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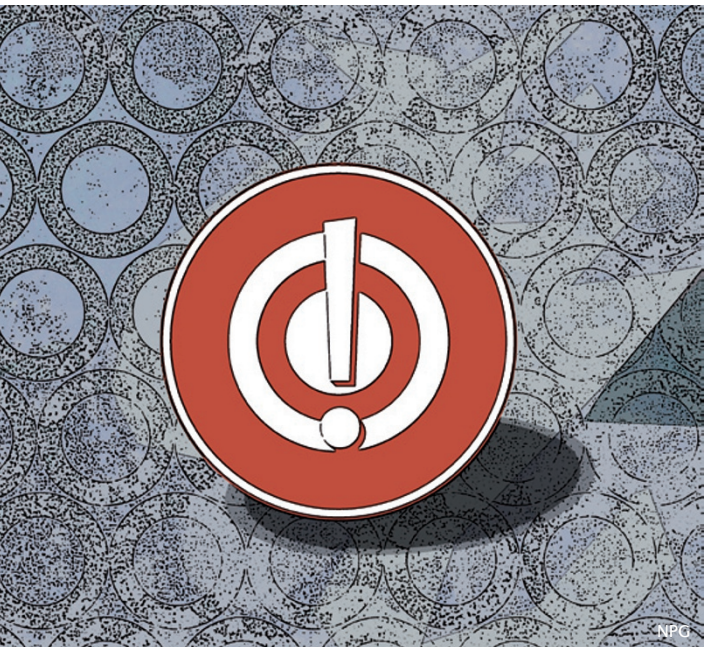
NEUROLOGICAL DISORDERS

Presynaptic glycine receptors become a startling target

Mutations in glycine receptors (GlyRs) are the most common cause of hyperekplexia, or startle disease, but the underlying mechanisms are not known. A study published in *Nature Neuroscience* has shown that a cannabinoid derivative that seems to target presynaptic GlyRs rescues startle responses in mouse models, which could open the door to therapeutic targeting of the glycinergic system in hyperekplexia.

Glycine is a key inhibitory neurotransmitter, and missense point mutations in the gene encoding the α1 subunit of GlyR (GlyRα1) disrupt receptor function and cause familial hyperekplexia. This rare disease is characterized by excessive startle responses to unexpected auditory and tactile stimuli, followed by muscle stiffness. Current treatment involves enhancing inhibitory GABA (γ-aminobutyric acid)-ergic signalling through benzodiazepines, but this provides incomplete symptom management.



For the new study, Xiong and colleagues used mice harbouring an R271Q mutation in GlyRα1; these mice displayed exaggerated startle responses to acoustic and air-puff stimuli. Previous investigations by the group had shown that a cannabinoid drug could mediate analgesia in rodents through potentiation of GlyRα3 signalling, highlighting this class of compounds as potential GlyR modulators. In the current study, intraperitoneal injection of dehydroxylcannabidiol (DH-CBD), a non-psychoactive cannabinoid, was found to dose-dependently inhibit the hyperekplexia-type behaviours of the mutant mice.

Next, the group sought to determine the identity and location of the GlyRs that were targeted by DH-CBD. GlyRs are known to be homomeric or heteromeric assemblies of α- and β-subunits. Whereas postsynaptic GlyRs are well defined as α1β assemblies, presynaptic GlyRs are less well characterized, although mounting evidence points towards a homomeric composition of α-subunits. Using various GlyR assemblies expressed in human embryonic kidney (HEK) cells, Xiong *et al.* showed that homomeric GlyRα1 mutants were considerably more sensitive to DH-CBD than were heteromeric GlyRα1β mutants, implicating presynaptic GlyRα1 in mediating the effects of the drug.

Application of DH-CBD to spinal cord slice preparations from GlyRα1-R271Q mutant mice restored glycinergic inhibitory postsynaptic currents in a manner consistent with the targeting of presynaptic GlyRs. Moreover, application of low-dose picrotoxin, which preferentially blocks homomeric or presynaptic GlyR activity, to the slice preparations abolished the effect of DH-CBD.

Last, the authors measured the activity of GlyRs in neurons in the calyx of Held of hyperekplexic mutant mice. This component of the brainstem auditory circuitry represents one of the few sites at which direct recording of presynaptic channel conductance is possible, and contains only GlyRα1 on presynaptic terminals. Compared with recordings from wild-type mice, the maximum GlyR-mediated current and the receptor affinity for glycine were reduced in presynaptic neurons of hyperekplexic mutant mice. Importantly, DH-CBD significantly enhanced the GlyR-mediated current in presynaptic mutant neurons.

Together, these findings suggest that presynaptic GlyRα1 could be targeted by cannabinoid drugs for the treatment of hyperekplexia and other neurological disorders involving GlyR deficiency.

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ORIGINAL RESEARCH PAPER Xiong, W. *et al.* Presynaptic glycine receptors as a potential therapeutic target for hyperekplexia disease. *Nature Neurosci.* **17**, 232–239 (2014)