S 16-4

N-TYPE Ca^{2+} CHANNELS IN BRAIN FUNCTIONS

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Voltage-dependent Ca^{2+} channels (VDCCs) play important roles in the regulation of diverse neuronal functions, including neurotransmitter release, regulation of cell membrane excitability, and control of gene expression. Voltage-dependent N-type (Cav2.2, α1B) Ca^{2+} channels, along with the P/Q-type, have a crucial role in controlling the release of neurotransmitters or neuromodulators at presynaptic terminals. Analyses of α1B knockout mice have revealed various physiological roles *in vivo* of N-type calcium channels, including nociception, sympathetic regulation in the autonomous system, control of motor activity and vigilance state, mediation of the anesthetic effect of profocol, and control of ethanol consumption. In my talk I will present results showing novel roles of N-type Ca^{2+} channels. First, N-type Ca^{2+} channels play a role in the hippocampus-dependent learning and memory and long-term synaptic plasticity. Thus, the mutant mice exhibited impairment in hippocampus-dependent learning and memory. Interestingly, activity-dependent long-lasting synaptic changes that are known to involve brain-derived neurotrophic factor (BDNF) and to contain presynaptic components were decreased in the mutant mice. In addition, BDNF-induced synaptic potentiation was reduced in the mutant. Second, N-type calcium channels are required in the synaptic circuit for suppression of serotonergic neuron firing in the DRN. Thus, the lack of this suppression in the mutant resulted in an elevated 5-HT level in the hypothalamus, which, in turn, enhanced AVP secretion, resulting in increased aggressiveness.

S 17-1

RECEPTOR-SPECIFIC PHOSPHOINOSITIDE SIGNALING TO NEURONAL ION CHANNELS

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In neurons, Ca^{2+} and K^+ channels can be regulated via 2nd-messenger cascades whose particular characteristics can be receptor-specific. Activation of several different types of receptors coupled to the $G_{q/11}$ class of G proteins induce phospholipase C (PLC) to hydrolyze plasma-membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol and IP_3. In sympathetic neurons and heterologous expression systems, both N-type Ca^{2+} channels and M-type K^+ channels (made by pore-forming $Ca_V2.2$ and K_V7 subunits, respectively), are shown to be sensitive to the abundance of PIP_2 in the plasma membrane. Thus, depletion of membrane [PIP_2] or an alteration in the affinity of the channels for PIP_2 presents possible mechanisms for channel modulation. In superior cervical ganglion (SCG) sympathetic neurons, stimulation of both $G_{q/11}$-coupled muscarinic acetylcholine M1 and bradykinin B2 receptors suppress the M current, but by different mechanisms. The former do not cause rises in intracellular Ca^{2+} (Ca^{2+}_i) and act by depletion of membrane PIP_2. The latter do induce rises in $[Ca^{2+}]_i$ and act in concert with calmodulin to suppress the channels, perhaps by Ca^{2+}/calmodulin binding altering their affinity for PIP_2. Stimulation of the muscarinic, but not the bradykinin, receptors depress the Ca^{2+} current in SCG cells, suggesting that stimulation of the former, but not the latter, can deplete the membrane of PIP_2. Since bradykinin, but not muscarinic, stimulation induces rises in $[Ca^{2+}]_i$, we hypothesized that such Ca^{2+}_i signals stimulate the synthesis of PIP_2 concurrently with its hydrolysis by PLC, preventing PIP_2 depletion. We tested such a pathway of receptor stimulation of PIP_2 synthesis in SCG neurons, mediated by Ca^{2+}- bound neuronal calcium sensor-1 (NCS-1) stimulation of PI4-kinase activity. Indeed, when PI4-kinase was acutely blocked, or when Ca^{2+}_i signals were prevented by depletion of intracellular Ca^{2+} stores, or when NCS-1 activity was blocked by expression of a dominant negative (Ca^{2+}-insensitive) NCS-1 mutant, bradykinin stimulation became capable of suppressing the Ca^{2+} current. We thus propose that receptor-specific modulation of channels by lipid signals is accomplished by differential promotion of intracellular Ca^{2+} signals and differential stimulation of PIP_2 synthesis. For receptors that do not cause such Ca^{2+}_i signals, PIP_2 synthesis is not concurrently stimulated, permitting depletion of PIP_2. For those that do induce rises in $[Ca^{2+}]_i$, concurrent stimulation of PIP_2 synthesis compensates for PLC-mediated PIP_2 hydrolysis, and the channels are likely modulated by an alteration in their PIP_2 affinity. We suppose such a mechanism for receptor-specific action generalizes to many types of excitable cells. Supported by NIH RO1 NS043394.

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