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Changes with aging in forskolin-stimulated and basal cAMP in the hippocampus.

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The cAMP signaling pathway appears to be essential in rodents for triggering sustained enhancement of synaptic transmission and for consolidation of spatial information into long-term storage. We and others have observed changes with aging in forms of hippocampal long term potentiation (LTP) that are mediated by the cAMP signal transduction pathway. These include age-related changes in L-LTP (Bach et al., PNAS 96:5280-5) and "chemLTP" induced by β-adrenergic receptor stimulation followed immediately by application of Mg^{++}-free aCSF (Raskin et al., SFN Abstracts 2002). In this study we examined whether such changes in LTP are related to changes in basal and/or stimulated cAMP levels. Cyclic AMP production was assayed in hippocampal slices from young (6-week-old) and aged (22-month-old) F344 rats after exposure to isoproterenol (1 :M) paired with 10 mM Ca^{2+}/0 Mg^{2+}/ 30 mM K^{+} (ISO-chemLTP), or following direct stimulation of adenylate cyclase with forskolin (10 :M) paired with the Mg^{++}-free depolarizing solution (FSK-chemLTP). Cyclic AMP production in response to the ISO-chemLTP protocol was similar in hippocampal slices from young and aged Fischer 344 rats. However, cAMP production following the FSK-chemLTP protocol was significantly lower in aged vs young rats. Interestingly, we observed higher basal levels of cAMP in aged tissue as compared to young. These findings suggest that the molecular defects responsible for age-related deficits in the β-adrenergic receptor-mediated form of chemLTP lie downstream of adenylate cyclase activation. Aged neurons appear to compensate for these downstream changes by up-regulating basal levels of cAMP. This elevation in basal [cAMP] could be due to decreases in cAMP phosphodiesterase activity, or increases in constitutive activity of adenylate cyclase. The ability to stimulate isoforms of adenylate cyclase that are not activated by β-adrenergic receptors (i.e., G_s), however, was diminished in aged hippocampus.

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