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MEMANTINE ATTENUATES HYPERLOCOMOTION AND RESTORES THE IMPAIRED STRIATAL GLUTAMATERGIC NEUROTRANSMISSION INDUCED BY GENETIC DELETION OF THE DOPAMINE TRANSPORTER IN RATS

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Background Dopamine Transporter Deficiency Syndrome (DTDS), also known as infantile parkinsonism-dystonia, is a rare and hereditary disease in which the functioning of Dopamine Transporter (DAT) protein is impaired. At the early stage of the pathology, patients show hyperkinesia that progressively evolves into motor deficits and stereotypical movements.
In the striatum dopaminergic and glutamatergic pathways interact at dendritic spines of medium spiny neurons, a critical interplay mediating top-down control, reward processing and depressive mood.
On these bases, our aim was to unveil the effect dopamine transporter (DAT) deletion, which causes hyperdopaminergia, on the homeostasis of the striatal glutamate synapse and understand its role in neurotransmission further deepening the dopamine-glutamate interaction in this condition. To better investigate the behavioural, functional, and molecular mechanisms that underlie this pathology, we took advantage of DAT knockout ($DAT^{-/-}$) rats, an animal model which shows all the major clinical features of DTDS.
Methods Adult male $DAT^{-/-}$ rats were created in the outbred Wistar Han background at SAGE Labs with a targeted inactivation of the dopamine transporter. Electrophysiological recordings using theta-burst stimulation (TBS) protocol were performed in the dorsolateral region of the striatum to induce a long-lasting long-term depotentiation (LTD).
Protein expression was measured in the striatal postsynaptic density (PSD) and extra-synaptic region of the glutamatergic synapse. Wild-type and $DAT^{-/-}$ rats were acutely treated with the non-competitive NMDA receptor antagonist memantine (30 mg/kg) and electrophysiological, molecular, and structural analysis were performed.
Results $DAT^{-/-}$ rats show elevated striatal extracellular dopamine levels, and hyperactive behaviors (distance travelled: +43506cm, $p<0.0001$). GluN1 (-21%, $t(10)= 3.422$, $p=0.0091$) and GluN2B (-49%, $t(10)= 2.274$, $p=0.0261$) NMDA receptor subunits expression were reduced in the PSD, while increased in the extra-synaptic sites (N1: +115%, $t(10)= 4.382$, $p=0.0023$; 2B: +125%, $t(10)= 2.614$, $p=0.0309$), indicative of an increased lateral trafficking. Moreover, $DAT^{-/-}$ rats show reduced spine density in the striatum (-6.92 spine/10 µm, $t(14)= 4.120$, $p=0.0010$) and impaired LTD (fEPSP amplitude: +21%, $E(2,14)= 6.537$, $p=0.0099$). Notably, memantine counteracted hyperlocomotion (distance travelled: -15656cm, $p<0.0001$), spine rearrangements (+6,46 spine/10 µm, $p=0.046$), lateral movement of NMDA receptors (N1-PSD: +23%, $p=0.028$; 2B-PSD: +26%, $p=0.0002$) and LTD loss in $DAT^{-/-}$ (fEPSP amplitude: -20%, $p<0.05$).
Conclusion We found a multistep dysregulation of the homeostasis of the glutamate synapse in the striatum of $DAT^{-/-}$. The hyperdopaminergia, induced via DAT deletion, reduces the retention of NMDA glutamate receptors in the striatal PSD highlighting an overall depotentiation and destabilization of the glutamatergic neurotransmission. Accordingly, these changes are paralleled by morphological alterations indicative of reduced spine density, suggesting dopamine-induced structural rearrangements, effects that together converge into a compromised plasticity, as shown by the impaired ability to promote LTD in the striatum of $DAT^{-/-}$ rats.
Of note, the blockade of NMDA receptors by memantine reverses the hyperdopaminergic phenotype providing critical evidence that dopamine influences NMDA-mediated neurotransmission, an effect that might be functionally relevant for disorders characterized by elevated dopaminergic activity.
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Conflict of interest
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IRISIN LEVELS IN CEREBROSPINAL FLUID CORRELATE WITH BIOMARKERS AND CLINICAL DEMENTIA SCORES IN ALZHEIMER'S DISEASE

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Background: A rapidly growing literature suggests the effectiveness of regular physical exercise (PE) as a non-pharmacological preventative and interventional strategy to slow down the decline of cognition and/or to improve the cognitive functions in both clinically normal subjects at risk of Alzheimer's disease (AD) and patients with AD [1]. PE neuroprotective effects seem to be linked to "exerkines" released into the bloodstream upon exercise [2]. Among them, irisin has recently been identified as neuroprotective factor in AD mouse models and in preliminary studies in AD patients [3, 4]. Here, we investigated whether there may be variations of irisin levels across the disease stages, identified through the recent amyloid/tau/neurodegeneration (ATN) scheme of the National Institute of Age-Alzheimer's Association [5].
Methods: We measured irisin levels in the cerebrospinal fluid (CSF) and plasma obtained from patients with AD dementia (AD, n=82), mild cognitive impairment (MCI, n=44) and subjective memory complaint (SMC, n=20) biologically characterized according to the ATN classification. We further correlated irisin levels with AD biomarkers [CSF Aβ 1-42 (Aβ42), hyperphosphorylated tau (p-tau), and total tau (t-tau), and Clinical Dementia Rating scale Sum of Boxes (CDR-SOB)]. As sex is suggested to be an important biological variable in AD research, we investigated the possible sex interaction with irisin in the CSF and plasma of AD patients. To compare CSF and plasma irisin levels among patient groups, we used ANOVA (or Kruskal-Wallis test), depending on data distribution. Differences between male and female subgroups were assessed by two-tailed unpaired Student's test and Mann-Whitney test. Correlations were performed using Spearman correlation coefficient test and with partial correlation coefficient test.
Results: CSF irisin was significantly reduced in both patients with MCI and AD ($p = 0.046$ and $p<0.0001$, respectively) compared to SMC. Lower CSF irisin levels in MCI and AD patients were observed when the comparison was restricted to female patients ($p=0.034$ for SMC vs. MCI patients and $p=0.0003$ for SMC vs. AD dementia patients). Subgroup analysis showed a significant reduction of irisin CSF levels in female AD patients compared with male ($p=0.031$). No difference was observed in the plasma irisin levels among group patients.
CSF irisin correlated positively with Aβ42 in both female ($r=0.379$, $p<0.001$) and male ($r=0.262$, $p<0.05$), and negatively with CDR-SOB ($r=-0.234$, $p<0.05$) only in female patients. A negative trend was also observed between CSF irisin and t-tau levels in all patients ($r=-0.144$, $p=0.082$) and in the female subgroup ($r=-0.189$, $p=0.084$). Partial correlation analyses revealed that correlation remained significant between CSF irisin and CSF Aβ42 when corrected for sex only ($r = 0.174$, $p = 0.037$), for sex and age ($r = 0.169$, $p = 0.043$), and for sex, age, and CDR ($r = 0.195$, $p = 0.027$). No significant correlations between irisin and the other biomarkers and CDR-SOB after correction were found.