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New insights into the impact of neo synthesized 17 beta-estradiol on cerebellar function

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Statement of the Problem: It is widely accepted that the steroid 17 beta-estradiol might regulate behavioral processes by influencing structural and functional proprieties of neuronal circuits. When synthesized de novo in brain tissue by an aromatase-dependent conversion of testosterone, the 17 beta-estradiol (E2), may act through fast nongenomic mechanisms involving specific E2 membrane receptors. However, it is still unclear if the E2 impacts the functioning of brain structures in which it is slightly synthesized like in the cerebellum of adult animal in some species including humans and rodents.

Aim: The aim of this study is to determinate whether E2 affects the vestibulo ocular reflex (VOR) adaptation, a simple model of a cerebellar dependent learning and underlying parallel fiber-Purkinje cell (PF) synaptic plasticity.

Methodology: We investigated the acute effect of blocking E2 synthesis on gain increase and decrease in VOR adaptation using an oral dose of the aromatase inhibitor letrozole in peri-pubertal and post-pubertal male rats (within this period cerebellar aromatase is very low expressed and localized to Purkinje cells). We also assessed the effect of letrozole on synaptic plasticity at the PF synapse *in vitro*, using cerebellar slices from peri-pubertal male rats.

Findings: We found that letrozole acutely impaired gain increase and decrease in VOR adaptation without altering basal ocular-motor performance and that these effects were similar in peri-pubertal and post-pubertal rats. Moreover, letrozole prevented long-term potentiation at the PF synapse (PF-LTP) without affecting long-term depression.

Conclusion & Significance: Thus, in adult male rats, E2 affects VOR adaptation and regulate exclusively PF-LTP. These findings suggest that E2 might modulate VOR adaptation by acting on cerebellar and extra-cerebellar synaptic plasticity sites and point to a novel mechanism used by the central nervous system to rapidly regulate adaptive behaviors through low and extremely localized E2 production.

Recent Publications

1. Dieni C V, Ferraresi A, Sullivan J A, Grassi S, Pettorossi V E and Panichi R (2018) Acute inhibition of estradiol synthesis impacts vestibulo-ocular reflex adaptation and cerebellar long-term potentiation in male rats. Brain Structure and Function 223:837-850.
2. Luine V (2016) Estradiol: Mediator of memories, spine density and cognitive resilience to stress in female rodents. Journal of Steroid Biochemistry and Molecular Biology 160:189-195.
3. Munetomo A, Hojo Y, Higo S, Kato A, Yoshida K, Shirasawa T, Shimizu T, Barron A, Kimoto T and Kawato S (2015) Aging-induced changes in sex-steroidogenic enzymes and sex-steroid receptors in the cortex, hypothalamus and cerebellum. Journal of Physiological Sciences 65:253-263.
4. Rudolph L M, Cornil C A, Mittelman-Smith M A, Rainville J R, Remage-Healey L, Sinchak K and Micevych P E (2016) Actions of Steroids: New Neurotransmitters. Journal of Neuroscience 36:11449-11458.
5. Tuscher J J, Luine V, Frankfurt M and Frick K M (2016) Estradiol-mediated spine changes in the dorsal hippocampus and medial prefrontal cortex of ovariectomized female mice depend on ERK and mTOR activation in the dorsal hippocampus. Journal of Neuroscience 36:1483-1489.

Biography

Roberto Panichi is a senior Assistant Professor at the Department of Experimental Medicine, Section of Physiology and Biochemistry at the University of Perugia, Italy. He has a PhD in Neurophysiology and Electrophysiology and his studies focus on understanding the processes by which the central nervous system acquires new skills in human and animal models as well. He spent many years studying the internal space representation and its relationship with ocular and other sensory-motor responses, building up a unique model for describing the adaptation in vestibular ocular reflex and self-motion perception. Regarding his cellular studies are targeted to characterize the activation patterns leading to some form of neural plasticity in vestibular nuclei, cerebellum and hippocampus with the main goal to clarify the relationship between cellular and behavioral adaptation.

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