The 21st Annual Meeting of the Canadian College of Neuropsychopharmacology 
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The 21st annual meeting of the Canadian College of Neuropsychopharmacology (CCNP) was marked by participation of an unprecedented number of registrants > 200, comprising psychiatrists, pharmacologists, and neuroscientists from Canada and the U.S.A. The presentations consisted of four plenary lectures, three award lectures, eight symposia, and 97 posters. The major themes in the meeting included schizophrenia, Alzheimer’s, substance dependence, affective disorder, pain, personality disorder, neural growth and degeneration, and pharmacogenetics. A special symposium entitled “Molecular Approaches to Neural Dysfunction” organized with the Canadian Association for Neuroscience highlighted the recent advances in the molecular basis of neurodegenerative diseases and mechanisms of neural growth. The scientific sessions were preceded by a public lecture, organized by the CCNP and given by J. Rapoport (NIMH, Bethesda), on attention deficit hyperactivity disorder.

SCHIZOPHRENIA

Plenary Lecture

Rapoport presented a lively discussion on the incidence, biology and treatment of childhood-onset schizophrenia (COS). She described the results of a study of these cases (to date 42 children have participated) ongoing at the NIMH since 1990. She presented data on the contribution of genetic factors in the development of COS as demonstrated by concordance rates of 0.57 to 0.86 and 0.3 to 0.4 in monozygotic and dizygotic twins, respectively. There is no relationship between the age of onset and familiarity. It was
stressed that symptoms of COS share similarities with what she calls multidimensionally impaired syndrome (MDI), which is characterized by transient hallucinations, daily emotional liability, and impaired interpersonal skills. Magnetic resonance imaging (MRI) shows loss of gray matter and increased ventricular volumes in COS. A major point of difference between COS and adolescent-onset schizophrenia is the evidence of disease progression in the former as revealed by MRI. Individuals with COS are generally more resistant to typical neuroleptics such as haloperidol, but the effects of clozapine are dramatic. J. Rapoport summarized COS as a disorder of early brain lesion with continuous progression of abnormal brain development, and with a differential response to medication.

Symposium: Is Schizophrenia a Neurodevelopmental Disorder?

E. Walker (Emory Univ., Atlanta) discussed the role of the hypothalamic-pituitary-adrenal (HPA) axis as mediator and moderator of schizophrenia symptoms. Several lines of evidence implicate cortisol, the stress hormone, in the etiology of schizophrenia. Plasma cortisol release shows a rise during adolescence/early adulthood, a period when prodromal signs appear first. Baseline cortisol levels are high in schizophrenics and its levels correlate positively with symptom severity. Animal research has shown that glucocorticoids increase dopamine release and dopamine receptors as well as behavioral sensitivity to dopamine agonists. Walker presented a neurodevelopmental model for the etiology of schizophrenia incorporating the role of HPA axis as moderator.

S. Akbarian (Harvard Medical School, Boston) presented neuropathological/cytoarchitectural studies on post-mortem schizophrenic brains. The results suggest that although the overall development of cortex appears to be normal, a subset of schizophrenics show evidence for a defect of the embryonic subplate, which may result in altered thalamo-cortical connectivity. Akbarian examined the cerebral cortex of 20 schizophrenics and 20 controls in terms of cell counts, histochemistry for NADPH-diaphorase positive neurons, and in situ hybridization for glutamate decarboxylase (GAD), GABA_A, NMDA, and AMPA receptor subunits. Seven out of twenty schizophrenic brains showed altered distribution of interstitial white matter neurons that are thought to be remnants of the embryonic subplate. A significant reduction in the levels of GAD mRNA was noted, but GABA or NMDA receptor subunit mRNAs were only subtly altered in the cortical laminae.

