Schizophrenia Research

NeuRA
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Determining the molecular underpinnings of neurotransmitter dysregulation in schizophrenia

Supervisor: Dr Tertia Purves-Tyson, t.purves-tyson@neura.edu.au

Introduction:

- Cognitive deficits play a major role in the disability and poor quality of life of people with schizophrenia (e.g. inability to study or work, difficulty maintaining social relationships). In clinical practice, there are no effective treatments for the cognitive deficits in schizophrenia
- The selective estrogen receptor modulator, raloxifene, can attenuate cognitive dysfunction and psychosis in schizophrenia.
- Dysfunction of dopaminergic, gamma aminobutyric acid (GABA)ergic and glutamatergic neurotransmission have been implicated in the cognitive dysfunction in schizophrenia.
- The maternal immune activation (MIA) rodent model of schizophrenia was developed based on epidemiological data showing increased risk of schizophrenia in progeny of mothers that had an infection during pregnancy. Rodent maternal immune activation results in schizophrenia-like molecular and cognitive deficits
- Evidence suggests that neuroinflammation contributes to the pathophysiology of schizophrenia. Estrogen and raloxifene can act as anti-inflammatories.

Knowledge Gap: **The underlying cellular and molecular mechanisms of raloxifene action are unknown**

Significance: **Uncovering the molecular and cellular mechanisms of action of raloxifene and the behavioural correlates that are improved by raloxifene in healthy rodents and in rodents with a schizophrenia-like phenotype will aid in prioritising downstream molecular targets to develop novel treatments aimed at reversing or preventing the MIA-induced cognitive deficits, with a view to translating this information to treatment of the debilitating cognitive deficits of schizophrenia.**

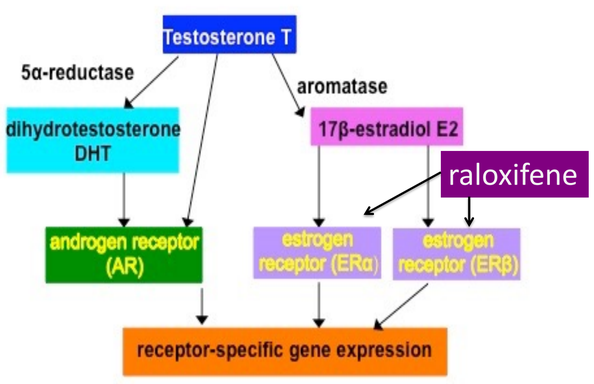
Hypothesis: Raloxifene treatment of healthy rats and maternal immune activation (MIA)-exposed rats will change dopaminergic-, glutamatergic- and GABA-related molecules and/or inflammatory-related molecules in the cortex, midbrain and hippocampus, and these changes will correlate with improved cognitive ability.

Aim: To investigate the molecular mechanisms of raloxifene in brain regions associated with psychosis (basal ganglia), and cognitive dysfunction (cortex), learning and memory (hippocampus) using a maternal immune activation rat model of schizophrenia.

1. Estrogen and raloxifene initiate gene expression via estrogen receptor action, estrogen receptors are found in dopaminergic neurons

- *We will determine whether dopaminergic, gamma aminobutyric acid (GABA)ergic and/or glutamatergic-related gene expression is altered by MIA and/or raloxifene treatment*

Sex steroid signaling



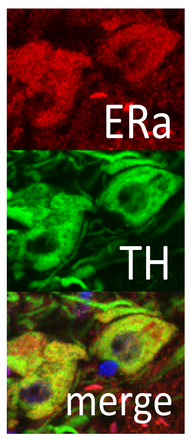


Figure: *Tyrosine hydroxylase (TH, green), a marker of DA neurons, co-localises (yellow when merged) with ERα (red) in the midbrain of male rats*

2. Raloxifene improves markers of midbrain neuropathology in MIA-exposed offspring

- *We will determine if raloxifene restores gene expression of molecules that are changed in the midbrain in schizophrenia*

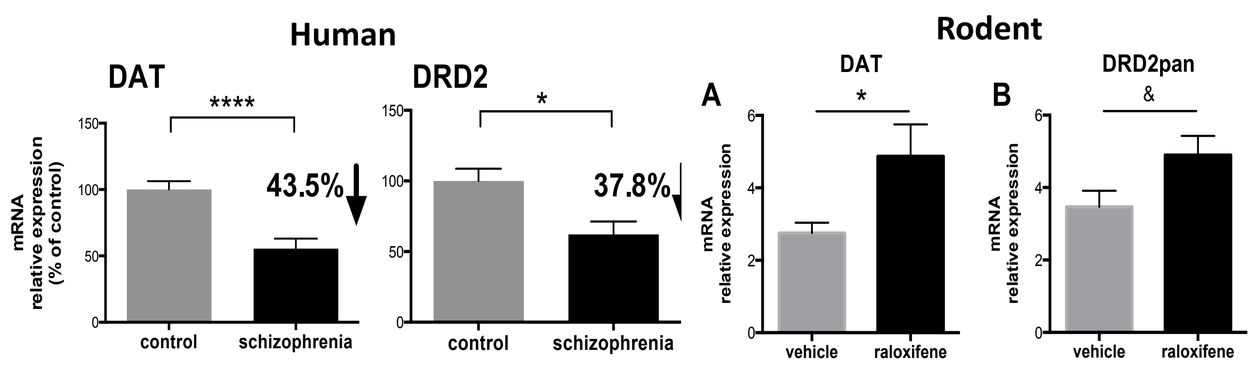


Figure: *Dopamine transporter and dopamine receptor gene expression are reduced in postmortem midbrain in schizophrenia and raloxifene treatment in adult male rats increased DAT and DRD2 gene expression &p<0.1 p<0.05* p<0.0001****

