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Glycosylation alters gating and inactivation of T-type calcium channels in the pain pathway

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Using acutely dissociated dorsal root ganglion (DRG) cells from diabetic leptin-deficient (ob/ob) mice, we explored the hypothesis that elevated glucose levels result in increased glycosylation of T-channels.

T-currents from small DRG neurons of ob/ob mice inactivated two times faster than those from wild-type (WT) mice. When neurons were incubated with 1.5U/ml neuraminidase (NEU), both WT and ob/ob channel inactivation slowed dramatically to similar rates. Similarly, T-channels from ob/ob mice activated two times faster than WT and after treatments of cells with NEU, both slowed to nearly the same level. Importantly, treatment with NEU completely reversed increase in T-current density in small DRG cells from ob/ob mice while had no significant effect on T-current density in small DRG cells from WT mice. Next, we cultured HEK-293 cells expressing the $Ca_V3.2$ channels in high glucose media. As expected, when the cells were incubated with NEU, channel displayed slower macroscopic activation and inactivation kinetics and decreased current density.

In conclusion, exposure to the NEU, enzyme thought to be selective for extracellular sialic groups in the proteins, reverses many of the effects produced by a high glucose environment on native and recombinant $Ca_V3.2$ currents. These results provide novel evidence that hyperglycemia promotes increased glycosylation of T-channels, and that this induces significant changes in the gating behavior of these channels. These changes may result in increased cellular excitability of sensory neurons and abnormal pain transmission associated with diabetic neuropathy.