P. Boksa (McGill Univ., Montreal) presented a rat model that addresses the influence of birth complications on dopaminergic neurotransmission in brain. Boksa subjected caesarian section (C-section)-born rat pups to acute global hypoxia and compared adult rat behavior and neurochemistry with normal vaginally or C-section-born animals. Animals born by C-section with or without hypoxia showed enhanced stress-induced dopamine release in the nucleus accumbens. Animals born by C-section also showed altered steady-state levels of dopamine in the nucleus accumbens and prefrontal cortex regions where dopamine modulates the stress response. Further, compared to vaginally born controls, C-section animals with or without hypoxia showed heightened behavioral responses to amphetamine. As developing dopaminergic systems are particularly vulnerable to adverse perinatal conditions, her results lend support to the epidemiological data suggesting obstetric complication as an important risk factor for schizophrenia.
L. DeLisi (State Univ., New York, Stony Brook) presented evidence that schizophrenia is a neurodevelopmental disorder with active changes occurring in the brain throughout life. She described a longitudinal 5-year follow-up study (Stony Brook first episode study) of 50 schizophrenic and 20 controls in terms of brain MRI scans and cognitive measurements. For the first 4 years, the rate of change for ventricular volume was larger for schizophrenics than controls, whereas the rate of change of temporal lobe or caudate volumes did not differ. Neuropsychological tests revealed worsening of verbal and spatial memory over time in the schizophrenic group. Changes in ventricular volume showed a variable course in a subgroup of patients with some showing early increases and then stabilization. She concluded that they are deteriorating, as opposed to stable, brain changes during the course of the illness.

ALZHEIMER’S DISEASE

Innovations in Neuropsychopharmacology Award Lecture

The Canadian College of Neuropsychopharmacology Innovations in Neuropsychopharmacology lecture this year went to a trio of researchers. S. Gauthier, J. Poirier, and R. Quirion (McGill Univ., Montreal) from the Douglas Hospital Research Centre, Montreal. The title of their lecture was “From gene to the clinics: Impact of genetics on the development of cholinergic drugs in Alzheimer’s disease.”

S. Gauthier started with an historical review of some of the attempts to develop therapies for Alzheimer’s disease. The first strategy, the use of acetylcholine precursors, choline and lecithin, was not successful. One of the next attempts was to infuse the choline ester bethanechol (which does not cross the blood-brain barrier) directly into the ventricles, but it also had limited clinical efficacy in Alzheimer’s disease. Tacrine, the first of the acetylcholinesterase inhibitors (which cross the blood-brain barrier) lacked specificity and produced autonomic side effects and toxic effects at clinically efficacious doses. However, a variety of acetylcholinesterase inhibitors with improved specificity are now available or in development. Attempts to target other neurotransmitter systems have not been successful. For example, low somatostatin levels in the CSF of patients led to preclinical studies in which a somatostatin agonist was infused into the ventricles of monkeys. However, this treatment produced severe Parkinsonian symptoms and was never tested in patients. In the near term the combination of an acetylcholinesterase inhibitor and vitamin E looks most promising. Other antioxidants and COX-2 inhibitors (to reduce inflammatory processes that may be important in Alzheimer’s disease) are currently the subject of investigation.

R. Quirion went into details about the cholinergic system in Alzheimer’s disease and possible targets for therapeutic agents. While Alzheimer’s disease is not a single neurotransmitter disease like Parkinson’s disease, the greatest therapeutic potential at the moment is through potentiation of acetylcholine function. Various strategies beyond acetylcholinesterase inhibitors are available. Postsynaptic receptors are muscarinic (M₁, M₄) as well as nicotinic. Agonists to any of them may be therapeutic. Another strategy is to use an antagonist of presynaptic receptors, which will activate the remaining acetyl-
choline neurons. In rats, antisense to oligonucleotides M₁ but not M₄ receptors increases extracellular acetylcholine, indicating that the presynaptic receptor is M₂. An M₂ blocker reverses age-induced impairment of memory in rats.

