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The unusual suspects: Regulation of retinal calcium channels by somatostatin

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Excessive calcium influx is a major driver of retinal cell death and a hallmark of pathological processes triggered by retinal injury and disease.[1] Finding new ways to stop aberrant calcium entry is imperative in order to develop better therapeutics for preventing visual impairment and blindness. This effort requires an important balance between targeting the pathological functions of the players involved in calcium-mediated excitotoxicity while ensuring that their physiological functions remain intact.

The L-type class of voltage-gated calcium channels is one of the culprits implicated in calcium-mediated excitotoxicity. An increase in synaptic excitation and neuronal depolarization can lead to enhanced activation of L-type channels, prolonged inward calcium currents and an accumulation of intracellular calcium ions. In retinal ganglion cells (RGCs) – the output neurons of the retina – L-type channels have been shown to be the only calcium channel subtype to mediate calcium currents in both the soma as well as in RGC axons.[2] From this recent finding, it is tempting to speculate that blocking L-type channels in RGCs could be an effective therapeutic approach for preventing calcium-mediated degeneration in both the retina and optic nerve. However, generally blocking the L-type calcium channels themselves will likely interfere with numerous L-type-dependent physiological processes, ranging from pacemaker activity to gene expression to secretion.

An alternative therapeutic strategy for treating excitotoxic disorders is to identify individual modulators of L-type calcium channels which would be predicted to target pathological processes with increased specificity. The neuropeptide somatostatin is a key regulator of neuronal excitability in the retina. All five subtypes of G-protein coupled receptors for somatostatin (sst_{1-5}) are expressed in the retina, and there are well-established roles for sst_1- and sst_2-mediated signaling in visual processing and retinal homeostasis.[1] In contrast, the sst_4 receptor has been the neglected child of the somatostatin receptor family, with little known concerning its physiological relevance.[3] In a recent impactful study, the laboratories of Steven Barnes and Nicholas Brecha demonstrated that the sst_4 subtype of somatostatin receptor is abundantly and specifically expressed in RGCs.[4] This study also showed for the first time that activation of sst_4 selectively inhibits the L-type class of voltage-gated calcium channels in RGCs.

In this issue of *Channels*,[5] Farrell and colleagues build upon their original study in neonatal RGCs to investigate modulation of L-type calcium channels by sst_4 in adult RGCs. Through this, they find that activation of sst_4 with the agonist L-803,087 inhibits calcium channel currents across RGC development. While a remaining caveat is that the selective inhibition of only L-type channels by sst_4 remains to be confirmed in acutely dissociated adult RGCs, the similarities found between the neonatal and adult cells strongly suggest developmental continuity. The unexpected twist in this study is the *unusual suspects* identified as mediating the inhibition of calcium channels via sst_4.[5] The authors show that in RGCs, calcium channel inhibition does not occur through the canonical $G\alpha_{i/o}$-mediated signaling pathway typically downstream of sst_4 activation.[3] Rather, they propose that sst_4 couples to the pertussis toxin-insensitive $G\alpha_q$ in RGCs. In support, they find that blocking PKC – which is downstream of $G\alpha_q$ activation – reduces the inhibition of calcium channels by L-808,087. Along with the contribution of PKC to the sst_4-mediated inhibition of calcium currents in RGCs, the authors show that Gβγ is also required for a portion of the calcium current inhibition by L-803,087. Inhibition of voltage-gated calcium channels by Gβγ is typically voltage-dependent and reversed by strong depolarizing prepulses,[6] yet Farrell and colleagues find that all sst_4-mediated inhibition of calcium currents is voltage-independent. Finally, the effects of Gβγ- and PKC-mediated signaling on calcium channels are additive: blocking both signaling pathways together completely abolishes the sst_4–mediated inhibition of calcium currents. Thus, in RGCs, the sst_4 receptor appears to activate distinct $G\alpha_q$/ PKC- and Gβγ- dependent signaling pathways, which converge to mediate the inhibition of putative L-type calcium channels.

Tapping into this unique endogenous sst_4 system may be an effective therapeutic strategy to selectively prevent calcium-mediated

excitotoxicity in RGCs, while leaving physiological sst_1- and sst_2-dependent processes unaffected. However, before this can occur the precise molecular events which couple sst_4 activation to L-type channel inhibition in RGCs need to be further understood. For example, which PKC isoform(s) are involved? Does the voltage-independent inhibition by $G\beta\gamma$ involve a direct physical interaction with calcium channels or, alternatively, is it through a secondary mediator such as the activation of potassium channels by $G\beta\gamma$[7]? While there are no doubt many questions remaining, the findings of Farrell and colleagues[5] represent a promising first step toward possible new treatment avenues for retinal trauma and disease. Beyond the eye, both sst_4 and voltage-gated calcium channels are involved in gating pain signaling in peripheral sensory neurons.[7,8] Thus, understanding mechanisms of coupling between sst_4 and calcium channels could also lead to new targets relevant to pain therapeutics.

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