INTRODUCTION

BACKGROUND

- Biogenic amines: dopamine (DA), serotonin (5-HT) and norepinephrine (NE) have been used empirically to find a treatment for various mental illnesses in recent decades.
- Schizophrenia (SZ) is one of the most common and devastating conditions for it has limited knowledge of their origin and mechanisms.
- Monoamine oxidase-A (MAO-A), is the key enzyme for the degradation of the three biogenic amines and suggested that plays a critical role in social behavior. Its catalytic activity is located in exon 12
- SZ is characterized by an increased concentration of DA and NE, while the concentration of 5-HT is smaller patients.
- The enzyme tryptophan hydroxylase-2 (Tph2), is responsible for the passage of tryptophan to 5-HT in the central nervous system.
- The circuits of the brain during adolescence is of obvious importance for the development of the SZ.

AIMS

- The central hypothesis of this study is based on:
  - The implications of biogenic amines for the clinical development of the SZ for obtaining a murine model for such mental pathology.
  - Needed two hits in neurotransmission: one is located during embryonic development, followed by further disruption during adolescence.
- The main aim is:
  - To increase the levels of DA and NE while lowering the 5-HT, causing major disturbance during adolescence.
- As specific aims, set out:
  1. Start from knockout mice Tph2 enzyme.
  2. F1 of these mice will insert a MAO-A vector, whose exon 12 will be flanked by two loxP sequences.
  3. During adolescence mouse will proceed to insertion a Cre vector for the removal of exon 12 of MAO-A.
  4. Check that the amendments effectively recreate the disease through neurochemical and behavioral analysis.

MATERIALS AND METHODS

ANIMALS & TARGETING VECTOR

Knocksouts animals Tryptophan Hydroxylase–2 enzyme (Tph2) from Lexicon Pharmaceutical incorporated (New Jersey, EEUU).

ASSAYS (F1)

- Test and behaviour measured
  - Late inhibition (LJ)
  - Prepulse inhibition (PPI)
  - Object and spatial recognition memory
  - Neurochemical analysis

- Relevance to Schizophrenia
  - LJ disruption: Model of the positive symptoms and model of negative symptoms
  - This deficiency is common in SZ patients and considered an endophenotype of the disease
  - Recognition memory is impaired in SZ
  - Study of the three biogenic amines in post-mortem brain tissue

- Translatability
  - Human LJ tasks substantially differ from animal analogues
  - Difference between animal and human PPI tests are minimal
  - Human analogues are available in the CANTAB
  - No human analogue

EXPECTED RESULTS

- Expected from significant changes between the control mice and mice modified as previously described.
- In the neurochemical analysis of brain tissue, are expected to find an increased DA and NE, while it should be a decrease of 5-HT, compared with control animals.
- In performance tests, it is conjectured find behavioral changes in animals Tph2 KO & MAO-A Hypomorphic to assimilate the behavior described in SZ.

DISCUSSION

- The importance of this work is that there are currently no animal models that recreate the symptoms of SZ.
- The SZ is a serious mental illness is a major health expenditure on an annual basis and can not live a normal life or the patient or relatives.
- It is a disease for which no treatment has been found effective palliative and definitive treatment whose understanding and improve the lives of not only the patient but also of society in general.