**J. Poirier** discussed the role of the apolipoprotein E4 allele (ApoE4) in Alzheimer’s disease. Animal work indicates that ApoE is produced by astrocytes in response to injury to neurons, as part of the regeneration process. In brain it is the main regulator of lipid transport. In humans, two copies of the ApoE4 allele increase the risk of Alzheimer’s disease, lower the age of onset, and increase the plaques and tangles, the brain markers of Alzheimer’s disease. ApoE4 alleles are also associated with greater acetylcholine cell loss, which is of interest because acetylcholine is the only neurotransmitter formed in part from a constituent of lipid. ApoE alleles predict, in part, response to therapeutic agents in Alzheimer’s disease. Thus, acetylcholinesterase inhibitors seem to work less well in patients with two copies of the ApoE4 allele.

### Young Investigator Award Lecture

This year’s Young Investigator Award was given to **J. Nalbantoglu** (McGill Univ., Montreal) for her innovative work on the metabolism and processing of amyloid precursor protein (APP) and its role in the pathology of Alzheimer’s disease (AD). She believes APP is central to the pathology of AD with other genes somehow interacting with the APP gene product. Nalbantoglu created transgenic mice overexpressing a C-terminal fragment of APP containing amyloid β peptide. Brain sections of 6 to 9 month old mice showed amyloid immunoreactive deposits extracellularly in the cortex and the hippocampus. The brains also showed increased immunoreactivity for glial fibrillar acidic protein and activated microglia, suggesting general injury/degeneration in the mice. Degeneration is more apparent in the hippocampus where a 15 to 20% loss of CA1 cells was observed. Behaviorally, the transgenic mice showed spatial learning defects in Morris water maze. Further evidence of memory impairment in these mice was shown by impaired long-term potentiation in hippocampal slices.

### Plenary Lecture

**R. Quirion** presented the state of the art of AD research especially as it pertains to interactions among putative markers of the disease. Although almost all neurotransmitters have been reported to be affected in AD, loss of forebrain cholinergic neurons is perhaps the most profound. He showed that choline acetyltransferase (ChAT) and muscarinic M₂ receptor levels were decreased by 40 to 60% in the cortical and hippocampal regions of AD brain. There was no change in postsynaptic muscarinic M₁ receptors. M₂ receptors are presynaptic receptors regulating acetylcholine release, as M₂ antagonist in rat hippocampal slices increase extracellular levels of acetylcholine. Five different muscarinic receptors, M₁, M₂, M₃, M₄, and M₅ have been cloned to date. Antisense oligonucleotide against M₂ but not M₄ receptor attenuate AF-DX-3384 (M₂/M₄ antagonist)-induced increase in acetylcholine release. A role of acetylcholine in spatial memory was further implicated by the observation of lower basal levels of acetylcholine in memory-impaired
aged Long–Evans rats. A new M₂ antagonist, BIBN-99 (Fig. 1), reversed Morris water maze deficits, possibly by facilitating acetylcholine release. Quirion further described results that demonstrate interactions between amyloid β protein and the cholinergic system in rats. Amyloid β peptides 1-28, 1-40, and 1-43 all inhibited acetylcholine release in hippocampal slices at a minimum effective dose of 10⁻¹² M. The same effects were obtained in frontal cortical but not striatal slices. He also described experiments that suggest a role of inflammatory cytokines such as IL-2 in the regulation of acetylcholine release. A role for growth factors, especially insulin-like growth factors (IGF) 1 and 2, in protecting neurones has been shown in Quirion’s laboratory. As IGF-1 can also induce some peripheral cancers; there is a need for IGF-mimetics that have selective central nervous system action.

Heinz Lehmann Award Lecture

B. Sherwin (McGill Univ., Montreal) addressed the role of estrogen in cognitive function in humans. She began work on the issue by examining changes in cognitive function across the estrous cycle in women. She found that there are no pronounced differences in young women across the cycle, likely because both estrogen and progesterone are produced in sufficient quantities across the cycle at this stage of life. She then turned her attention to more long-term deficiencies in estrogen function, including post-menopausal women, women having undergone ovariectomy, and infertile young women receiving pharmacological treatments that suppress ovarian function. In each case she reported significant memory deficits (primarily in tests assessing verbal memory), which were reversed by estrogen replacement. There are several compelling reasons to assume that estrogen might exert a beneficial effect in Alzheimer’s, including the facts that estrogen facilitates acetylcholine function, inhibits neuronal damage incurred by glucocorticoids, increases cerebral blood flow, and acts as an antioxidant (thereby reducing neuronal atrophy). She reported that women with Alzheimer’s disease treated with estrogen did better on a memory test assessing daily behavioral function.

