CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1
January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

Founding Members of CIMR:
Dr. Sophie Grigoriadis
Dr. Sidney Kennedy
Dr. Roger McIntyre
Dr. Sagar Parikh
Dr. Franco Vaccarino

University Health Network

Welcome to the Centre for Integrative Mood Research

The Centre for Integrative Mood Research (CIMR) has been established at the University Health Network to promote understanding of depression and mood disorders; to develop innovative evidence-based therapeutic interventions, and to disseminate and apply this knowledge to the general public, the health care community, and policy makers. CIMR is integrative in that we will integrate research and knowledge at many levels of analysis, both biological and psychosocial, and we will integrate with other medical fields at UHN and around the world to provide the best possible treatments and outcomes for patients with mood disorders.

Our location in Canada's largest academic health sciences centre with the greatest concentration of neurosciences, and a strong commitment to research and patient care, means that we can see patients from diverse medical populations, and establish integrated research teams. We have the resources and the people to become a world-leader in research into the causes and treatments of mood disorders, to put our discoveries into practice with our patients, and to share our knowledge with the medical community and with society as a whole.

We conduct collaborative research and education opportunities from all areas of UHN. Ongoing research projects in the CIMR focus on:

1. Neurostimulation: Non-pharmacological, brain-based interventions for treatment resistant depression
2. Psychopharmacology: Developing novel disease-modifying therapies for mood disorders
3. Mood and Metabolic Factors: Exploring depression and bipolar disorder in patients with diabetes and metabolic syndrome
4. Mood and Inflammation: Depression in medical populations with inflammatory disease
5. Depression in the Workforce: Examining new treatments and interventions
6. Women's Mental Health: Discovering the links between hormones and mood
7. Geriatric Depression: Understanding mood disorders in the elderly.
8. Psychosocial interventions
9. Systems research on best practices in health care delivery

CIMR
Centre for Integrative Mood Research

Quarterly Newsletter

Volume 1, Issue 1

January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

Emerging Interventions in the Treatment of Depression

NK-1 antagonists: General Information

Currently available antidepressant drugs work very well for about 60% of patients. However, they do not work for everyone, and some people experience side effects that make the use of antidepressants unpleasant or even intolerable.

Although scientists understand how the drugs work in the laboratory, what is not understood is the underlying disease mechanism and the way drugs modulate symptoms. This makes it very challenging to design new and better drugs. There are many new antidepressant drugs being developed.

Most existing medications work on the neurotransmitters serotonin, norepinephrine or dopamine. These chemicals are very important in regulating mood and other symptoms of depression. There are many other types of chemical messengers in the brain, however, and many of these show promise as regulators of mood. Peptides are short proteins that are abundant in the brain, and are located in regions that are known to be important for the regulation of mood, emotion, and response to stress.

Substance P is a peptide that is found in key emotion and stress-regulating areas of the brain. It acts on a receptor known as NK-1 (for neurokinin-1). Blockers, or antagonists, of NK-1 receptors have been developed for the treatment of depression. These potential antidepressants have been studied over the past decade and renewed efforts to find a well tolerated and effective NK1 antagonist are underway.

University Health Network

Continued on next page

CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1
January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

NK-1 Antagonists: Information for the Clinician

What is Substance P?

Substance P is a neuropeptide (a small protein found in the brain) that was originally discovered to play a role in pain perception, although it has since been implicated in a wide range of physiological and behavioural functions, including stress responses and emotional regulation. As such, it is being studied as a potential antidepressant target .

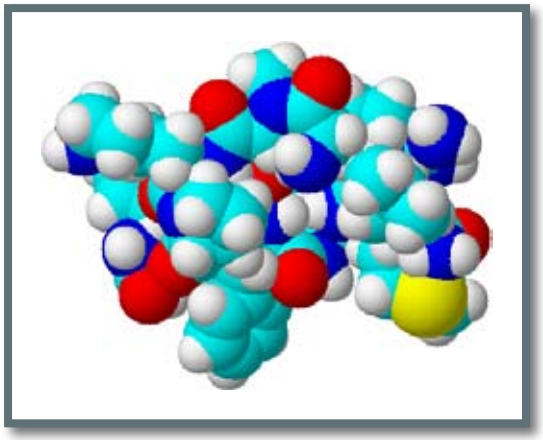
Substance P binds to neurokinin (NK) receptors. In humans, the NK-1 receptor subtype is the most abundant subtype, and are highly expressed in areas of the brain involved in emotional regulation, such as the limbic regions.

Substance P is found in neurons that also contain the neurotransmitter serotonin, suggesting that substance P can influence the function of serotonin. Serotonin is a well known target of antidepressant drugs, and thus a compound which can influence serotonergic function would be a good candidate for novel antidepressant drug development.

Preclinical Evidence for the Role of Substance P in Depression

There is an abundance of preclinical evidence suggesting that increases in substance P neurotransmission increases depression-like behaviour. Therefore, drugs that block the NK-1 receptor, known as NK-1 antagonists, have been tested for their potential antidepressant effects.

