism underlying behavioural modifications by maternal care. His findings suggest a process of environmentally regulated chromatin plasticity that can involve stable alterations to DNA methylation in post-mitotic cells such as neurons. Finally, Meaney suggested that because neurons in adult animals also possess the molecular machinery for both methylation and demethylation, such "plasticity" could extend across the lifespan.

CCNP Young Investigator Award lecture

The winner of this year's CCNP Young Investigator Award was Dr. Jeffrey Meyer (Centre for Addiction and Mental Health, University of Toronto, Toronto), and the title of his lecture was "Modernizing the monoamine model of depression." As Dr. Meyer noted, most monoamine hypotheses of depression have proposed that mood disorders result from reduced neurotransmission in each or all of the monoamine systems. These proposals are based on observations that antidepressant medications increase monoamine transmission while experimentally induced monoamine depletions lead to mood lowering and the transient reinstatement of depressive symptoms. More recent versions of the monoamine hypothesis emphasize that each of the monoamine systems may be preferentially and dimensionally related to specific symptom clusters. For example, recent functional neuroimaging studies by Meyer and his colleagues, using the positron emission tomography (PET) tracers [^{11}C]DASB (for the serotonin transporter) and [^{18}F]setoperone (for serotonin-2A receptors), suggest that individual differences in serotonin transmission in the frontal cortex and subcortical projection sites affect tendencies toward negative dysfunctional attitudes. The acute administration of the serotonin uptake inhibitor plus releaser, fenfluramine, decreases these dysfunctional attitudes, while the α-2 adrenoceptor agonist, clonidine, has no effect. Finally, individual differences in motor retardation correlate with indices of striatal dopamine function: [^{11}C]raclopride binding (dopamine-2 receptors) is increased in patients in mood disorders, relative to healthy controls, while [^{11}C]RTI-32 binding (the dopamine transporter) is decreased; the striatal binding of both tracers correlated with individual differences in psychomotor retardation. Together, these findings support the view that heterogeneity in mood disorders might be better understood as reflecting a dimensional relation between specific monoamine transmitters and symptom clusters. This view may account for the large number of negative studies in the literature when depressed patients as a group are compared with healthy controls. It also supports the proposition that patients exhibiting the above symptoms may respond well to monoamine-specific pharmacotherapy irrespective of the diagnostic category.

Symposia

Immune mechanisms in psychiatric and neurodegenerative diseases (Chair: Dr. Cai Song)

The focus of Dr. Adrian Dunn's (Louisiana State University Health Sciences Center, Shreveport, La.) talk, entitled "Proinflammatory cytokines and the function of the HPA axis: implications for psychiatric disorders," was the impact of cytokines, particularly interleukin-1 (IL-1), on the hypothalamic–pituitary–adrenal (HPA) axis. Administration of IL-1 to an animal produces rapid increases in adrenocorticotropic hormone (ACTH) and corticosterone. IL-1 can activate the HPA axis at the hypothalamus, the pituitary or the adrenal cortex. Both subdiaphragmatic vagotomy and the cyclo-oxygenase inhibitor indomethacin prevent the hypothalamic noradrenergic response to IL-1β, as well as the plasma cortisol and ACTH responses. This suggests that IL-1β may be able to access the HPA axis at both the hypothalamic and pituitary/adrenal levels. Under normal conditions, the HPA axis response is mediated by the hypothalamus; however, in pathological states the pituitary or adrenal may become able to respond. Other cytokines (IL-6, 2, 10 and 12, tumour necrosis factor-α [TNF-α]) and interferons (interferon-α [INF-α] and INF-γ, leukocyte inhibitory factor [LIF]) have the ability to induce HPA axis activity, but do not have the potency of IL-1. Dr. Dunn then reviewed current evidence for the cytokine hypothesis of depression. This hypothesis proposes that cytokine activation can induce depressive symptoms, that depressed patients often have activated immune systems, that immune diseases cause more depression than other diseases, that antidepressant drugs can prevent infection-related depressive symptoms, and that cytokines can act on the HPA axis and the noradrenergic and serotonergic systems. Dr. Dunn highlighted the variability of the evidence supporting these ideas, and suggested that cytokines are probably not sufficient causes of clinical depression, but may induce symptoms in some patients or exacerbate existing depressive symptoms.