PHARMACOGENETICS

Symposium:
Using Genetics to Target Pharmacotherapy for Mental Disorder

J. Poirier (McGill Univ., Montreal) reviewed the role of genes in AD. He discussed that ApoE4 allele copy number affects a number of AD features, such as age of onset, neuropathological lesions, cholinergic markers, and response to memory-enhancing drugs. He described a 30-week study of AD patients on various doses of tacrine (acetylcholinesterase inhibitor) or placebo carried out at 23 centers in the USA and Canada. In the placebo group, the disease progressed as a function of ApoE genotype, i.e., those with E4 alleles tended to progress slowly but had early-onset disease, whereas those with the E3 alleles had late-onset illness and tended to progress quickly. In terms of drug response,
non-E4 groups (i.e., E3 group) showed better improvement in global assessment. The results were similar with another AD drug metrifonate.

**M. Alda** (Univ. Ottawa, Ottawa) described his group’s efforts to map and identify genes causing bipolar disorder in individuals that respond to lithium therapy. Alda has confirmed that the mode of inheritance in lithium responders is compatible with a major gene model. He has initiated an international collaborative study to map the gene(s) predisposing to illness or response to treatment. Both candidate gene approach and full genome scans are being explored.

**R. Joober** (McGill Univ., Montreal) described an investigation into the genetic basis of neuroleptic-responsive (R) schizophrenic patients. Genes-containing CAG repeat were tested as candidate genes in R, non-responsive (NR), and normal controls by means of an antibody against polyglutamine proteins (encoded by CAG repeats). An abnormal protein was detected in two schizophrenic patients, but not in healthy volunteers. Further, CAG repeat allelic variants of the hGT1 gene were significantly shorter in R patients compared to other groups, suggesting its association with schizophrenia.

**P. Szatmari** (McMaster Univ., Hamilton) reviewed the evidence for the involvement of genetic factors in the etiology of autism and other pervasive developmental disorder. He cautioned that a number of issues in the genetic epidemiology of autism must be resolved before attempts to identify the gene will be successful.

### AFFECTIVE DISORDERS

**Symposium:**

**Neuropharmacology of Pain, Illness, and Depression**

**N. Breslau** (Henry Ford Health System, Detroit) reported the results of an epidemiological study demonstrating that the relative risk of developing depression in migraine sufferers was identical to the relative risk for developing migraines in depressed patients, suggesting no causal relationship between the two disorders, but rather a shared etiology. People suffering from severe headaches are more likely to become depressed in contrast to the likelihood that depressed patients will develop severe headaches.

**F. Abbott** (McGill Univ., Montreal) reported on the use of over-the-counter (OTC) analgesics in the Montreal area. Of interest, her survey suggested that OTC use is not restricted to pain relief (this variable explained a mere 3% of the variance in her sample), but rather may also be attributable to mood-altering effects of these agents. To demonstrate that these compounds do have psychotropic effects, she demonstrated that three of the most commonly used OTC analgesics are capable of inducing a conditioned place preference in animals, suggesting that they may have rewarding properties not directly related to their analgesic effects.

**P. Blier** (McGill Univ., Montreal) reported on the possible therapeutic mechanism of action of antidepressants for depression, obsessive-compulsive disorder (OCD) and pain. Blier noted that an effect common to most antidepressants is a down-regulation of somatodendritic (5-HT$_{1A}$) and terminal (5-HT$_{1B/1D}$) inhibitory autoreceptors on serotonergic neurons, and that the time course of these receptor regulations parallel the 3 to 6 week
time course necessary for a therapeutic response in the human. In contrast, only serotonin-specific reuptake inhibitors (SSRIs) appear to be effective in OCD, a greater dose is generally required, and a minimum of 8 weeks is needed to achieve therapeutic benefit. Finally, Blier reported that relatively low doses of antidepressants can be beneficial in the treatment of chronic pain, and that peripheral 5-HT$_{2A}$ receptors likely mediate the pain response.

