The cerebellar $\alpha 6$ subunit-containing GABA_A receptor: A novel therapeutic target for disrupted prepulse inhibition in neuropsychiatric disorders

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The pathophysiological role of the $\alpha 6$ subunit-containing GABA_A receptors ($\alpha 6$ GABA_ARs), which are mainly expressed in cerebellar granule cells, remains unclear. Recently, we demonstrated that hispidulin, a flavonoid isolated from a local herb that remitted a patient's intractable motor tics, attenuated methamphetamine-induced hyperlocomotion in mice by acting as a positive allosteric modulator (PAM) of the cerebellar $\alpha 6$ GABA_ARs (1). Here, using hispidulin and a recently identified selective $\alpha 6$ GABA_AR PAM, the pyrazoloquinolinone Compound 6 (2), we revealed an unprecedented role of cerebellar $\alpha 6$ GABA_ARs in disrupted prepulse inhibition (PPI). PPI disruption can be measured in animals and humans, and reflects the sensorimotor gating deficits manifested in several neuropsychiatric disorders, such as schizophrenia, Tourette syndrome, attention deficit disorders, obsessive compulsive disorder and so on. We induced PPI disruptions in mice by methamphetamine and several NMDA receptor blockers. GABA_AR modulatory effects of tested compounds were measured in *Xenopus* oocytes expressing recombinant $\alpha 6 \beta 3 \gamma 2s$ GABA_ARs. Hispidulin given by i.p. or bilateral intra-cerebellar (i.cb.) injection significantly rescued PPI disruptions induced by methamphetamine, ketamine, MK-801 and phencyclidine. Intra-cerebellar effects of hispidulin were mimicked by Ro15-4513 and loreclezole (two $\alpha 6$ GABA_AR PAMs), but not by diazepam (an $\alpha 6$ GABA_AR-insensitive benzodiazepine), and were antagonized by furosemide (i.cb.), an $\alpha 6$ GABA_AR antagonist. Importantly, Compound 6 (i.p.) also significantly rescued methamphetamine-induced PPI disruption in a manner prevented by furosemide (i.cb.). Both hispidulin and Compound 6 significantly potentiated $\alpha 6 \beta 3 \gamma 2s$ GABA_AR-mediated GABA currents. These results suggest that positively modulating cerebellar $\alpha 6$ GABA_ARs can rescue disrupted PPI via attenuating granule cell activity, and $\alpha 6$ GABA_AR-selective PAMs are potential medicines for treating sensorimotor gating deficits in neuropsychiatric disorders. A mechanistic hypothesis is provided based on increasing evidence for a cerebellar contribution in cognitive functioning including sensorimotor gating.

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2. Varagic Z, Ramerstorfer J, Huang S, Rallapalli S, Sarto-Jackson I, Cook J, Sieghart W, Ernst M (2013). Subtype selectivity of $\alpha 6$ site ligands of GABA_A receptors: identification of the first highly specific positive modulators at $\alpha 6 \beta 2 \gamma 2$ receptors. *Br J Pharmacol* 169: 384-399.