Animal Model for Schizophrenia

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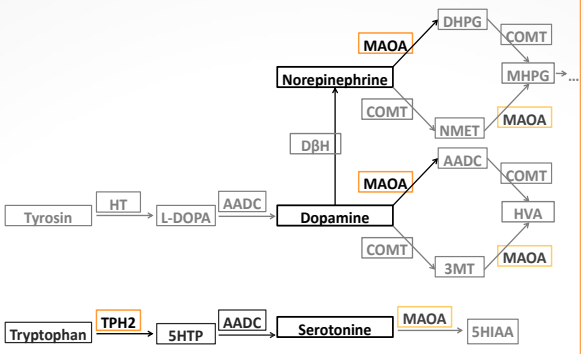
INTRODUCTION

BACKGROUND

- Biogenic amines: dopamine (DA), serotonin (5-HT) and norepinephrine (NE) have been used empirically aim to find a treatment for various mental illnesses in recent decades.
- Schizophrenia (SZ) is one of the most common and devastating conditions for it have 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.



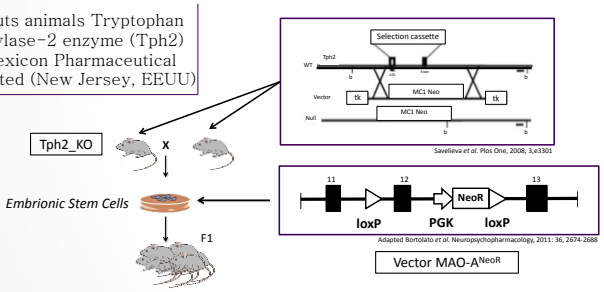
AIMS

- 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 specifics 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.

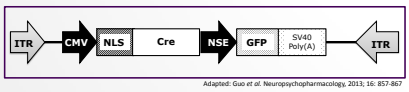
MATERIALS AND METHODS

ANIMALS & TARGETING VECTOR

Knockouts animals Tryptophan Hydroxylase-2 enzyme (Tph2) from Lexicon Pharmaceutical Incorporated (New Jersey, EEUU)



After two months, during adolescence in F1...



Exon 12 is removed by Cre recombinase which acts on the loxP sequences

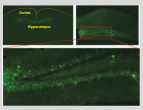
The vector will be introduced through an adeno-associated virus

AAV-Cre-GFP

F1

Tph2_KO & MAO-A_Hypomorphic

ASSAYS (F1)

Test and behaviour measured	Relevance to Schizophrenia	Translationability
Latent Inhibition (LI) 	LI disruption: Model of the positive symptoms and model of negative symptoms	Human LI tasks substantially differ from animal analogues
Prepulse Inhibition (PPI) 	This deficiency is common in SZ patients and considered an endophenotype of the disease	Difference between animal and human PPI tests are minimal
Object and spatial recognition memory 	Recognition memory is impaired is SZ	Human analogues are available in the CANTAB
Morris water maze 	Used to model affecting flattening, a negative symptom of SZ and	No human analogue
Neurochemical analysis 	• Study of the three biogenic amines in post-mortem brain tissue. • GFP protein expression and confirmation of the action of Cre recombinase • Comparison of concentrations in animals genetically unmodified and modified through a statistical test ($p < 0.05$)	

Adapted Benjamin *et al.* Cell Tissue Res., 2013

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.

REFERENCES:
Bortolato M *et al.* Social deficits and perseverative behaviors, but not overt aggression, in MAO-A hypomorphic mice. Neuropsychopharmacology, 2011; 36: 2674-2688.
Savelieva KV *et al.* Genetic disruption of both tryptophan hydroxylase genes dramatically reduces serotonin and affects behavior in models sensitive to antidepressants. Plos One, 2008: 3: e3301.
Guo, M. *et al.* Selective deletion of leptin receptors in adult hippocampus induces depression-related behaviours. Int J Neuropsychopharmacol, 2013:16: 857-867.
Benjamin K *et al.* A conceptual and practical guide to the behavioural evaluation of animal models of the symptomatology and therapy of schizophrenia. Cell Tissue Res, 2013