K. Franklin (McGill Univ., Montreal) began his presentation by noting that most psychoactive drugs are not only rewarding, but also evoke antinociceptive (i.e., analgesic) effects. The prototypical illustration is morphine, however, Franklin summarized evidence that other psychoactive agents (e.g., amphetamine, nicotine) also share these properties. The analgesic effects of amphetamine and morphine appear to be mediated in part through striatal dopaminergic substrates. He concluded by arguing that, in general, the anatomical systems mediating reward and those mediating the perception of pain are inhibitory on each other, and addressed the behavioral significance of this inhibition.

### Plenary lecture

The theme of W. Potter’s (Lilly Research Laboratories, Indianapolis) lecture revolved around strategies that should be adopted in the development of novel antidepressants. He began the lecture with a general overview of the drug development process, highlighting the difficulties encountered and the low success rate in bringing a drug to market. Given the low success rate, alternative strategies are needed. Whereas it remains important to assess the effects of potential new antidepressant compounds on monoaminergic systems (in particular serotonin and norepinephrine), new biological endpoints need to be looked at in order to increase the success rate for drug marketing. He then noted that several groups are currently addressing potential new biological endpoints, including an examination of new drugs on post-signal transduction mechanisms (e.g., protein kinase C). Several groups are, in addition, assessing the efficacy of pharmacological agents with non-traditional mechanisms of action (drugs that do not inhibit monoamine oxidase or block monoaminergic reuptake) in the treatment of depression. Into this category fall drugs that act as corticotrophin releasing factor-receptor antagonists, estrogen receptor modulators, and drug that target excitatory amino acid receptors.

### SUBSTANCE DEPENDENCE

#### Symposium: Pharmacotherapy of Substance Dependence

The symposium opened with a presentation from G. Ko (New York Univ. and Schering Plough Research Institute, Kenilworth) who noted that there has been a recent shift in the criteria for selecting appropriate dependent outcome measures. In particular, on the basis of a recommendation made by the US Food and Drug Administration, more clinical trials are being evaluated against a criterion of reduced usage, rather than complete abstinence.
Whereas this has permitted a more liberal estimate of treatment efficacy, it is not free of interpretive problems.

The next three speakers addressed the efficacy of the three pharmacotherapies currently used most frequently in the treatment of alcohol abuse.

**C. Naranjo** (Univ. Toronto, Toronto) reported that SSRIs are effective in reducing alcohol consumption in approximately 16 to 18% of patients, and that this effect occurs, in part, due to a decrease in alcohol craving and liking. Naranjo reported on the use of fuzzy logic to build nonlinear regression models to predict response outcome. He ended his presentation by reporting a series of impressive nonlinear regression models derived from fuzzy logic, which predict outcome in > 95% of the patients tested to date.

**R. Swift** (Brown Univ., Providence) reported on the use of the opiate receptor-antagonist naltrexone in the treatment of alcoholism. Again, given the variability in response, the problem is one of predicting which patients will respond. He reported that outcome is best in patients with a high degree of alcohol craving. Among these patients, naltrexone appears to significantly reduce the desire to drink alcohol.

**R. Anton** (Medical Univ. South Carolina, Charleston) reported on the recent introduction of acamprosate in the treatment of alcoholism. Although its neuropharmacological effects are yet to be characterized. Anton speculated that acamprosate may influence Ca\(^{2+}\) inflow, which is mediated by the NMDA receptor. Anton summarized a series of studies showing that acamprosate significantly inhibits craving for alcohol, suppresses withdrawal symptoms, and prolongs the duration of abstinence up to one year after treatment in a subset of alcoholics. Principle side effects include gastrointestinal discomfort and changes in libido.

