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

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Abstract

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.

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.

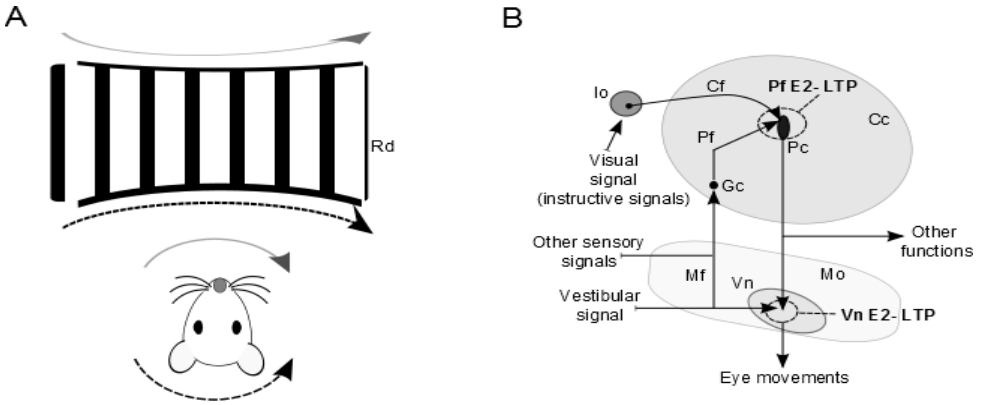


Fig 1. Experimental setup and impact of E2 on the plasticity of neural VOR circuitry. A, Cartoon showing visuo-vestibular stimuli used for conditioning the VOR. Rats were blocked with the head fixed at the rotation center of a turntable (not showed) positioned inside a striped rotating drum (Rd). In gain up conditioning the head and striped drum moved in opposite directions (black dashed arrows) whereas in gain down, the head and drum moved in the same direction (grey solid arrows). **B**, Schematic representation of VOR circuitry. Synaptic plasticity at the parallel fiber–Purkinje cells is thought underlie VOR adaptation. Additional sites of synaptic plasticity could be in the vestibular nuclei (Vn). The schema shows the possible dependence of the LTP at the parallel fiber–Purkinje cell synapses (PF E2-LTP) and in the vestibular nuclei (Vn E2-LTP) by neurosteroid E2. Modulating the LTP at both level, cerebellar cortex (Cc) and extra cerebellar plasticity sites the E2 would influence gain down and up adaptation, respectively and maybe other forms of adaptive behavior depending on cerebellum. Cf, climbing fiber; Gc, granule cells; Io, inferior olive; Mf, mossy fiber; Mo, medulla oblongata; Pc, Purkinje cell; Pf, parallel fiber.

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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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