Dr. Cai Song (University of Prince Edward Island, Charlottetown) gave a lecture entitled "The role of cytokines in depressive illness: an update." Depression is a common side effect of serious illness, and it has been suggested that immune factors may be a cause. In the macrophage theory of depression, pro-inflammatory cytokines affect the brain and induce depression. In support of this theory Dr. Song detailed immune changes in depressed patients, such as an altered pro-inflammatory to anti-inflammatory cytokine ratio and imbalances between T lymphocyte subtypes Th1 and Th2 cytokines. A possible mechanism for these depressive symptoms was suggested. The increases in cytokines seen in depression appear to reduce tryptophan availability through activation of a tryptophan-metabolizing enzyme, indoleamine dioxygenase (IDO). Increases in IDO are also thought to reduce serotonin availability, by increasing monoamine oxidase activity, and to stimulate the HPA axis. Dr. Song detailed experiments in animal models demonstrating that the administration of pro-inflammatory cytokines induces signs of stress, anxiety and hopelessness. Administration of IL-1, IL-6 and TNF appears to induce changes in the plus-maze and Morris water maze tests. IL-1, IL-2 and IL-6 are also able to change the release of norepinephrine and serotonin and levels of the dopamine metabolite, homovanillic acid. Dr. Song then described differences in

inflammation-related genes such as *PTX3* and the *MCP-1* promoter in patients with depression. She then described experiments with rats with olfactory bulbectomy, a model of depression, showing increased expression of IL-1β and COX-2 cDNA in the hypothalamus, amygdala and hippocampus. These animals also exhibit increased corticotropin-releasing factor (CRF) mRNA following immune response induced by lipopolysaccharide (LPS). Together these findings suggest that depression is associated with inflammatory responses, and that pro-inflammatory cytokines can induce depressive symptoms. IDO is suggested as an important link between the depressive symptoms and HPA axis abnormalities seen during illness.

Novel pharmacological approaches to dementia treatment: How rats inform the clinic (Chair: Dr. Hans C. Dringenberg)

Dr. Peter Cain (University of Western Ontario, London) in his talk entitled "Studying adaptive behaviour and spatial memory with multiple combinations of neurotransmitter antagonists as a model of Alzheimer disease" suggested that a useful approach to studying the loss of memory and adaptive behaviour in an animal model of Alzheimer's disease may be to antagonize multiple neurotransmitters simultaneously. He presented water maze data showing that combined antagonism of muscarinic cholinergic and *N*-methyl-D-aspartate (NMDA) receptors, or antagonism of muscarinic plus β-adrenergic receptors, causes a specific spatial memory impairment in the absence of impairments in general adaptive behaviour. In contrast, combining antagonism of muscarinic cholinergic receptors with disruptions of serotonergic activity causes a more severe and global impairment of adaptive behaviour even in rats that are thoroughly familiar with the general requirements of the task. Testing with either muscarinic cholinergic or serotonergic antagonism alone indicated that the global impairment induced by the combined treatment was multiplicative rather than additive. Taken together, Dr. Cain's findings confirm that, when used with a detailed behavioural analysis, the water maze task can clearly distinguish between degrees and kinds of impairment. This may prove useful in planning selective treatments for patients with Alzheimer's disease.

Dr. Hans C. Dringenberg (Queen's University, Kingston) gave a talk entitled "Combined monoaminergic-cholinergic enhancement for the effective restoration of cortical activation: evidence from EEG studies in rats." He observed that the close correlation between progressive electroencephalogram (EEG) slowing and cognitive decline suggests that the inability of cortical circuits to maintain an activated state contributes to the behavioural disorganization in Alzheimer's disease. Data from rodent studies indicate that EEG activation depends on parallel cholinergic and monoaminergic inputs to the cortex. Thus, an effective restoration of EEG activation is seen with combined acetylcholine esterase (AChE) inhibition and monoaminergic stimulation in the form of inhibitors of monoamine oxidase or selective serotonin reuptake. He suggested that effective reversal of EEG slowing by cholinergic–monoaminergic stimulation can result in greater improvement in behavioural performance in rodent tests of learning and memory, such as the Morris water maze. Therefore, stimulation of monoaminergic activity, in conjunction with cholinergic therapies, could provide a more effective therapeutic option for Alzheimer's than treatment with AChE inhibitors alone.

Dr. J.N. Reynolds (Queen's University, Kingston) gave a talk entitled "Cognitive deficits in rats after forebrain cholinergic depletion are reversed by a novel nitric oxide mimetic." He presented data showing that the novel nitrate, GT1061 (4-methyl-5-(2-nitroxyethyl) thiazole HCl) reverses cognitive deficits induced by lesions of the forebrain cholinergic system. The memory tasks that he used included spatial learning in the water maze, fear conditioning and delayed visual matching-to-sample task. Oral administration of GT1061 and the acetylcholinesterase inhibitor, donepezil, reversed the cognitive deficits in all memory tasks in a dose-dependent manner. GT1061 is absorbed rapidly after oral administration, crosses the blood–brain barrier and achieves brain concentrations that are slightly higher than those found in plasma. The activity of GT1061 is nitric oxide (NO) mimetic: soluble guanylyl cyclase (sGC) is activated, but selectivity is observed for sGC in the hippocampus relative to the vasculature. Moreover, hippocampal levels of phosphorylated ERK1/2 (extracellular signal-regulated kinase), which is a postulated intermediary in the formation of long-term memory, are increased by GT1061. Dr. Reynolds concluded that the beneficial effect of GT1061 on multiple memory tasks supports the concept that stimulating the NO/sGC/cyclic guanosine monophosphate (cGMP) signal transduction system can provide new, effective treatments for cognitive disorders.

