



Vivian M. Rakoff Positron Emission Tomography Centre

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Research at the Vivian M. Rakoff Positron Emission Tomography (PET) Centre continues to concentrate on PET methodology (radiochemistry and PET instrumentation), schizophrenia, mood neurochemistry, basic neurosciences and addiction. In addition to our own research, we maintain active collaboration with other scientists within CAMH and with researchers at the University of Toronto and its teaching hospitals.



PET Radioligands Development

The radiochemistry group, led by Dr. Alan Wilson, continues its innovative work in radioligand development. In collaboration with Dr. Paul Verhoeff, from the Clinical Research Unit at Baycrest Centre for Geriatric Care, we have initiated human studies of potential PET imaging agents for amyloid plaques. Amyloid plaques are a characteristic feature of Alzheimer's disease. This work may lead to an objective way to assess potential therapies for Alzheimer's disease.

Our new radioligand for the serotonin transporter, [C-11]-DASB, continues to generate great interest. The serotonin transporter is the target of the selective serotonin reuptake inhibitors, medication widely used to treat depression. We can now measure accurately the effects of these antidepressants on the serotonin transporters. Several leading PET research groups around the world are now using [C-11]-DASB for their own research.

PET Instrumentation

Our new high-resolution, high-sensitivity 3D research brain PET tomograph is now installed. This scanner is currently the most sophisticated in existence for brain research and will strengthen our international leadership in psychiatric PET research. Funding for the new scanner was secured by a grant from the Canada Foundation for Innovation and the Ontario Innovation Trust fund. Peter Bloomfield, an internationally renowned PET physicist, continues to work on maximizing the potential of the new scanner.

Investigation of the Mechanism of Action of Antipsychotics

The PET Schizophrenia research program, under the leadership of Dr. Shitij Kapur, continues to explore how medications work. This work proceeds from the bench-to-bedside with studies in animal models and patients.

Using PET-like techniques in animal models, we have

found that the doses of antipsychotics used in animal models do not represent usual clinical conditions. Some doses used are much higher than necessary. Using PET, Dr. Kapur and our team have proposed new clinically relevant doses, thereby providing a new standard for the field.

At a clinical level, the unique effects of clozapine remain a mystery. Dr. Johannes Tauscher and colleagues have shown that clozapine binds not only to dopamine D2 receptors, but also to dopamine D1 receptors. This opens up a new line of research examining the role of dopamine D1 receptors in helping patients with refractory schizophrenia.

Dr. David Mamo is examining the effects of different forms of administration of already available drugs. He is studying depot forms of olanzapine and risperidone and a long-acting form of seroquel. Dr. Mamo and colleagues have helped identify the "optimal" clinical doses of seroquel. These data are now being used to design clinical trials.

Finally, in related work, Dr. Jimmy Jensen is trying to combine fMRI, a brain imaging technique, with PET. While PET provides neurochemical sensitivity, fMRI has exceptional temporal resolution. Dr. Jensen and colleagues are developing conditioning paradigms that can be simultaneously used in PET and fMRI.

The Neurochemistry of Depression

Headed by Dr. Jeffrey Meyer, this program aims to investigate the neurochemical basis of symptoms for mood disorders and the neurochemical effects of antidepressant medications.

We continue to focus on the relationship between changes in serotonin and dopamine receptors and the specific cognitive and neuropsychological abnormalities that are observed during depressive episodes.

We continue to investigate serotonin and dopamine transporter regulation. We find that the regulation of these transporters has an important role as a vulnerability factor



for low monoamines and accompanying symptoms. Our treatment studies focus on the mechanism of selective serotonin reuptake inhibitors (SSRIs).

Using [C-11]-DASB, we measured the percentage of serotonin reuptake sites occupied during treatment with five different SSRIs at different doses. The results of our work will improve SSRI dosing and future antidepressant development.

Basic Neurosciences

Dr. Nathalie Ginovart has developed an extensive animal PET program aimed at complementing human PET studies. This program is based on multidisciplinary research using a variety of approaches. The central theme of this work is to use PET in research to investigate the serotonin and dopamine neurochemical systems that are of utmost importance for mental illnesses and addiction. For example, one of our projects explores the effect on the brain of different dosing regimens of an antipsychotic medication used to treat schizophrenia.

Another aspect of this work will characterize new PET imaging agents before they are used in humans. One of the latest developments in our PET neuroscience program is a new method that uses positron sensitive microprobes, surgically implanted in the brain of rodents, to measure drug-induced occupancy of neuroreceptors in vivo. This technique is of great interest, as the brain of rodents is too small for accurate imaging with human PET scanners. Dedicated small-animal scanners are available, but they are expensive, and their use is still being validated. Our new method has already delivered exciting results that will benefit our human research.

Investigation of the Neurochemical Sequelae of Ecstasy Use

The effects on the brain of MDMA, better known as ecstasy and widely used by young adults in Canada, remain contro-

versial. Dr. Stephen Kish is using [C-11]-DASB to find definite evidence about the presence or absence of ecstasy's effects on the serotonin transporter.

This work also illustrates the translation of PET research into public policies, as it will establish the extent to which ecstasy is harmful to the human brain. Current policies on ecstasy were influenced by the results of a PET study carried out in the United States. This study has now been shown to be wanting technically, particularly because of the lack of a suitable PET radiotracer.

Using a meticulous approach and our superior PET imaging agent, we are carrying out a study (preliminary data already obtained) to determine definitively if ecstasy and a more potent related drug, MDA (which is often sold as "ecstasy" to drug users), are actually toxic to human brain cells. The results of this study will be important to the general public, governmental agencies involved in drug policy and the judiciary. The results will also provide, for the first time in this controversial area, accurate information for drug education and awareness programs about recreational drugs.