**PERSONALITY DISORDERS**

**Symposium: Genetics of Personality Traits and Disorders**

**J. Livesley** (Univ. British Columbia, Vancouver) described how family is important in personality disorders, particularly those from cluster A. There are problems in studying this area, however, because the concept of family does not separate contribution of the genes from that of environment, and the phenotypes are poorly defined. A twin study was used to assess the genetic factors, the common environmental factors, and the non-shared environmental factors in these traits and dimensions. Among the 18 main traits, common environmental factors were not significantly different from zero. For the 18 traits, the heritability and the non-shared environmental effects each ranged from ~40 to 60%. Further analysis revealed great complexity in the hierarchical organization of personality, with the genetic contributions to some traits being related to others, while some exhibited independent genetic control.

The second talk was by **V. Bolivar** (State Univ. New York, Albany), who has undertaken a quantitative trait loci (QTL) analysis of complex behavior in the mouse. The methodology involves intercrossing two strains of mice, and then doing a backcross. The behavioral measures were contextual conditioning, which gives a measure of learning and memory, and fear and cued conditioning, which give information on emotionality (e.g.,
freezing). The genetic analysis revealed important associations on chromosome 1. For contextual conditioning much of chromosome 1 gave a significant LOD score, with two regions towards either end of the chromosome showing especially high values.

The next talk was by R. Palmour (McGill Univ., Montreal), who described some of the complexities in relating gene polymorphisms to aspects of temperament in humans and monkeys. The focus was on a genetic polymorphism of the dopamine D4 receptor, in humans the 7 repeat of the DRD4-VNTR. DRD4-7 has been reported to be related to novelty-seeking behavior. In a group of adolescents who have been studied longitudinally, however, DRD4-7 was associated with extraversion and strongly with IQ, but not with novelty seeking or aggression. In monkeys DRD4-5 was found to be related to the degree to which the juveniles oriented out of the cage and to motility.

The fourth talk was by D. Goldman (NIAAA, Rockville), who described genetic studies on alcoholics from two groups, Finns and Southwestern American Indians. There were significant associations on chromosome 4 near the GABA_A receptor gene cluster (also seen in mouse QTL studies), and near the alcohol dehydrogenase gene cluster. On chromosome 11 there was a significant association near the DRD4 gene, but this is also close to the tyrosine hydroxylase gene. An association with the dopamine D2 receptor was not seen in the Southwestern American Indians. A marker in the 5-HT_{1B} receptor gene showed a modest but significant association with antisocial alcoholism.

**NEUROIMAGING**

**Symposium: Imaging the Serotonin System in Human Brain**

H. Koenigsberg (Mount Sinai School of Medicine, New York) described the use of fenfluramine in PET studies employing fluoro-deoxyglucose (FDG). Fenfluramine releases serotonin, and a variety of studies have shown a decline in the prolactin response to fenfluramine in aggressive or suicidal patients, suggesting decreased serotonergic function in these studies. Koenigsberg described a preliminary study on patients with impulsive aggressive personality disorders. After receiving fenfluramine, normal controls demonstrated increases in glucose consumption in various cortical regions, while the patients did not. Orbital and cingulate cortex may be underactivated by the serotonin system in impulsive aggression.

The second speaker was M. Leyton (McGill Univ., Montreal), who reviewed techniques to study serotonin synthesis using PET. Tryptophan is not a suitable tracer, because it is incorporated into protein, while 5-hydroxytryptophan bypasses the rate-limiting step in serotonin synthesis, tryptophan hydroxylase. \(\alpha\)-Methyl-L-tryptophan (AMT) is not incorporated into protein and is converted to \(\alpha\)-methylserotonin, which is not metabolized further. Studies on experimental animals support the idea that using labeled AMT as a tracer gives a valid index of the rate of serotonin synthesis. Preliminary studies on humans indicate that serotonin synthesis is low in the brains of impulsive patients with borderline personality disorder.

Z. Szabo (Johns Hopkins Medical Institutions, Baltimore) summarized the current state-of-the-art in studying the serotonin transporter. Of the various ligands that
have been tried, specificity for the transporter was seen with the + isoform of McN5652 (trans-1,2,3,5,6,10 β-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]-isoquinolone), which has now been synthesized with a 11C label, to make it suitable for PET studies. McN5652 binding to mouse brain is decreased by the serotonin neurotoxin, 5,7-dihydroxytryptamine, and acutely by the serotonin reuptake inhibitor, paroxetine. Its brain distribution in monkeys and humans is similar to that of serotonin. Thus, it behaves in the manner that would be expected for a compound that labels the serotonin transporter.