Dr. Remi Quirion (McGill University, Montréal) gave a talk entitled "Neuroprotective effects of IGF-1 and natural products: possible relevance to the treatment for dementia." He described many cellular pathways to dementia in Alzheimer's disease that include changes in amyloid precursor protein processing as well as in intracellular signalling leading to neuronal death. He presented data showing inhibition of hippocampal acetylcholine release by amyloid peptides, in particular, amyloid-β 1–28 (Aβ 1–28). His research shows that insulin-like growth factor-1 (IGF-1) protects against Aβ-induced cell death in cultured rat hippocampal neurons. The intracellular signaling cascade involved in IGF-1 protection includes IGF-1-induced activation of PI3K/Akt and consequent protection of hippocampal neurons/PC12 cells from N2/serum deprivation. Further studies showed that IGF-1 induces the phosphorylation of the forkhead transcription factor, FKHRL1, a substrate of Akt kinase, via the PI3K/Akt pathway. He also presented evidence that the amnesic effects of the NMDA blocker, MK-801, and scopolamine may be mediated by reductions in phosphorylated Akt. In conclusion, Quirion noted that GF, being a peptide, may not be suitable as a central nervous system medication, whereas other agents such as *Ginkgo Biloba* extracts and red wine extracts (e.g., resveratrol), which might act via overlapping signalling cascades, could be effective novel strategies for neuroprotection and the treatment of dementia.

Cholesterol, lipid metabolism and mental health (Chair: Dr. Gustavo Turecki)

The first speaker was Dr. Katja Nieweg (Max-Planck/CNRS Group and University of Hamburg, Hamburg, Germany) who gave a talk entitled "Cholesterol, homeostasis and function in the CNS." As Dr. Nieweg noted, the class of drugs known as statins was originally developed to lower cholesterol and treat vascular diseases, but recent work suggests that they may have intriguing neurological effects and affect risk for disorders such as Alzheimer's disease. Other cholesterol-lowering treatments appear to increase risk for mood disorders and suicidal behaviour, though this has not been seen with the statins, perhaps because recent clinical trials have been careful to exclude those at risk for these behaviours. Given these intriguing observations, Dr. Nieweg has been studying mechanisms related to cholesterol metabolism in the brain. In brief, cholesterol does not appear to be exchanged between the periphery and the brain, but effects might be induced by as-yet-unknown mechanisms. Moreover, both neurons and astrocytes produce cholesterol (albeit with differences in their metabolic pathways), and this can affect synaptic activity; indeed, some evidence suggests that cholesterol in the brain may function as a nerve growth factor. For example, mice with deficits in cholesterol transport exhibit neuronal loss and morphological changes indicative of neurodegeneration. Together, this research is furthering our understanding of mechanisms by which individual differences, or medication-induced changes, in brain cholesterol levels could affect brain function, and susceptibility to various neurological and neuropsychiatric disorders.

The second speaker was Aleksandra Lalovic (Douglas Hospital Research Centre, McGill University, Verdun, Quebec), and the title of her talk was "Brain lipid metabolism and suicidal behaviour." As the speaker reviewed, early studies found that treatment with cholesterol-lowering drugs was associated with a small, but statistically significant, increase in the number of deaths from suicide. In animal studies, low cholesterol diets increase aggressive behaviour. To investigate this implicated association further, Lalovic interviewed people who are heterozygous for the gene for Smith–Lemli–Opitz syndrome (SLOS). The SLOS genetic mutation markedly decreases cholesterol synthesis. An SLOS knockout mouse model exhibits aggressive behaviour and increased postsynaptic serotonin receptors. Patients who are SLOS homozygotes exhibit learning disabilities, low IQ and aggressive self-injurious behaviour. Feeding them a high-cholesterol diet improves behaviour. Relatives who are SLOS heterozygotes do not have the SLOS disease, but they do have strikingly low cholesterol levels. The central finding of the first study by Lalovic and colleagues was that biological relatives of SLOS carriers have an elevated rate of suicide attempts. In a second study, Lalovic measured cholesterol levels in the post-mortem cortical brain tissue of individuals who had committed suicide. It was found that cholesterol levels were significantly reduced in those who died from suicide, as compared with healthy controls, in 2 areas of the ventral prefrontal cortex, Brodmann's area 11 and 47, both of which have been implicated in functional neuroimaging and post-mortem tissue studies of serotonin function in individuals with a history of suicidal behaviour. Together, these observations suggest that cholesterol in the brain can influence vulnerability to suicidal behaviour. Moreover, because this is the first study of the relation between brain cholesterol levels and behaviour in humans, future work seems of great interest.

