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PERSPECTIVE

Making the T-Type Even Tinier: Corticotropin-Releasing Factor-Mediated Inhibition of Low-Voltage–Activated Calcium Channel Activity

Diego L. Varela, Tamara Hermosilla, and Gerald W. Zamponi

Hotchkiss Brain Institute, Departments of Physiology & Biophysics, Pharmacology & Therapeutics, and Cell Biology & Anatomy, University of Calgary, Calgary, Canada

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ABSTRACT

T-type calcium channels are important for a variety of physiological processes such as brain and heart function. Proper regulation of these channels by second messengers is fundamental; however, our knowledge of the molecular pathways that regulate T-type calcium channels is limited in comparison with other voltage-dependent calcium channels. In this issue of *Molecular Pharmacology*, Tao et al. (p. 1596) demonstrate that Cav3.2 is regulated by activation of the corticotropin-releasing factor receptor 1 in a G$\beta\gamma$-dependent manner.

T-type calcium channels are important regulators of physiological processes, such as neuronal firing, hormone secretion, and cardiac function (Leuranguer et al., 2000; Molineux et al., 2006; Vassort et al., 2006). Therefore, a precise control over T-type calcium channel activity is necessary, and acute regulation is obtained by G-protein-coupled receptors that trigger downstream transduction pathways, such as phosphorylation by protein kinases such as protein kinase C, calcium/calmodulin kinase II, tyrosine kinase, or Rho kinase (Chemin et al., 2006; Iftinca et al., 2007). Many hormones and neurotransmitters, including dopamine, serotonin, acetylcholine, and angiotensin, have been reported to activate or inhibit T-type currents (Chemin et al., 2006). The regulation of these channels by these hormones is less well understood than that of the high-voltage calcium channels. This may be partly because it is difficult to clearly distinguish individual T-type calcium channel isoforms from each other in native cells, thus giving rise to varied responses that range from decreases to increases of T-current amplitudes, depending on tissue type, species, or the recording condition.

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In their well designed study, Tao et al. (2008) have provided novel evidence for another hormone regulation for the Cav3.2 channel via the activation of the corticotropin-releasing factor receptor 1 (CRFR1). This receptor belongs to the superfamily of G protein-coupled receptors and is part of the family of corticotropin-releasing factor receptors, which in mammals include CRFR1 (with eight splice variants) and CRFR2 (with three splice variants) (Hemley et al., 2007). The main physiological role of these receptors is to mediate responses to stress, including the control of the hypothalamo-pituitary-adrenal axis by regulating the secretion of adrenocorticotropin (CRFR1), and the control of metabolism, vasculature, and muscular responses (CRFR2) (Hillhouse and Grammatopoulos, 2006).

In their exciting article, Tao et al. (2008) show that specific activation of CRFR1, which leads to an increase in cAMP production, selectively induces a reversible inhibition of Cav3.2 T-type calcium channel activity, whereas other channels of the same family (Cav3.1 and Cav3.3) show no modulation by CRFR1. The effect on this calcium channels is dose-dependent, is prevented by the use of CRFR1 antagonist, and dependent on membrane potential. In particular, the authors show that receptor activation is able to induce a hyperpolarizing shift in the steady-state inactivation potential, whereas the voltage-dependence of activation seems to

ABBREVIATIONS: CRFR, corticotropin-releasing factor receptor.

