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Dual Role of an mps-2/KCNE-Dependent Pathway in Long-Term Memory and Age-Dependent Memory Decline

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Activity-dependent persistent changes in neuronal intrinsic excitability and synaptic strength are underlying learning and memory. Voltage-gated potassium (K; v;) channels are potential regulators of memory and may be linked to age-dependent neuronal disfunction. MinK-related peptides (MiRPs) are conserved transmembrane proteins modulating K; v; channels; however, their possible role in the regulation of memory and age-dependent memory decline are unknown. Here, we show that, in C. elegans, mps-2 is the sole member of the MiRP family that controls exclusively long-term associative memory (LTAM) in AVA neuron. In addition, we demonstrate that mps-2 also plays a critical role in age-dependent memory decline. In young adult worms, mps-2 is transcriptionally upregulated by CRH-1/cyclic AMP (cAMP)-response-binding protein (CREB) during LTAM, although the mps-2 baseline expression is CREB independent and instead, during aging, relies on nhr-66, which acts as an age-dependent repressor. Deletion of nhr-66 or its binding element in the mps-2 promoter prevents age-dependent transcriptional repression of mps-2 and memory decline. Finally, MPS-2 acts through the modulation of the K; v; 2.1/KVS-3 and K; v; 2.2/KVS-4 heteromeric potassium channels. Altogether, we describe a conserved MPS-2/KVS-3/KVS-4 pathway essential for LTAM and also for a programmed control of physiological age-dependent memory decline.
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