The third speaker was Dr. Mathew Muldoon (Center for Clinical Pharmacology, University of Pittsburgh, Pittsburgh, Pa.) who gave a talk entitled "The potential effects of low or lowered cholesterol on cognitive performance." As the speaker noted, individuals who take cholesterol-lowering statins have a 70% lower rate of Alzheimer's disease. It is unclear, however, whether this is an effect of the statins or a reflection of a self-selection bias in individuals who seek the treatment. In support of the second possibility, recent observational studies indicate that being in the bottom versus the upper tenth percentile of cognitive performance is associated with lower cholesterol. Similarly, studies by Muldoon and his colleagues have found that treating high cholesterol with lovastatin or simvastatin diminishes the usual cognitive improvement that occurs following repeated testing. However, although these effects were statistically significant, they were clinically small, which suggests that the effects are not a cause for clinical concern. They do, however, add to the evidence that changes in plasma cholesterol levels can have neurocognitive effects.

The final talk of the session was given by Dr. Francois Lespérance (Department of Psychiatry, University of Montréal, Montréal). He reviewed the evidence that there is an association between "Fatty acids and major depressive disorder." Dr. Lespérance noted that epidemiological evidence suggests that mood disorders precede cardiovascular disease (CVD). Moreover, work by Drs. Lespérance and Nancy Frasure-Smith suggests that high depression scores are associated with poor survival following myocardial infarction (MI). In the model proposed by Dr. Lespérance, depression and CVD have a bidirectional association. In brief, the modern diets that have developed with agricultural and industrial societies provide relatively more omega-6 and fewer omega-3 fatty acids. Accumulating evidence suggests that diets relatively higher in omega-3s protect against depression and inflammatory diseases. Fish oil supplements that are high in omega-3 fatty acids decrease mortality from MI, stroke and other CVD. Dietary fish intake predicts cross-cultural differences in rates of depression, suicide and homicide. Three of 4 placebo-controlled clinical studiers have found that omega-3 supplements are effective treatments for depression. A recent open-label study by Dr. Lespérance also identified the clinical efficacy of omega-3 supplements for depression, and a large, multisite, double-blind, placebo-controlled study is being prepared. The mechanisms that might account for these effects remain poorly understood, but preliminary studies conducted by others suggest that, in humans, plasma levels of the omega-3 fatty acid, docosahexaenoic acid, correlate with cerebrospinal fluid concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid, and, in laboratory animals, omega-3 fatty acid supplements affect cortical serotonin levels.

Together, these observations suggest that increasing omega-3 fatty acid intake could provide a novel, safe treatment for CVD, depression and other serotonin-related disorders.

The amygdala and bed nucleus of the stria terminalis: effects of motivational and emotional factors (Chair: Dr. Jane Stewart)

Dr. Suzanne Erb (University of Toronto, Toronto) opened the session with a talk entitled "Long-lasting effects of cocaine pre-exposure on responsiveness to CRF and footshock stress: implications for stress-induced relapse." As Dr. Erb noted, stress-induced relapse to cocaine seeking after prolonged abstinence is mediated in large part by actions of corticotropin-releasing factor (CRF) in the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala (CeA). Previous work indicates that cocaine pre-exposure has long-lasting effects on responsiveness to CRF and footshock stress (an environmental stressor that induces cocaine relapse via CRF-mediated mechanisms). Her more recent studies, however, show that cocaine pre-exposure does not produce lasting changes in CRF mRNA or binding protein basal expression in the BNST or CeA of adult rats but, instead, produces long-lasting changes in neuronal activation within the CeA in response to intracranial injections of CRF and footshock stress. These enduring changes in brain responsiveness to CRF and to stress may be implicated in the long-lasting vulnerability to relapse experienced by cocaine-dependent humans.

Dr. Eric Dumont (The Vollum Institute, Portland, Ore.) gave a talk entitled "Self-administration enhances excitatory synaptic transmission in the bed nucleus of the stria terminalis." His studies suggest that cocaine self-administration results in enhanced excitatory synaptic transmission within the BNST. In comparison, this effect is *not* observed when the drug is passively administered. Interestingly, the self-administration of palatable food also produces increased excitatory synaptic transmission within the BNST but, again, this effect is not observed when food is passively delivered. These data suggest that the BNST may be part of the neuronal circuitry underlying reward-seeking behaviour.

