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Understanding the pathophysiology of schizophrenia: Contributions from the Melbourne Psychiatric Brain Bank

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ABSTRACT

The Melbourne Psychiatric Brain Bank came into existence 25 years ago. This review focusses on lines of research that have used tissue from the Brain Bank over periods of time. Hence there is a discussion on the significance of changes in levels of serotonin 2A receptors in the cortex of patients with schizophrenia and the relevance of such changes with regards to the pathophysiology of the disorder. The extensive contribution made by studies using tissue from the Melbourne Psychiatric Brain Bank to understanding the role of muscarinic receptors in the pathophysiology and treatment of schizophrenia is summarised. Finally, findings using brain bank tissue and "omics" technologies are reviewed. In each case, findings using tissue from the Melbourne Psychiatric Brain Bank is placed in context with research carried out on human postmortem CNS in schizophrenia and with findings in other lines of research that can help explain the causes or consequences of changes in CNS molecular cytoarchitecture. This timely review of data from the Melbourne Psychiatric Brain Bank reinforces the challenges faced in trying to increase our understanding of the molecular pathophysiology of schizophrenia. Continuing to increase our understanding of the disorder is important as a precursor to identifying new drug targets that can be exploited to improve the treatment of a disorder where treatment resistance remains a significant problem (Millan et al., 2016).

1. Introduction

The Melbourne Psychiatric Brain Bank came into existence 25 years ago and remains committed to collecting tissue postmortem that can be used to help elucidate the pathophysiologies of psychiatric disorders such as schizophrenia. In the spirit of this special edition, it was thought timely to review the contribution made to the understanding of the pathophysiology of schizophrenia using tissue from the Melbourne Psychiatric Brain Bank.

The Melbourne Psychiatric Brain Bank has grown from a long and fruitful collaboration between the Mental Health Research Institute and the Victorian Institute of Forensic Medicine, the institution through which tissue has been collected. The Melbourne Psychiatric Brain Bank is now part of the Victorian Brain Bank Network which is housed at the Florey Institute for Neuroscience and Mental Health. Whilst many people have made significant contributions to the ongoing operations of the Brain Bank the development of the Diagnostic Instrument for Brain Studies by Professor Nicholas Keks and Doctor Christine Hill (Hill et al., 1996; Roberts et al., 1998) is of particular note having been used to ensure the standardisation of psychiatric diagnoses since the foundation of the Brain Bank. In addition, it is notable that all frozen brain samples have been processed using a standardised procedure developed by Mr Geoffrey Pavey (Dean et al., 1999b) who has curated the collection since its inception. At the time of writing, the Bank held fresh frozen tissue from 106 individuals who had had schizophrenia, 34 major depressive disorders, 23 bipolar disorders and 95 controls. Formalin fixed tissue from 64 individuals with schizophrenia, 25 with major depressive disorder, 23 with bipolar disorder and 62 controls was also available. Contact details for the Administrative Manager of the VBBN are available at http://www.florey.edu.au/research/brain-bank-network.

Whilst these practical issues are crucial to having a collection of well characterised material, the focus of this review will be to outline major contributions to understanding the pathophysiologies of schizophrenia by knowledge gained using the tissue from the Brain Bank.

2. The molecular basis of schizophrenia

It has been increasingly accepted that schizophrenia occurs in individuals with a genetic predisposition and that progression to frank illness is triggered by encounters with as yet unknown environmental factors (Tsuang, 2000). However, studies on individuals who were adopted within three days of birth show that the incidence of schizophrenia is the same as those individuals who stay with their biological

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parents (Heston, 1966). These data suggest that the environmental factors that trigger the changes that lead to the onset of schizophrenia likely occur between conception and birth. Independent of when environmental factors act to trigger the changes that eventually lead to the onset of schizophrenia it is now recognised that such factors act through a number of epigenetic mechanisms to cause changes in gene expression (Jirtle and Skinner, 2007). Hence, it is reasonable to postulate that the pathophysiologies of schizophrenia involve the interactions between genetic predisposition and epigenetic mechanisms. These interactions result in altered gene expression leading to changes in cellular functions, which in turn result in changes in behaviour that are characteristic of the disorder. Significantly, such gene × environment driven changes in gene expression can only be studied in tissue from patients who have developed schizophrenia; a notion that underpins the use of postmortem brains (CNS) to identify changes in molecular architecture associated with the pathophysiology of schizophrenia.

3. Cortical serotonin 2A receptors and schizophrenia

There is a significant body of evidence to support a role for abnormal serotonergic activity in the pathophysiology of schizophrenia (Selvaraj et al., 2014). The involvement of the serotonergic system in disorders of the human CNS is perhaps not surprising given its role in cortical development and the control of cognition, mood and impulse control (Celada et al., 2013). Serotonin achieves these outcomes by affecting the activity of other cortical neurotransmitters systems such as the glutamatergic, GABAergic, cholinergic and dopaminergic systems.

