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Title

**Glucose and related sugars are allosteric potentiators of glycine receptor-mediated signalling**

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Abstract

The inhibitory glycine recptor (GlyR), a member of the cysteine loop superfamily of ligand gated ion channels, is involved in the control of muscle tone, movement, pain signaling, and also healing and regeneration of spinal cord injury.

Study of glycine receptor function requires patch-clamp electrophysiology on primary neurons or in recombinant systems, where up to 10-fold differences in glycine-mediated currents and EC50 values have been reported. Even within one recording system, cell-to-cell variations by a factor of 5 – 10 were observed.

Here we show that glucose and related saccharides are positive allosteric modulators of the inhibitory glycine receptor, reducing average EC50 values of recombinant human 1 GlyR’s in HEK 293 cells up to 4-fold and eliminating the large cell-to-cell variability of currents. Related saccharides, showed similar effects but with different kinetics. Enhancement of wildtype GlyR’s by glucose was irreversible, persisting even after removal of sugar, consistent with a covalent modification of the GlyR protein.

Thus, saccharides stabilized a high-activity form of the glycine receptor. Positive modulation occurs at physiological glucose concen­trations and may be a key element in fine-tuning of receptor responses. Furthermore, glucose modulation of glycine receptors may be clinically relevant in anaesthesia, neurological disorders, and spinal cord regeneration which all involve glycinergic signaling, and in disorders where glucose levels in the cerebrospinal fluid escape control.