On their own, NK-1 antagonists have antidepressant properties in preclinical models, and also enhance the effects of other antidepressants, such as the selective serotonin reuptake inhibitors citalopram and paroxetine (Chenu et al., 2006). However, not all NK-1 antagonists have shown an antidepressant effect. Differences between laboratories in how the tests are carried out likely contributed to these inconsistencies. As well, preclinical studies do not always translate directly into clinical findings. This is particularly true with substance P, as the neurokinin receptor system differs substantially between animals and humans.



Continued on next page

University Health Network

CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1
January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

University Health Network

Substance P levels in Depressed Patients

The levels of substance P in cerebrospinal fluid (CSF) have been measured in an attempt to index the importance of Substance P in the brain in mood disorders. Rimon and colleagues (1984) were the first to report increased substance P-like immunoreactivity in depressed patients, as compared with patients with schizophrenia and controls. Similar studies have been conducted using various methodologies, with both positive (Bondy et al., 2003) and negative (Berrettini et al., 1985) results. Methodological issues such as the way in which the samples are handled after collection can also greatly influence substance P levels (Berrettini et al., 1985), and therefore such studies must be carefully controlled.

Although others did not find a relationship between depression severity and CSF levels of substance P (Deuschle et al., 2005), a more recent study found that patients with treatment resistant depression (TRD), had lower mean cerebrospinal fluid (CSF) substance P levels than a group of healthy subjects (Carpenter et al., 2008).

Clinical Trials with NK-1 Antagonists

If elevated levels of substance P do contribute to Major Depressive Disorder (MDD), then it would follow that compounds that block the receptors upon which substance P acts (NK-1 receptors) should help alleviate symptoms of depression. Several different NK-1 antagonists have been developed and are in various stages of clinical testing.

The first compound to be tested clinically was aprepitant, which showed clinical efficacy for treating major depressive disorder (Kramer et al., 1998). A second compound was developed, L-759274, which showed antidepressant efficacy superior to placebo in a randomized, double-blind placebo controlled study (Kramer et al., 2004). Both were shown to be safe and generally well tolerated with low incidence of side effects. However, a subsequent report on aprepitant found no statistically significant differences from placebo in five, randomized, double-blind, parallel-groups, placebo-controlled, multicenter trials in outpatients with MDD (Keller et al., 2006). Three of the trials used the active comparator paroxetine, which did show antidepressant efficacy.

An interesting study that examined neural responses to facial expressions of emotion found that, in healthy volunteers, a single dose of aprepitant increased the neural response to happy facial expressions in the rostral anterior cingulate and the right amygdala as measured by functional magnetic resonance imaging

Continued on next page

CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1

January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

(fMRI) (McCabe et al., 2009). There were also increased responses to the presentation of positive words. This occurred without any effect on mood or subjective state. Thus, aprepitant did have immediate effects on neural function in emotion-related areas of the brain. The same group has demonstrated similar responses to standard antidepressants.

Other NK-1 antagonists are being evaluated for the treatment of chemotherapy-induced nausea and vomiting, post-operative nausea and vomiting, as well as major depressive disorder (casopitant), post traumatic stress disorder (PTSD) (vofopitant), and for MDD and PTSD (orvepitant). A clinical study involving orvepitant in the treatment of MDD is currently underway at several Canadian sites including the University Health Network.

Future Directions

For many years, antidepressant treatments have relied on the direct modulation of monoaminergic (serotonin, norepinephrine, dopamine) function. Newer drugs are being developed that act upon modulators of the monoamine systems, and neuropeptides as a group are being targeted. The neuropeptide substance P shows promise for the development of a novel class of antidepressant medications.

References

Berrettini WH, et al.. Biol Psychiatry. 1985;20(9):965-70.
Bondy B, , et al. Biol Psychiatry. 2003;53(6):538-42.
Carpenter LL, et al. Psychiatry Res. 2008; 157(1-3):123-9.
Chenu F, et al.. Behav Brain Res. 2006;172(2):256-63.
Deuschle M, et al. Psychiatry Res. 2005; 136(1):1-6.
Keller M, et al. Biol Psychiatry. 2006; 59(3):216-23.
Kramer MS, et al.. Science. 1998; 281(5383):1640-5.
Kramer MS, et al. Neuropsychopharmacology. 2004; 29(2):385-92.
McCabe C, et al. Int J Neuropsychopharmacol. 2009; 12(9):1261-74.
Rimón R, et al. Biol Psychiatry. 1984; 19(4):509-16.

University Health Network

CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1
January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

University Health Network

Mood Disorders and Metabolic Syndrome

It has been known for some time that individuals with mood disorders are also at increased risk for obesity, hypertension and diabetes mellitus. It is now thought that there may be common underlying biological factors which predispose to these illnesses. The Metabolic syndrome positions insulin resistance as a central and defining feature. A cross-sectional as well as a longitudinal association exists between mood disorders and metabolic syndrome.