Serotonin modulates the activity of the cortex by activating a family of receptors and neuroimaging, postmortem CNS and neuropsychopharmacological data suggests a potential role for one of these receptors, the serotonin 2A receptor (HTR2A) in the pathophysiology of schizophrenia (Dean, 2003). Some of these data drove much of the early research using tissue from the Melbourne Brain Bank. One consistent finding from these studies was that levels of [^{3}H]ketanserin binding to the HTR2A was lower in the cortex of patients with schizophrenia (Dean and Hayes, 1996; Dean et al., 1996b, 1998, 1999a; Pralong et al., 2000). This finding is supported by other researchers using radioligand binding (Bennett et al., 1979; Gurevich and Joyce, 1997; Hernandez and Sokolov, 1997; Mita et al., 1986) or measuring levels of mRNA (Burnet et al., 1996; Hernandez and Sokolov, 2000; Lopez-Figueroa et al., 2004) but using tissue from other brain banks. Significantly, the lower levels of HTR2A where not associated with single nucleotide polymorphisms in the gene encoding the receptor (Kouzmenko et al., 1997, 1999) which at that time where reported as being associated with an increased risk of developing schizophrenia (Williams et al., 1997). Moreover, the lower levels of HTR2A were not due to generalised changes in the serotonergic system as we failed to show changes in levels of HTR1A, HTR1D, HTR1F, HTR4 and the serotonin transporter (SLC6A4) (Dean et al., 1999c, 2006) in the cortex of patients with low levels of HTR2A. By contrast, a finding of lower levels of HTR7 in the cortex of patients with schizophrenia (Dean et al., 2006) suggests that changes in cortical serotonergic markers were not limited to HTR2A.

As with all studies on schizophrenia that do not involve drug naïve individuals drug treatment is a potential confound that must be acknowledged. This is particularly the case for the HTR2A which is unusual in that down regulation of the receptor occurs after treatment with both agonists and antagonists (Gray and Roth, 2001). Hence, a number of studies have reported a down-regulation of HTR2A after treating rats with antipsychotic drugs which bind to that receptor but not by antipsychotic drugs that do target the receptor (Gray and Roth, 2001; Tarazi et al., 2000). Notably, our studies on HTR2A in patients with schizophrenia on different antipsychotic drugs before death suggested that the decrease in that receptor in the cortex of subjects with schizophrenia was not a simple antipsychotic drug effect (Dean et al., 1998; Pralong et al., 2000). This conclusion has gained support from neuroimaging studies on HTR2A in patients with schizophrenia (see below).

Although initial neuroimaging studies on HTR2A failed to show changes in receptor levels in patients with schizophrenia (Lewis et al., 1999; Okubo et al., 2000; Trichard et al., 1998), subsequent molecular neuroimaging studies on certain sub-classes of people with schizophrenia are in accord with post-mortem CNS data (drug naïve patients with schizophrenia (Ngan et al., 2000; Rasmussen et al., 2010), prodromal phase of the disorder (Hurlemann et al., 2005)). In addition, one study has reported higher levels of HTR2A in the cortex of patients in their first psychotic episode (Erritzoe et al., 2008). Thus, neuroimaging data suggests that changes in HTR2A in the cortex of patients with schizophrenia may vary with clinical stages of the disorder (McGorry et al., 2007) and treatment status. A significant proportion of patients with schizophrenia may have been off drugs for some time before death (Rodda et al., 2006) and this might be why findings on HTR2A in postmortem studies may be more reflective of neuroimaging studies using drug naïve patients.

With advances in molecular techniques that can be used in conjunction with postmortem CNS tissue it is now becoming possible to obtain data on the mechanisms underlying molecular changes in the CNS from patients with schizophrenia. For example, data currently suggests that the lower levels of HTR2A in the cortex of patients with schizophrenia may be mediated by a component of the cytosol (Dean et al., 2008a). Whilst the cytosolic component regulating the levels of HTR2A remains to be identified, such data opens up the possibility that pathways that regulate levels of HTR2A, such as Erg3 mediated pathways (Williams et al., 2012), may be affected in the CNS of patients with schizophrenia. In addition, it has been recently reported that levels of HTR2A can be up-regulated by stimulation of the cannabinoid 2 receptor (Franklin and Carrasco, 2013). This is of interest because cannabidiol, which acts in part through the CB2 receptor (Pertwee, 2008), has been suggested to reduce the severity of symptoms in patients with schizophrenia (Leweke et al., 2012). Thus, a better understanding in the regulation of HTR2A levels may present new opportunities to develop drugs to treat schizophrenia. In addition, determining if markers involved in the mechanisms that regulate levels of HTR2A in human CNS are altered in tissue from people with psychiatric disorders should be a priority as they could inform on whether the changes in levels of cortical HTR2A reported in mood disorders (Baeken et al., 2012; Dean et al., 2014) and suicide (Dean et al., 2014; Escriba et al., 2004) involve the same or different mechanisms.

4. A role for muscarinic receptors in the pathophysiology of schizophrenia

The cholinergic system may be the archetypical neurotransmitter system that evolved from what began as a chemo-detection system in single cell organisms (Dean, 2009). Acetylcholine is the neurotransmitter that controls the activity of the cholinergic system in the CNS which, in humans, is important in many functions such as learning and memory (Perry et al., 1999). Acetylcholine functions by activating two families of receptors, the nicotinic receptors which are ligand gated ion channels and muscarinic receptors which a G-protein coupled receptors (Dean, 2009).

The notion that muscarinic receptors were involved in the pathophysiology of schizophrenia came from early clinical neuropsychopharmacological studies (Forrer, 1951). However, it was the demonstration that [^{3}H]pirenzepine binding was lower in the caudate–putamen from patients with schizophrenia (Dean et al., 1996a) that began an effort to better understand the role of muscarinic receptors in the pathophysiology of schizophrenia. Subsequently, lower levels of [^{3}H]pirenzepine binding have been reported in the cortex (Crook et al., 2001; Deng and Huang, 2005; Zavitsanou et al., 2004), hippocampus (Crook et al., 2000; Scarr et al., 2007) but not in any nuclei of the thalamus (Dean et al., 2004) from patients with schizophrenia. These findings in postmortem CNS gained face value from a neuroimaging study that reported a widespread decrease in [I-123]iodoquinuclidinyl

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