S. Kapur (Clarke Institute of Psychiatry, Toronto) dealt with 5-HT2 receptors. 5-HT2 receptors can be labeled with [18F]setoperone, which labels the 5-HT2A receptor more than the 5-HT2C. Studies in neuroleptic-naive schizophrenic patients and controls indicate a significant decrease in 5-HT2 receptors with age, but no alteration in schizophrenia. While haloperidol has little effect on 5-HT2 receptors, the atypical neuroleptics: risperidone, olanzapine, and clozapine all blocked setoperone binding at low doses. While blockade of serotonin receptors is probably not related to the antipsychotic action of atypical neuroleptics, it may be responsible for the low incidence of extrapyramidal side effects.

**NEURONAL GROWTH AND REGENERATION**

*Joint Symposium with Canadian Association of Neuroscience: Molecular Approaches to Neural Dysfunction*

M. Hayden (Univ. British Columbia, Vancouver) described that the molecular nature of Huntington’s disease (HD) was revealed in 1993 with the identification of CAG triplet repeat expansion in the huntingtin gene. The CAG repeats add a polyglutamine tract in the huntingtin protein, a 40-kDa intracellular protein. The toxicity of polyglutamines is due to the formation of intracellular aggregates of the huntingtin protein, which results in apoptotic cell death. He showed that huntingtin protein is cleaved by caspases, which result in shorter Huntingtin fragments, these truncated fragments form aggregates more readily. These fragments of huntingtin form aggregates when polyglutamine expansion is beyond a threshold. He mentioned that a new therapeutic strategy for HD may be the prevention of huntingtin cleavage by intracellular caspases.

T. Kennedy (McGill Univ., Montreal) gave an overview of the discovery and roles of netrins, the axon guidance molecule initially identified in the embryonic spinal cord as chemoattractants for commisural axons. Netrins — of which two, netrin1 and netrin2, are currently known — are laminin-related molecules with homology to *C. elegans* UNC6, serving a chemoattractant or chemorepellant function for the growing axon. Kennedy showed data that netrins continue to be expressed in the adult mammalian brain and may play a role in maintaining and modifying synaptic connections. He presented evidence that netrin expression in adult brain changes in response to injury such as chemically induced seizures.

R. Slack (Univ. Ottawa, Ottawa) described the role of the retinoblastoma (Rb) gene in neurogenesis and differentiation. While developing neurons undergo apoptosis *in vivo*, neural precursor cells cultured from Rb-deficient embryos appear to differentiate and survive; however, these neurons exhibit a delay in terminal mitosis relative to wild type
progenitor cells. Her results show that Rb is involved in E2F 1 and 3 regulation, but is not required for cell survival.

**P. H. St. George-Hyslop** (Univ. Toronto, Toronto) presented a lucid overview of the molecular genetics of AD and the role of presenilins in the pathology of AD. As a large number of familial AD cases do not arise from mutations in the PS, β amyloid or ApoE genes, St. George-Hyslop believes other as-yet unidentified genes may be involved. Through genetic linkage studies, he has identified a susceptibility gene on chromosome 12 near marker D12S378-D12S96. There is a possibility that this gene could code for an ApoE receptor or an amyloid protein receptor.