Psychopharmacological treatment of aggression, self-injurious behaviour and destruction/disruption in the developmentally disabled: exploration of a parallel universe (Chair: Dr. David Janowsky)

Dr. Bonita Blake (University of North Carolina, Chapel Hill, NC) delivered a talk entitled "Neurochemical and anatomical underpinnings of aggression and SIB in a rat model of mental retardation." Dr. Blake's talk focused on studies using a rodent model of Lesch–Nyhan disease. These animals received prefrontal 6-hydroxydopamine (6-OHDA) lesions 4 days after birth. As adults, these animals demonstrate high aggressivity and self-injurious behaviours (SIB). Dopaminergic mechanisms are implicated in this behaviour, because dopamine agonists exacerbate the symptoms, and both typical and atypical antipsychotic drugs, as well as NMDA blockers, prevented these behaviours. Voltage-gated calcium channel (L-CA^{2+}) agonists, such as BAY K-8644, induce SIB in healthy animals, whereas nefidepine, a L-CA^{2+} blocker, appears to prevent apomorphine-induced SIB in some lesioned animals. These experiments suggest that the postsynaptic L-CA^{2+} channels mediate the interaction with D_1 receptors. Dr. Blake then detailed experiments suggesting that the downstream interaction of the calcium channels and dopamine receptors is mediated through ERK. Lesioned animals show increases in ERK phosphorylation in the striatum and prefrontal cortex when primed with a D_1 agonist. Increased ERK phosphorylation is also thought to induce decreases in microtubule-associated protein 2 (MAP2) and changes in dendritic bundling, which are similar to those seen in patients with schizophrenia and autism. Inhibiting the ERK kinase MEK prevents these changes. BAY K-8644 administration appears to resolve the MAP2 and bundling changes, through a calcium–calmodulin-dependent protein 2 (CAMK2)-dependent mechanism.

Dr. Rob Nicolson (University of Western Ontario, London) spoke about the "Use of serotonergic and other antidepressants in the treatment of aggression and self-injurious behaviour in the developmentally disabled." Dr. Nicolson's talk focused on the use of SSRI and tricyclic antidepressants in the treatment of developmental disorders, particularly autism. He began his talk by noting that aggression or SIB is the most common reason for initiating pharmacotherapy in the developmentally disabled. Studies of tricyclic agents in managing developmental disorders suggest that they are of limited use. In some cases, they produce improvements, particularly with clomipramine, but behavioural worsening, increased irritability, aggression and temper are also commonly observed. SSRIs appear to be more promising agents, especially because reduced serotonin may be an underlying cause of aggressivity. Many open-label studies suggest that SSRIs have beneficial effects; however, few controlled studies have been conducted. Improvements in social function, irritability and stereotypy have been observed in adults with autism following administration of escitalopram. Fluvoxamine improved aggressive behaviours in adults with autism; however, in children it was less well-tolerated and less effective. Similarly fluoxetine had serious side effects in children with autism and, while it improved repetitive behaviours, it did not reduce aggressive ones. On the whole, SSRIs appear to be a better choice than tricyclic drugs in adults with developmental disabilities. In children, neither class of drug reliably reduces aggressive behaviours, and side effects tend to be difficult to tolerate.

Dr. David Janowsky (University of North Carolina, Chapel Hill, NC) presented a talk entitled "Treatment of aggression, SIB and destruction by atypical and conventional antipsychotic agents in the mentally retarded." Dr Janowsky retrospectively analyzed the records of institutionalized mentally retarded patients being treated with antipsychotic drugs. He began by describing tactics for assessing the severity of mental retardation (MR), the behavioural problems associated with MR and the available pharmacotherapy in these populations. Dr. Janowsky then reviewed work that suggests that olanzapine and risperidol, but not quetiapine, are effective in managing aggressive, self-injurious and destructive

behaviours in adult MR. Improvements were also noted following treatment with serotonergic antidepressants and with topiramate. Dr. Janowsky then discussed the long-term follow-up of patients whose antipsychotic drugs had been withdrawn. Two-thirds of patients successfully withdrawn from drugs were completely medication free up to 13 years later, and most other patients were taking only 1 drug at follow-up. However, for a minority of patients who had a relapse early after withdrawal of the drug, the prognosis was not as good. A decade later, only 9% of these patients were drug free, and many required typical and atypical antipsychotic co-therapy. Dr. Janowsky suggested that early relapse is a good predictor of a need for sustained antipsychotic therapy, and withdrawal of antipsychotics from patients who have had a relapse should be done with great care.