3. MIA-offspring show deficits in cognition-related tasks and raloxifene improves performance on a conditional discrimination task in normal male rats

- *The improvement in conditional discrimination suggests a substantial potential for raloxifene to enhance cognitive behaviours in a rodent model of cognitive deficits.*
- *We will determine whether raloxifene ameliorates PPI deficits and/or improves conditional discrimination in MIA-offspring.*

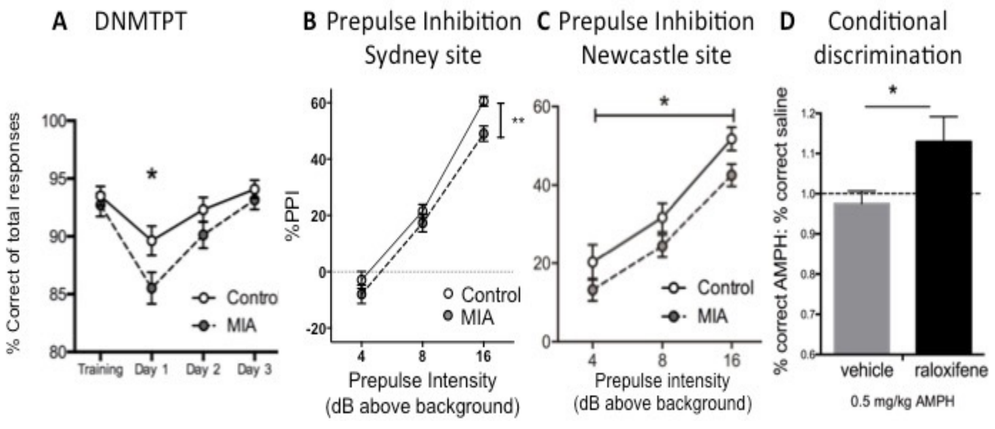


Figure: *Adult rat MIA-offspring, from dams treated with poly(I:C) at GD19, exhibit reduced % correct of total response on the DNMTP task (**A**) and reduced %PPI. **D**. Raloxifene treatment of adult rats enhanced their discrimination performance under low dose AMPH challenge compared to vehicle-treated rats.*p<0.05*

4. Neuroinflammation occurs in the brain in schizophrenia and in adult MIA-exposed offspring

- *We show that gene expression of pro-inflammatory cytokines is elevated in the midbrain of adult rat MIA-offspring, similar to inflammatory-related gene expression changes in the midbrain in schizophrenia.*
- *We will determine the extent to which raloxifene may ameliorate these inflammatory-related changes.*

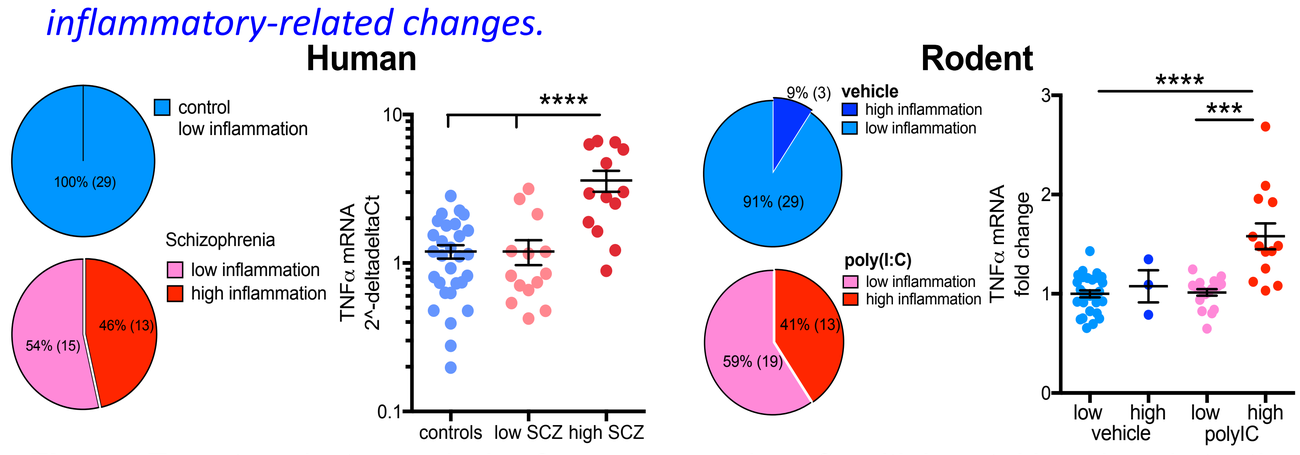


Figure: *Two-step cluster analysis of gene expression of multiple cytokines in substantia nigra from humans (control and schizophrenia) and rodents (adult poly(I:C) or vehicle offspring) identified high and low immune groups (pie graphs). TNFα gene expression is increased in both the high immune schizophrenia and poly(IC) groups. p<0.001*** p<0.0001******

Opportunity:

- Work with an animal model of aspects of schizophrenia;
- Gain knowledge of wet lab molecular techniques (immunohistochemistry; RNA extraction, gene expression, Western Blotting) and rat behavioural phenotyping, rodent brain anatomy.
- Learn experimental data analyses

Talk to me about other potential projects: **B. Glial cell (microglia, astrocytes)-related contributions to dopamine dysregulation in schizophrenia**