LONG-TERM STIMULATION OF PPARα RELIEVES CORE SYMPTOMS OF AUTISM SPECTRUM DISORDER IN THE RAT VALPROIC ACID MODEL

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Introduction: Autism Spectrum Disorder (ASD) is a heterogenous neurodevelopmental disorder characterized by impairments in social interaction, deficits in verbal and non-verbal communications and stereotyped, repetitive patterns of behaviors. Increasing amount of data posits that the mechanism underlying social deficit in ASD reflects abnormalities in processing the reward value of social stimuli. The PPARa agonist fenofibrate demonstrated antidepressant-like and pro-motivational properties after repeated administration in an experimental model of depression, relieving the motivational anhedonia that develops in rats following the exposure to a chronic stress protocol. In addition, fenofibrate reinstated the dopaminergic response to salient stimuli in the Nucleus Accumbens shell (NAcS) disrupted by stress exposure, restoring the dopamine D1receptor-DARPP-32signaling in response to palatable food. Thus, based on the hypothesis that ASD could be considered an extreme case of early-onset social anhedonia, we examined the effects of repeated fenofibrate administration on ASD core symptoms in a rat model of ASD. Next, we studied whether phosphorylation levels of Thr-34DARPP-32(an index of dopamine D1receptor activation) in response to social and non-social cues were impaired in the ASD-like model and whether fenofibrate administration reinstated the physiological responses.

Materials and methods: Valproic Acid (VPA) was injected in pregnant females at 12.5gestational day to induce autism-related behavioral alterations in the offspring. Then rats, after weaning, were fed with fenofibrate-enriched diet from postnatal day 21(PND 21) to PND 48. Social (Three-chamber social test and Social Transmission of Food Preference test), repetitive/locomotor and perseverative (marble burying) behaviors were assessed. In addition, anxiety was evaluated (Elevated Plus Maze). The dopaminergic response in the NAcS to social and non-social stimuli was studied analyzing the phosphorylation levels of Thr34DARPP-32by immunoblotting.

Results: Male rats in utero exposed to VPA showed repetitive and perseverative behaviors, social impairments and anxiety. In addition, these animals showed a reduced dopaminergic response in terms of DARPP-32phosphorylation levels to salient stimuli in the NAcS. Four-week administration of fenofibrate relieved ASD-like perseverative behaviors and social interaction deficits.

Discussion and conclusions: The selective PPARa agonist fenofibrate improved social behaviors in the VPA-induced ASD-like phenotype, likely by modulating the dopaminergic reward system reactivity in the NAcS. Thus, fenofibrate, that is already clinically used for hyperlipidemia with a low toxicity profile, could represent a new therapeutic strategy for ASD patients.