Molecular mechanisms of behavioural change: implications for psychiatric disorders (Chair: Dr. Richard J. Beninger)

Altered corticolimbic glutamate transmission is implicated in the origin of neuropsychiatric disorders. Homer proteins are a family of postsynaptic scaffolding proteins that regulate the synaptic localization of glutamate receptors. Dr. Karen Szumlinski (University of California at Santa Barbara, Santa Barbara, Calif.) in her talk "Homer regulations of corticolimbic glutamate: implications for neuropsychiatric disorders" presented a series of studies aimed at examining the role of Homer proteins in mesocortical glutamate transmission and behaviour. She showed that, in mice, deletion of *Homer1* or *Homer2* produces specific glutamatergic abnormalities that are associated with specific changes in behaviour, including changes in drug self-administration and drug-induced motor activation. The changes in glutamatergic function and behaviour are dependent on the type of Homer protein that is deleted. In addition, she showed that *Homer1*, but not *Homer2*, mutant mice exhibit abnormalities in cognitive and sensorimotor function that resemble those observed in schizophrenia, suggesting that *Homer1* mutant mice may be used as a potential animal model of schizophrenia.

Dr. Sheena Josselyn (University of Toronto, Toronto) talked about potential "Molecular mechanisms involved in fear learning" by placing special emphasis on the role of the CREB (cyclic AMP response element binding protein) family of transcription factors. CREB mutant mice have been shown to exhibit deficiencies in synaptic plasticity that correlate with deficits in several forms of long-term memory function, including auditory fear conditioning. By means of viral-mediated gene transfer, Dr. Josselyn showed that "replacing" CREB directly in the amygdala of CREB mutant mice restores long-term memory for auditory conditioned fear, specifically. These data suggest that the amygdala is implicated in the storage of memory for auditory fear conditioning and that CREB-mediated mechanisms are involved in this process.

Dr. Elena Chartoff (Harvard University, Boston, Mass.) talked about "Behavioral adaptations associated with nucleus accumbens CREB activation: Implications for depression." Increased CREB within the nucleus accumbens (NA) has been previously associated with aversive states in rats. Dr. Chartoff hypothesized that activation of dopamine D_1 receptors (which stimulate cAMP production) during morphine withdrawal leads to increased CREB activation in the NA, triggering or exacerbating aversive states in rats. In both in-vitro and in-vivo models, she found that CREB is indeed activated in striatal regions during morphine withdrawal and that this effect may be mediated by D_1 receptor stimulation. However, place-conditioning paradigm studies revealed that the systemic administration of a D_1 receptor agonist to morphine-dependent rats does not increase place aversion, but instead increases place *preference*. She speculated that D_1 receptor-dependent activation of CREB in the NA during morphine withdrawal serves to lessen aversive states.

In his talk entitled "Signalling molecules in reward-related learning: Implications for schizophrenia," Dr. Richard Beninger (Queen's University, Kingston) talked about possible signalling mechanisms mediating the effects of dopamine on incentive learning. Intra-NA injections of indirect dopamine agonists increase incentive learning and locomotor activity. Dr. Beninger showed that intra-NA injections of inhibitors of the signalling molecules protein kinase A, protein kinase C, extracellular signal-regulated kinase or p38 block the effects of amphetamine on incentive learning. Interestingly, a clear dissociation between learning and locomotor processes was observed because injections of the protein inhibitors did *not* block amphetamine-induced locomotor activity. In contrast, intra-NA injections of an inhibitor of the protein phosphatase, calcineurin, potentiate amphetamine-enhanced incentive learning. These findings, together with evidence that dopamine function and incentive learning are altered in schizophrenia, raise the possibility that agents that regulate signalling molecules may have potential as therapeutic drugs.

Imaging studies of the serotonergic system in affective disorders (Chair: Dr. Mirko Diksic)

The first talk in this session was given by Dr. Jeffrey Meyer (Center for Addiction and Mental Health, University of Toronto, Toronto), and was entitled "Brain serotonin 2 receptors and the serotonin transporter during depression in vivo: relationship to dysfunctional attitudes." As the speaker noted, identifying the optimal antidepressant dose for individual patients has proven difficult. A new strategy developed at the Centre for Addiction and Mental Health is to use recent developments in positron emission tomography (PET) to investigate the relation between clinical response and drug distribution in the human brain. Following extensive validation studies, the novel PET tracer, [^{11}C]DASB, appears to have excellent features for characterizing the serotonin transporter (SERT) in the brain and its level of blockade by selective serotonin reuptake inhibitors (SSRI). The subsequent studies suggest that a range of SSRI antidepressants, including citalopram, fluoxetine, sertraline and venlafaxine, exhibit increasing SERT blockade as plasma levels increase. All exhibit a maximum SERT blockade of 80%–85%. The reason for the upper limit remains unclear, but the studies also suggest that the probability of clinical improvement increases as

the 80% level of SERT blockade is approached. Whether greater clinical efficacy would be seen if antidepressants could be developed that blocked over 85% of the SERT remains a challenge for future research efforts.

