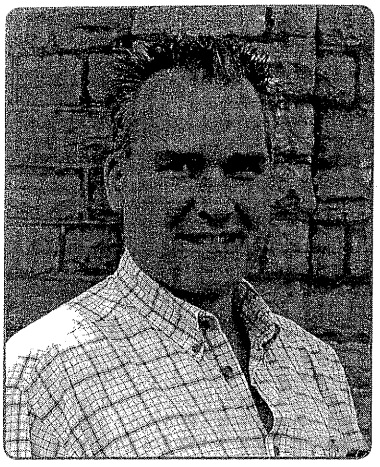

A LIFETIME OF RESEARCH ON DOPAMINE

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I would like to thank Dr. Julio Arboleda-Flórez and the Department of Psychiatry for honouring me with the 2005 Annual Faculty Award for Excellence in Research. As the second recipient after Dr. Jeanette Holden, I feel that I am in good company. Like anyone, I enjoy being recognized for my work but it is particularly gratifying to receive this recognition from my colleagues, in many ways the most important people in my professional career, who provide the support and the environment that has made it possible for me to pursue my research interests.

In this article, I will describe some of the background to my research activities and the larger picture into which my research fits. I will attempt to link the findings of behavioural pharmacological studies in rats to some of the most complex psychiatric diseases that we face. The demands of modern funding agencies require this sort of translational approach, and the accumulated findings of modern neuroscience and biological psychiatry make it ever more possible.

I never dreamed, however, that within this rat learning paradigm might be hidden the secrets to understanding psychotic states seen in humans suffering from schizophrenia and other psychiatric diseases.

In September 1969, when I began my undergraduate studies at the University of Western Ontario, I asked my introductory psychology professor whether I could volunteer in his lab and, fortunately, he agreed. Soon after, I found myself in a darkened room with a number of boxes the size of picnic coolers on tabletops. Each of these boxes contained a rat in an operant testing chamber. I bent down and peered into the peephole (like those found on hotel doors) of one of the outer boxes. What I saw was remarkable and left a lasting impression on me. Inside was a white rat, which moved in a very purposeful and co-ordinated manner over to a lever that protruded from the side of the chamber, placed its paw on the lever, paused, and then pressed. There was a click and the rat moved to the feeder to get the reward – a food pellet. I was transfixed, fascinated by the obvious learning demonstrated by this rat and by the experimental control that the laboratory set-up clearly provided over this behaviour – I was hooked. I never dreamed, however, that within this rat learning paradigm might be hidden the secrets to understanding psychotic states seen in humans suffering from schizophrenia and other psychiatric diseases.

Over a period of some 35 years, I pursued an understanding of what was going on when a rat learned to press a lever for food. When I began my graduate studies at McGill University in 1973, the dopamine pathways had recently been discovered and there was intense research interest in the possibility that these pathways were the biological substrate of reward. My doctoral research and especially the work I did at the University of British Columbia during my post-doctoral studies (1977-1980) took me into the controversy that surrounded the question of the role of dopamine in reward. My work at that time contributed to the body of findings that eventually confirmed that dopamine neurons form a critical link in the neural circuitry mediating the effects of reward on behaviour.

I continued my studies into the role of dopamine in reward when I came to Queen's in 1980. Dopamine was involved in reward, but how? What was the mechanism? For the next decade or so I focused on the possible contribution of dopamine receptor subtypes. Related work had shown that receptors that activated signalling cascades within cells played a role in learning and this suggested that dopamine D1-like receptors should be the ones that are critical for the effects of reward on behaviour. I published a theoretical paper in 1983 in which I suggested this hypothesis but it took another 10 years before

the accumulated empirical data from my own laboratory and those of many others made it clear that this was the case. In the same theoretical paper, following on the emerging dopamine hypothesis of schizophrenia, I suggested that excessive activity in dopamine neurons could produce excessive learning similar to that produced by reward and that this might form a basis for understanding the underlying mechanisms of psychosis.

Following the discovery that dopamine was critical in reward and that D1-like receptors played a central role, the next question became: "Which signalling pathways within cells are involved?" This question has dominated the studies carried out in my laboratory for the last 10 years or so. We have made significant advances in identifying those molecules that play a role and this has led to new and more detailed descriptions of the neurochemical mechanisms underlying learning produced by reward. Since I first saw that rat pressing a lever in 1969, we have come a long way toward providing a detailed description of the underlying mechanism.