Interview with Dr. Roger McIntyre, MD, FRCPD
Associate Professor of Psychiatry and Pharmacology, University of Toronto
Head, Mood Disorders Psychopharmacology Research Unit
www.mdpu.ca
University Health Network, Toronto, Canada

Q: Dr. McIntyre, you have proposed that major depressive disorder and bipolar disorder may be types of "metabolic disorders" in that there is a great deal of evidence for abnormal glucose tolerance, insulin resistance, and diabetes mellitus in mood disorder patients. Can you please explain the relationship between these disorders?

A: Mood disorders and diabetes mellitus share many features in common; they are both highly prevalent and chronic conditions associated with substantial illness burden. Moreover both conditions are associated with significant morbidity and premature mortality. Results from studies conducted in the general population as well as in clinical samples indicate that individuals with mood disorders have an approximate twofold increased risk of type II diabetes mellitus and metabolic syndrome when compared to the general population. The increased hazard for metabolic disruption in the mood disorder population parallels a separate body of literature that has documented a higher rate of mood disorders in individuals with diabetes mellitus (types 1&2) as well as metabolic syndrome. What we are particularly interested in is the consequences of mood and metabolic disorders on somatic health. For example, we now know that individuals with mood disorders (and diabetes mellitus) have much higher rates of overweight/obesity/abdominal obesity, cardiovascular disease as well as neurodegenerative disorders (e.g. Alzheimer's disease) when compared to the general population.

Continued on next page

CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1

January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

Q: Do we know if mood disorders precede the metabolic abnormalities, or vice versa, or if they emerge in parallel from some other underlying factors?

A: Longitudinal studies indicate that abnormalities in metabolics (e.g. overweight obesity; diabetes) are risk factors for incident mood disorders. Moreover mood disorders are a risk factor for incident metabolic disruption. Historically it has been simplistically presented that individuals with metabolic difficulties were at greater risk for mood disorders as a "reaction" to living with a chronic medical disorder. Available evidence indicates that this is an insufficient explanation as many individuals with undiagnosed abnormal insulin sensitivity are also at increased risk for a mood disorder.

Q: What percentage of mood disorder patients would you estimate also have metabolic disorders?

A: It is currently estimated that over half of individuals with a mood disorder are overweight with approximately 30-40% exhibiting increased rates of obesity/abdominal obesity. The rates of diabetes mellitus type 2 as well as the metabolic syndrome in the mood disorder population is estimated at approximately 1.5-3 times the rate of the general population after adjusting for sex, socioeconomics, and educational attainment.

Q: Do treatments that help control diabetes have any effect on concomitant depressive symptoms? Similarly, do antidepressant drugs have any effect on metabolic factors?

A: Indeed, antidiabetic medications may possess antidepressant and cognition enhancing properties. For example, the class of agents referred to as "thiazolidinedione" have been documented to reduce cognitive deterioration in individuals with Mild Cognitive Impairment (MCI) and Alzheimer's disease. Conventional antidepressants exert complex and variable effects on insulin glucose homeostasis. Antidepressants that are weight gain promoting (e.g. paroxetine, mirtazepine, TCAs); disrupt insulin glucose homeostasis and have an adverse effect on lipid parameters. Generally speaking, contemporary antidepressants that primarily engage serotonin (e.g. non-weight gain promoting SSRIs – fluoxetine), favorably influence insulin sensitivity independent of their effect on body weight, composition and consummatory behavior. Agents that engage norephinepherine (e.g. venlafaxine, desvelnafaxine, duoloxetine), decrease insulin sensitivity and increase insulin glucose levels. It must be emphasized however that this is an oversimplification with several exceptions.

University Health Network

Continued on next page

CIMR
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 1

January 2010

In this issue

Contact: For more information on the CIMR, or for comments and suggestions, please contact: Susan.rotzinger@uhn.on.ca

Q: Are there special treatment considerations for individuals with symptoms of both metabolic syndrome and depressive disorders?

A: Individuals with metabolic disorders should be routinely screened and carefully monitored for clinical presentations suggestive of major depressive disorder or bipolar disorder. It seems very reasonable to include a clinical rating tool such as the PHQ9 or the HAMD7 as a mechanism to evaluate the severity of depressive symptoms in the diabetic population. For individuals presenting with mood disorders, they should be screened for bipolar disorder with the Mood Disorder Questionnaire (MDQ). Extant evidence indicates that effectively treating a mood disorder in a diabetic individual improves diabetic outcomes (e.g. HbA1C). For individuals with mood disorders they should be screened on a regular basis for risk factors for metabolic disorders (e.g. family history). All patients should have their weight, body mass index (BMI) and preferably waist circumference evaluated as well as routine surveillance of glucose and lipid parameters. The selection and sequencing of guideline-concordant pharmacotherapy should take into consideration metabolic profiles as part of personalized approaches to the patient.

Q: Who can people contact for further information?

A: For further information, people can go to www.mdpu.ca

References:

McIntyre RS, et al. Annals Clin Psychiatry, 2007; 19(4):257-264.
McIntyre RS, et al. Current Diabetes Reports, 2009, 9:51-59.

University Health Network