The second presentation was by Dr. Hideo Tsukada (Central Research Laboratory, Hamamatsu Photonics K.K., Hamakita, Shizuoka, Japan). His talk was entitled "Animal PET research for functional imaging of the serotonergic neuronal system." As Dr. Tsukada noted, improvements in PET camera resolution have made it possible to conduct detailed functional neuroimaging studies in progressively smaller research animals. The studies described here were carried out in rhesus macaque monkeys (*Macaca mulatta*) using a small animal PET camera with spatial resolution of 2.6 mm. Novel tracers are being developed for various components of the serotonin system, including improved tracers for the SERT, serotonin receptors and post-receptor second messengers. Dr. Tsukada's studies suggest that, as primates age, there are decreases in the levels of SERT, as measured by [^{11}C]McN5652 binding, serotonin-2A activity, as measured by [^{11}C]MDL100,907 binding, and serotonin-1A cAMP activity, as measured by [^{11}C]rolipram binding. Serotonin-1A receptor binding, as measured by [^{11}C]WAY100635, does not change with age, but 8-OH-DPAT-induced changes in [^{11}C]WAY100635 binding do appear to diminish with age. Both [^{11}C]WAY100635 binding and [^{11}C]McN5652 binding correlate negatively with plasma cortisol levels. Together, these results suggest that aging-related changes in circulating levels of cortisol may be associated with alterations in serotonin transmission, changes that might account for altered vulnerability to mood disorders and efficacy of antidepressant medications.

The final talk of the session was given by Dr. Mirko Diksic (Montreal Neurological Institute, McGill University, Montréal) and was entitled "Serotonin synthesis and its modulation with drugs." As the speaker noted, a now quite large body of validation studies supports the use of the labelled tryptophan analogue, α-methyl-L-tryptophan (α[^{11}C]MTrp), as an index of brain serotonin synthesis. Like the endogenous serotonin precursor, α[^{11}C]MTrp crosses the blood–brain barrier, is taken up into serotonin neurons, and enters the metabolic pathway for synthesizing serotonin. Because the affinity of α[^{11}C]MTrp for the rate-limiting enzyme in serotonin synthesis, tryptophan hydroxylase (TPH), is 1000-fold less than that of the endogenous precursor, relatively little α[^{11}C]MTrp is converted into α[^{11}C]M-5HT during the time frame of most neuroimaging studies; however, autoradiography studies indicate that the rate at which α[^{14}C]MTrp is trapped in brain tissue during this time-frame correlates highly with the rate at which tryptophan is converted into serotonin. Moreover, αMTrp trapping is reduced by the TPH inhibitors, *p*-chlorophenylalanine (PCPA) and [3-(3-methoxyphenyl)-3-(3-dimethylaminopropyl)-4,4-dimethylpiperidine-2, 6-dione] (AGN-2979), and increased by the TPH co-factor, molecular oxygen. Serotonergic agents have also had expected effects. For example, the serotonin-1A agonist, buspirone, decreases αMTrp trapping, whereas the serotonin-1A antagonist, pindolol, increases αMTrp trapping. SSRIs, such as citalopram and paroxetine, have regionally specific effects that change following extended administration regimens. In rats with olfactory bulbectomy (OBX), an animal model of depression, αMTrp trapping is decreased in the cell-body region and increased in terminal regions. In patients with a current major depression, α[^{11}C]MTrp is decreased in the anterior cingulate, relative to healthy controls, and this effect may be greater in women and in those with more severe symptoms. Together, these findings add to the evidence that perturbations to serotonin transmission are related to symptoms of clinical depression.

The next generation (Chair: Drs. Patricia Boksa and Meir Steiner)

Sean Barrett (McGill University, Montréal) gave a talk entitled "The effects of dopamine depletion on alcohol self-administration in men." He described a study that examined the role of dopamine on alcohol self-administration in heavy social drinkers using the acute phenylalanine/tyrosine depletion (APTD) method and progressive ratio (PR) breakpoints, a behavioural measure of motivation to seek reward. In a first session, cardiac responses to the acute ingestion of alcohol were determined. In 3 other sessions, before alcohol self-administration, participants ingested a nutritionally balanced amino acid mixture, a mixture deficient in dopamine amino acid precursors (i.e., APTD) or APTD followed by the dopamine precursor L-DOPA. Relative to the control mixture, alcohol self-administration PR breakpoints were decreased in both the APTD and APTD + L-DOPA conditions. This effect of amino acid condition on alcohol self-administration was observed only in individuals who exhibited a high cardiac response to ethanol ingestion. Dopaminergic regulation of alcohol self-administration appears, therefore, to be predicted by the cardiac response to acute alcohol.