So what has a rat pressing a lever got to do with psychotic delusions? The key to answering this question may be dopamine, which provides the link from the animal studies to the human disorder. The dopamine hypothesis of schizophrenia, stating that the dopamine system is hyperactive in the disease, is based

Dr. Arboleda-Flórez presents Queen's Department of Psychiatry Annual Faculty Award for Excellence in Research to Dr. Rick Beninger

on three pillars: all known antipsychotic medications reduce dopaminergic neurotransmission, drugs like amphetamine and cocaine that activate the dopamine system are psychotogenic, and imaging studies provide evidence of enhanced dopaminergic neurotransmission in people suffering from schizophrenia. Coupling these observations to those showing that dopamine plays a critical role in the neural circuitry that mediates the effects of reward on behaviour suggests that the kind of learning that is mediated by rewards is excessive in schizophrenia.

Rewarding stimuli, for example food to a hungry person, activate the dopamine system, leading to stimulation of D1-like receptors and a cascade of intracellular signals that participate in changing the strength of synapses in the brain that are activated by the environmental stimuli that signal reward, e.g., an odour or a place. As a result, those stimuli that signal reward acquire an enhanced ability to elicit approach and other responses in the future. Our mental experience of such changed stimuli might be that we find them more attractive or interesting. This form of learning, mediated by reward and the activation of dopamine neurons, is termed incentive learning.

Hyperactivity of the dopamine system in schizophrenia would lead to excessive incentive learning. As a result, the affected person would be attracted to or more interested in stimuli that normally would remain neutral. Studies of people with schizophrenia that were carried out more than 50 years ago led to the conclusion that they were more distractible than normal, suffering from an attentional filter deficit. That distractibility can now be understood to be the consequence of excessive incentive learning.

One of the most important pieces of the puzzle was found with the realization that dopamine-mediated reward-related incentive learning is non-conscious. This type of learning takes place without people's awareness, whether they have schizophrenia or not. Learning and memory have been the topic of psychological research for over a century. One thing that almost everyone agrees on is that there are different types of memory. One model breaks memory down into declarative and non-declarative categories. Declarative memory refers to the memory for facts or events and is conscious; this is probably the type that most of us think of when we think about memory. It turns out, however, that a lot of the information that we learn is of the non-declarative type, and we are not conscious of learning this material. Examples include a number of types of motor skill learning and reward-related incentive learning. One of the ways that these different memory types were discovered was through testing people with amnesia that resulted from damage to the temporal lobe. Although these individuals could not remember new information like facts or

events, they showed intact learning on some tasks including those involving motor skill learning and incentive learning. Patients with schizophrenia may thus suffer from excessive incentive learning, and be unconscious of this type of learning taking place.

The systems in the brain that underlie our ability to organize information and solve problems are different from those that mediate incentive learning. People who suffer from excessive incentive learning would use those systems to make sense of the world as it appears to them. If excessive incentive learning is causing the walls to appear more interesting or attractive than normal, for example, the brain might make sense of this by suspecting that there are listening devices in the walls. Likewise, if other people who normally would not seem important begin to appear important because of incentive learning, the brain might interpret this as meaning that those people are plotting or otherwise threatening. To the person suffering from schizophrenia these ideas are reasonable interpretations of the world as it appears to them. To the rest of us, they are delusions.

The preceding provides an answer to the question, "what has a rat pressing a lever got to do with psychotic delusions?" Dopamine may be the key. Dopamine mediates the learning produced by rewards. Dopaminergic neurotransmission is overactive in schizophrenia. Thus people with schizophrenia may suffer from excessive incentive learning, in which they build an interpretative framework that makes sense of the stimuli, things and people that are attracting them. To the people around them, these interpretative frameworks are perceived as delusions.

I would like to finish by suggesting what the future may hold for better understanding and treating schizophrenia. The idea that dopamine is involved in learning about social stimuli is quite new and not extensively studied. Imaging studies have recently shown increased metabolic activity in regions of the brain that receive strong dopaminergic innervation when people are presented with social stimuli. For example, after playing a game with two individuals, one who co-operated and one who did not, the brain showed more activation in a dopamine terminal region when presented with a picture of the co-operator as opposed to the non-co-operator. This result suggests that dopamine is activated by social stimuli. Future studies will lead to a better understanding of how our complex social environments shape our interpretations of the people around us and may provide a new level of understanding of the delusional thinking of people with schizophrenia.

I believe that advances in understanding the intracellular signalling pathways underlying incentive learning will influence the future treatment of schizophrenia. Instead of targeting neurotransmitter receptors as all current medications do, future treatments may target specific intracellular signalling molecules that can modulate the strength of learning. From our studies with rats we have learned that manipulations of signalling molecules generally do not influence the effect that neurotransmitters have on on-going motor activity, although they do change learning. These results provide a basis for expecting that newer medications will be more effective and have fewer side effects.

During my research career I have seen amazing advances in neuroscience and biological psychiatry. I have had the resources and colleagues that have made it possible for me to participate in a small way in this enterprise. All of the information that has been and continues to be gathered and synthesized into new theories and models of brain function and dysfunction belongs to all of us. It has been a privilege to be part of this process.