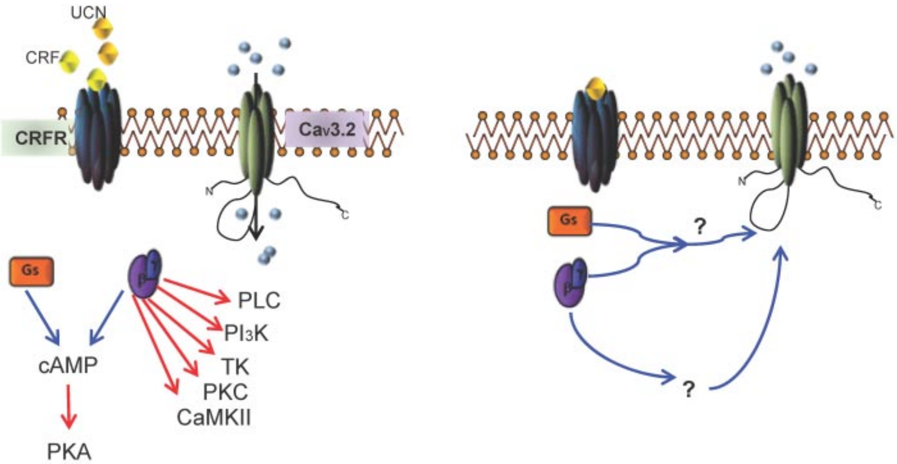

Fig. 1. Cav3.2 inhibition by CRFR activation. Upon CRFR1 receptor activation, G protein dissociate in to $G\alpha_s$ and $G\beta\gamma$ subunits, which activate different signaling pathways. Left, red arrows show pathways that were shown not to be involved in the inhibition of the channel according to Tao et al. (2008) Right, blue arrows show possible mechanisms for the observed inhibition. $G\beta\gamma$ may indirectly act via an intracellular signaling pathway, or $G\alpha_s$ and $G\beta\gamma$ might directly inhibit channel activity via concerted action.

be unaffected. Through a carefully pharmacological approach, the authors show that this effect is dependent on $G\alpha_s$ signaling, whereas $G\alpha_{i/o}$ and $G\alpha_{q/11}$ are not involved. Moreover, the authors rule out a contribution from phospholipase C or any of the other kinases known to be associated with CRFR1 activation (Fig. 1). Instead, the authors demonstrate that the regulation critically depends on $G_\beta\gamma$-mediated signaling. Taken together, the authors have identified a novel mechanism of Cav3.2 T-type calcium channel inhibition, involving a cholera-toxin sensitive, $G_\beta\gamma$-dependent pathway that is triggered by corticotropin-releasing factor receptor 1 activation. The fact that cholera toxin mimicked the effect of CRFR1 activation suggests that this type of regulation may perhaps also be observed with other types of $G\alpha_s$-linked receptors.

In a previous study, Wolfe et al. (2003) showed that $G\beta_2\gamma_2$ inhibits Cav3.2 calcium channels directly without affecting the voltage-dependent gating properties of the channel, whereas other types of G protein β subunits do not mediate this type of direct regulation. This then suggests that the CRF1 receptor-mediated regulation does not involve a direct action of $G\beta\gamma$ on Cav3.2 channel activity but instead probably occurs via a $G\beta\gamma$-dependent activation of a downstream signaling pathway that has yet to be identified (Fig. 1). Alternatively, it is possible that the concerted action of $G\beta\gamma$ and $G\alpha_s$ on the channel may produce the observed effects on steady-state inactivation of the channel.

The wide expression of CRFR in the central nervous system (Swinny et al., 2003), together with the established expression of T-type calcium channels in different neuronal types (McKay et al., 2006), underscore the potential physiological implications of the findings of Tao et al. (2008). T-type calcium channels are known to be involved in rebound bursting, a phenomenon in which a transient membrane hyperpolarization sufficiently recovers T-type calcium channels from tonic inactivation, thus allowing them to become active and thus contribute to the membrane depolarization that in turn underlies the initiation of a train of successive of sodium spikes. Rebound burst activity is a key feature associated with the transition between the awake state and sleep (Contreras, 2006), a process in which agonists of CRF receptors have been implicated (Zoumakis et al., 2006). In this context, the observed hyperpolarizing shift in half-inactivation potential in response to CRF1 receptor activation has the propensity to regulate sleep rhythm. Along these lines, the shift in the steady-state inactivation curve also decreases the amount of overlap between steady-state inactivation and activation curves, thus decreasing the size of the window current and thus a reduced level of basal T-type calcium channel activity (Vassort et al., 2006). Such a decrease in the window current is thus expected reduce basal intracellular calcium and consequently hormone secretion (Leuranguer et al., 2000). Finally, it should be reiterated that T-type channel expression is not confined to the nervous system but also seen in other excitable tissues known to express CRF receptors, such that alterations in the activity profiles of Cav3.2 T-type channels as a result altered window currents may well affect the excitability of cardiac output.

As noted above, CRF receptors undergo extensive alternate splicing, although not all possible splice isoforms may be physiologically important (Hemley et al., 2007). It remains to be determined if the coupling between CRF receptors and T-type calcium channels is dependent on the type of splice variant present in a given cell. Nonetheless, the findings by Tao et al. (2008) clearly identify a novel means by which T-type calcium channels are regulated by G protein-coupled receptors, with potentially far-reaching consequences for neuronal and possible cardiac function, which will need to be explored in greater detail in future studies.

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Address correspondence to: Dr. Gerald W. Zamponi, Department of Physiology and Biophysics, University of Calgary, 3330 Hospital Dr. NW, Calgary, T2N 4N1, Canada. E-mail: zamponi@ucalgary.ca