Changes in 5-HT$_{1A}$ receptor function are implicated in the origin and treatment of mood disorders. Freud-1 is a novel transcription factor that mediates repression of the 5-HT1A gene in neurons. In his presentation entitled "Freud-2: A novel repressor of 5-HT1A receptor gene," Mahmoud Hadjighassem (University of Ottawa, Ottawa) talked about Freud-2, a recently identified protein involved in the regulation of the expression of the 5-HT$_{1A}$ gene. Freud-2 RNA is detected in the brain, but also in the peripheral tissues of both mice and humans. Molecular studies showed that, like Freud-1, Freud-2 represses the 5-HT$_{1A}$ receptor gene by binding to the dual repressor element of the gene. Furthermore, he showed that the human Freud-2 homologue is located on chromosome 1p32. These findings suggest that genetic alterations in the expression and/or function of Freud-2 may lead to changes in 5-HT$_{1A}$ receptor function, rendering individuals more or less vulnerable to mood disorders.

Inflammatory cytokines (e.g., TNF-α, IL-1 and IL-6) appear to be involved in the origin and/or symptomatology of depression. Virginia Misener (University of Toronto, Toronto) gave a talk on "Cytokine network genes and childhood-onset mood disorders." She described an ongoing study aimed at addressing whether alterations in cytokine system genes are

implicated in the highly heritable childhood-onset mood disorders. Polymorphic markers in 6 genes, including IL-1α, IL-1β, IL-6 and TNF-α, IL-10 and IL-1Ra were investigated in a large sample of families that have a member with childhood-onset depression. However, no evidence for biased transmission of any of the studied genes was obtained. These findings are in contrast to previous results of studies conducted by other groups showing an association between alterations in IL-1β and TNF-α genes and depressive illness. Examination of additional polymorphisms and candidate genes are currently in progress.

Amanda Wintink (Dalhousie University, Halifax) talked about the effects of dopamine D_3 stimulation on adult neurogenesis, in a presentation entitled "Dopamine D_3 receptor stimulation selectively increases adult neurogenesis in dopamine-rich regions of the brain." Using bromodeoxyuridine (BrdU), a marker of cell proliferation, dopamine D_3 stimulation was found to significantly and specifically increase neurogenesis in dopamine-related regions. These results confirm that D_3 stimulation produces neurogenesis in the adult brain and provide further support for the idea that D_3 agonists may have therapeutic effects in Parkinson's disease.

Catherine Ogilvie (University of Alberta, Edmonton) presented her work on the "Reliability and validity of in vivo γ-aminobutyric acid (GABA) measurement in the prefrontal cortex using ^{1}H-MRS." A novel proton spectroscopy (^{1}H-MRS) double quantum filter technique was tested for reliability and validity of GABA activity in the prefrontal cortex. Eight young healthy male volunteers were scanned before and 24 hours after administration of a drug known to increase GABA neurotransmission. Baseline as well as drug-induced increases in GABA concentrations were measured before and after drug administration. For 14 of 16 sessions, a second GABA scan was obtained within the same test. For these repeated GABA measures, the within-subject coefficient of variation was 8.4% and the intraclass correlation was 0.89, demonstrating the validity and reliability of prefrontal GABA measurement using this novel technique.

Helen Ashdown (McGill University, Montréal) gave a talk entitled "Bacterial infection during pregnancy as a risk for schizophrenia — direct or indirect effects on the fetal brain?" Bacterial and viral infection during pregnancy have been associated with an increased incidence of schizophrenia in the offspring. Exposure of pregnant rats to the bacterial endotoxin lipopolysaccharide (LPS) results in behavioural deficits in the adult offspring that are similar to those observed in schizophrenia. These effects may be the result of the direct action of the endotoxin on the developing fetal brain or to activation of cytokines in maternal and/or fetal tissues. In the presented study, the distribution of labelled endotoxin and the induction of pro-inflammatory cytokines were assessed in maternal and fetal tissues following LPS injection to dams. Labelled LPS was detected in maternal tissues and placenta, but not in fetal tissue. Significant increases in the cytokines TNF-α and IL-1β were observed in maternal plasma and placenta, but not in fetal liver or brain. These results suggest that the effects of maternal LPS exposure on the offspring are mediated indirectly by cytokine induction at maternal and/or placental sites.

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