**Plenary Lecture**

**P. Aguayo** (McGill Univ., Montreal) has shown that severed CNS neurons have the ability to regrow if an appropriate milieu in the form a PNS graft is provided. He showed that severed optic nerves, when grafted with a piece of sciatic nerve, regrow and eventually make appropriate synaptic connection with the tectum restoring the physiology of functional response of the eye. Since growth factor receptors TrkB and TrkC are expressed on retinal ganglion cells (RGC), administration of neurotrophin-4 (NT-4) to the injured site causes most RGC cells to survive. However, chronic administration of NT-4 does not prevent eventual cell loss. Even chronic injection of viral vectors expressing brain-derived growth factor (BDNF) cannot prevent RGC loss. Thus, growth factors are good for short-term but not long-term survival of neurons. Aguayo hypothesized that following injury or experimental axotomy, there are changes in the receptors (TrkA, TrkB) in RGC. Maybe they are reduced, thus making the cells resilient to available neurotrophins. He concluded that gene targeting of glial cells is a viable option for regeneration of CNS cells, but a lot remains to be understood.

**SPECIAL SYMPOSIUM**

**CCNP: The Next Generation**

This symposium consisted of six short presentations by research trainees who had submitted the best abstracts. The first speaker was **S. Boye** (McGill Univ., Montreal), whose talk centered on a current controversy concerning the role of dopamine in the locomotor-stimulating effects of nicotine in the rat. Using intracerebral injections of the dopamine neurotoxin, 6-hydroxydopamine, and the dopamine antagonist, eticlopride, she demonstrated that dopamine is involved in the stimulation of locomotor activity, and that the core of the nucleus accumbens has an important role in this effect.

The second speaker was **L. Du** (Univ. Ottawa, Ottawa), who studied various gene polymorphisms related to the serotonergic system in the brains of depressed suicides and controls. While there was no difference in the frequency of two polymorphisms of the 5-HT_2A_ receptor, or in a polymorphism of the tryptophan hydroxylase gene, the depressed suicides had a significantly higher frequency of the serotonin transporter gene long allele, which is present in the promoter region.

**N. DeSousa** (Univ. Toronto, Toronto) described the role of cholecystokinin (CCK) in cocaine addiction in the rat. The CCKA receptor antagonist PD-140158 (Fig. 1) had no
effect on cocaine self-administration during intravenous cocaine self-administration conditioning. During a relapse phase, exposure to cocaine-paired stimuli elicited increase responding relative to control stimuli. This effect was blocked in animals previously treated with PD-140158. Thus, CCKA receptors may be involved in relapse, although not in the initiation of cocaine self-administration.

**S. Kumra** (NIMH, Bethesda) looked at smooth-pursuit eye tracking impairment in pediatric patients with multidimensionally impaired (MDI) syndrome. Children with MDI have severe and persistent deficits in affective regulation, social functioning, and cognitive processing, and exhibit psychosis under stress. They are often co-morbid for ADHD. The pattern of smooth pursuit eye tracking was compared in MDI children, in children with COS, in patients with ADHD, and in normal controls. Both MDI and COS children showed similar deficits in eye tracking. These data support other findings that MDI children resemble those with COS rather than ADHD.

**G. Wood** (McGill Univ., Montreal) studied the effect of environment on the outcome of neonatal ventral hippocampal lesions in rats. Rats neonatally lesioned in the ventral hippocampus become sensitized to amphetamine in adulthood. This effect is seen in Fisher rats but not in Lewis rats. In a cross-fostering study it was shown that when neonatal Fisher rats are lesioned neonatally and cross-fostered by Lewis dams, they do not demonstrate sensitization to amphetamine in adulthood, while cross-fostering the other way round causes sensitization to amphetamine in adult Lewis rats. Thus, environmental factors play a role in mediating the effects of the lesions, which are considered an animal model of some aspects of schizophrenia.

**H. Robertson** (Dalhousie Univ., Halifax) described the results of a consumer evaluation of pharmacological and non-pharmacological treatments of adolescents with mood disorders. Although both unipolar and bipolar youths demonstrated subclinical mood and interpersonal symptomatology, their quality-of-life index was in the low normal range. Medication was described as helpful by 88%, and medication psychoeducation by 90%. While the nuclear family, friends, teachers, illness education, hospitals, psychiatrists, clinic nurses, and psychotherapy were all rated highly in dealing with the illness, self-help groups were not rated highly and family physicians were not found helpful by one-third of the respondents.

![Fig. 1. Chemical structures of BIBN 99 and PD 140548.](image-url)