COLLOQUIA IN CELLULAR SIGNALLING

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Wednesday 8.5.2013 11:00 s.t. **Emilio Carbone (host: A. Koschak)**

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"L-type calcium channels as controllers of pace-making, secretion and endocytosis in adrenal chromaffin cells"

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L-type calcium channels (LTCCs) are highly expressed in the chromaffin cells of the adrenal medulla. They effectively control cell firing, neurotransmitter release (exocytosis) and vesicle retrieval (endocytosis). In humans and rodents, LTCCs carry almost half of the Ca^{2+} currents that are generated during cell depolarization [1,5-7]. Of the four LTCCs currently identified (Cav1.1 to Cav1.4), chromaffin cells express equal densities of the Cav1.2 and Cav1.3 isoforms [7,10], which play distinct roles due to their different gating properties. Using chromaffin cells of Cav1.3$^{-/-}$ mice it has been possible to highlight the critical role that this LTCC plays in generating the pacemaker current sustaining spontaneous or stimulus-induced firing [7,9,10]. Mouse chromaffin cells firing is irregular and appears to derive from the critical equilibrium of inward Ca^{2+} and outward K^{+} currents carried by Cav1.3 and Ca^{2+}-activated BK and SK channels during the interspikes interval. Due to their different Ca^{2+} and voltage-sensitivity, BK and SK channels are shown to be differently coupled to Cav1.3 and contribute in a quite different way to the firing frequency and spike frequency adaptation during sustained depolarization [7,9,10].

LTCCs are also shown to contribute to Ca^{2+}-driven catecholamine secretion [2,3]. They appear uniformly distributed near the secretory granules at an average distance of about 200 nm [2] and control a fraction of exocytosis proportional to the quantity of Ca^{2+} ions that they drive in the cell [3]. Recent findings show that LTCCs do also control the Ca^{2+}-dependent endocytosis that occurs following a sustained exocytosis [8], although there is not yet clear evidence of any specific role of Cav1.2 and Cav1.3 in this process.

Cav1.2 and Cav1.3 are also effectively modulated by the cAMP/PKA and NO/cGMP/PKG pathways and their current density may vary tenfold when the two signaling cascades are oppositely activated [4]. The implications of these recent findings on chromaffin cell functioning could help explaining the different response of the adrenal gland to *stressful* or *relaxation* body conditions.

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