Mechanism of Fenfluramine in a Zebrafish Mutant Model of Dravet Syndrome?

Jo Sourbron1, Angéla Kecskés1, Liven Lagae2, Ilse Smolders3, Peter de Witte1

1Laboratory for Molecular Biodiscovery, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
2Department of Development and Regeneration, Section Pediatric Neurology, University Hospitals KU Leuven, Leuven, Belgium
3Center for Neuroscience, C4N, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium

INTRODUCTION

1) Behavior and brain activity

• Abnormal behavior and brain activity in scn1Lab-/- mutants.
• Drug screening of serotonergic analogs in locomotor assay leading to
  confirmation of hits by measuring local field potentials and elucidating the mechanism of action

2) Neurotransmission

LC-ECG7

• Determination of the amount of neurotransmitters in heads of ZF larvae by Microbore Liquid Chromatography with Electrical Chemical Detection (LC-ECG)

3) Drug screening

Locomotor behavior

• Treatment of fenfluramine and serotonergic agonists at maximum tolerated concentration (MTC)
• Combined treatment of fenfluramine and serotonergic antagonists at MTC

Brain activity

• Confirmation of hits if a significant decrease in epileptiform brain activity

METHODS

Flow

Drug screening

Zebrafish larvae in 24-well plate

Behavioral assay (4–7 dpf)

Brain activity

LC-ECG

RESULTS

1) Behavior and brain activity

Locomotor behavior
• Higher activity of scn1Lab-/- mutants, compared to wildtype scn1Lab+/+
  may reflect tonic-clonic onset of seizures in Dravet syndrome patients

Brain activity
• Reduction of serotonin in DS ZF larvae = highlights role of serotonin "also observed in animal and human studies of drug-resistant epilepsies"
• Fenfluramine, the 5-HT1D-, 5-HT1E-, 5-HT2A-, 5-HT2C-, and 5-HT7-agonist reduced epileptiform locomotor and brain activity
• \(5-HT_{1D}\)-receptor not involved

2) Neurotransmission

Locomotor behavior

• Combined treatment of fenfluramine and serotonergic antagonists

Brain activity

• Combined treatment of fenfluramine and serotonergic antagonists

CONCLUSIONS

• Drug screening: fenfluramine specifically lowers locomotor behavior in scn1Lab-/- mutants
• Combined treatment experiments (15 larvae for each condition, in triplicate)
• Confirmation of fenfluramine-induced decrease by the

REFERENCES