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Roles of the calcium sensing receptor in the central nervous system

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The calcium sensing receptor (CaSR) is expressed by sub-populations of neuronal and glial cells throughout the brain and is activated by extracellular calcium ($Ca^{2+}{}_o$). During development, the CaSR regulates neuronal cell growth and migration as well as oligodendroglial maturation and function. Emerging evidence suggests that in nerve terminals, CaSR is implicated in synaptic plasticity and neurotransmission. In this review, we analyze the roles attributed to CaSR in regulating diverse brain functions, including central regulation of body fluid composition and blood pressure. We also discuss the potential relevance of Ca^{2+}-sensing in brain by other family C G protein-coupled receptors. Finally, evidence that the CaSR contributes to the pathogenesis of various brain disorders raises the possibility that pharmacological modulators of the CaSR may have therapeutic benefit.

For many years, calcium (Ca^{2+}) has been known to be of major importance for the proper functioning of the nervous system (for review,[1,2]). First, Ca^{2+} is critical for growth and development by regulating gene expression and participating in dendrite development or synaptogenesis. It is also required for neurotransmission, being involved in most forms of activity-dependent synaptic plasticity. While changes in intracellular Ca^{2+} (Ca_i^{2+}) have been widely studied in signal transduction associated with these processes, roles for changes in the physiological range of extracellular Ca^{2+} ($Ca^{2+}{}_o$) have only been proposed more recently. Although the level of $Ca^{2+}{}_o$ is generally considered to be relatively stable in the brain, it fluctuates substantially during physiological processes such as synaptic

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transmission and sleep, or pathophysiological conditions such as seizures, ischemia and hypoglycemia.[3] As in peripheral organs involved in Ca^{2+} homeostasis, such as the parathyroid or thyroid glands, kidneys or bone, the calcium-sensing receptor (CaSR) identified in nerve terminals has been proposed to detect and monitor $Ca^{2+}{}_o$ levels in the brain.[4] However, the precise functions of CaSR are only beginning to be uncovered in this tissue. The purpose of this review is to provide an up-to-date overview of our current understandings of how $Ca^{2+}{}_o$ signals through the CaSR in the central nervous system (CNS) building on previous reviews of the field.[5–8] Remarkably, the CaSR is expressed in brain regions involved in memory, cognition, motor reflexes, thirst, growth and energy homeostasis. Studies conducted in recent years have provided important data not only on the physiological and homeostatic roles of the CaSR, but also on its putative involvement in neurodegenerative diseases and brain tumors.

CaSR expression in the CNS

After isolation of the bovine[9] and human[10] CaSR sequences, the receptor was also cloned from a rat brain striatal cDNA library by homology screening.[4] The subsequent distribution of CaSR transcripts and protein in the brain were then widely investigated using specific riboprobes and antibodies, respectively. Northern analyzes showed the existence of two transcripts of around 4 and 8 kb that were highly expressed in the hypothalamus and striatum and to a lesser extent in the pituitary, hippocampus, cerebellum and brainstem.[4,11] Antibodies recognizing epitopes in the N-terminal domain of rat CaSR either at the extreme N-terminus or in the middle of the domain allowed the detection of a single and specific immunoreactive band around 160 kDa in the adult striatum[4] and the developing postnatal hippocampus.[11] An antiserum developed using this N-terminal immunogenic sequence detected CaSR expression in acutely isolated nerve terminals and synaptosomes of rodent neocortex.[12] The visualization of CaSR in brain slices revealed various types of subcellular localization depending on the antiserum that was used. On the one hand, CaSR was detected throughout the brain at rather high levels and with a distinct laminar distribution in Ammon's horn and in the cerebellum in both nerve fibers and terminals but not cell bodies.[4] On the other hand, the developmental expression profile of CaSR in the hippocampus revealed time-dependent changes in expression in the cell bodies of the pyramidal cell layer.[11]

Detailed mapping of CaSR transcripts showed expression at different levels in several regions of the developing and adult brain in both the grey and white matter (Refs. 13–15 and Fig. 1). In the grey matter, many areas displayed isolated, widely scattered CaSR-expressing cells. A limited number of nuclei, however, including the CA2 region of the hippocampus, orbital cortex, thalamus and hypothalamus contained a high density of CaSR-expressing neurons identified by labeling of the specific marker NeuN. Cells located in the circumventricular organs, mainly the subfornical organ (SFO), but also in the area postrema and the most external layer of the median eminence, which are all in direct contact with ions in the extracellular fluids outside the blood–brain barrier, highly expressed CaSR. An interesting localization of CaSR-expressing cells was also found in a subset of small neurons in the adult rat dorsal root ganglia. Another notable feature was the evident similarity displayed by the spatial and temporal expression profiles of Ca*SR* and myelin basic protein (MBP)-expressing cells from the early postnatal period until adulthood. In both cases, the highest cell densities were detected in the white matter of the cerebellum and in the major fiber tracts. Like MBP, CaSR expression increased until postnatal day 20 (P20) with a caudo-rostral gradient characteristic of the period of myelination in the brain. In the spinal cord, the high number of scattered, CaSR-positive cells present in both the grey and white matter was also reminiscent of the expression profile of MBP suggesting CaSR expression in mature oligodendrocytes, an hypothesis confirmed by the co-expression of CaSR and MBP mRNAs in the fiber tracts.[13] Other glial cells, including astrocytes and microglia, were devoid of CaSR labeling in the rat brain.[13,14,16,17] However, primary cultures of microglial cells derived from rat brain expressed the CaSR.[17] In addition, CaSR mRNA and protein expression was reported in human astrocytes[16,18] and in the astrocytoma cell lines, U87 and U373.[16,19,20]

Although most studies have focused on rodent brain or human cell lines, the distribution of CaSR was also investigated in the Mozambique tilapia fish.[21] Antibodies directed at the extracellular and intracellular domains of the receptor revealed a 100 kDa immunoreactive signal consistent with the expected size of tilapia CaSR. The same tools revealed CaSR expression in the neurointermediate lobe of