cGMP MODULATES LONG-TERM POTENTIATION AND MEMORY BY ENHANCING ABETA PRODUCTION

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It is well known that cyclic guanosine monophosphate (cGMP) is involved in the regulation of long-term potentiation (LTP), a synaptic plasticity phenomenon that is generally considered the electrophysiological substrate of learning and memory formation. As a matter of fact, a large body of evidence has shown that inhibition of phosphodiesterase(PDE)-mediated degradation of cGMP enhances LTP and ameliorates memory in healthy and diseased brains1. Interestingly, in the last decade it has been consistently demonstrated that, contrary to its deleterious effects in Alzheimer's disease, the amyloid-beta (Aβ) peptide is necessary at low physiological concentrations for LTP expression and cognitive processes2-4.

Therefore, in the present study we investigated whether cGMP and Aβ could functionally interact to trigger LTP and, therefore, memory formation.

First, we investigated if cGMP could influence Aβ42 production in cultured neuronal cells (N2a). Indeed, blockade of the cGMP-metabolizing enzyme PDE5 with sildenafil or vardenafil (100 □M) increased intracellular cGMP in N2a cells by 5 and 23 folds, respectively, and this effect was paralleled by a 50 to 100% enhancement of Aβ42 levels. Pearson's correlation coefficient between PDE5 inhibitor-induced cGMP and Aβ42□production was 0.97, indicating a very strong relationship between the two events. This view was confirmed by the observation that the sildenafil/vardenafil-induced increase of Aβ42□was significantly reduced when cGMP synthesis was inhibited by the selective soluble guanylyl cyclase blocker ODQ (50 □M). Of note, sildenafil and vardenafil (100 □M) were able to increase Aβ42 production also in slices of rat hippocampus, a brain region with a key role in learning and memory.

Analyzing the amyloidogenic pathway, we found that, both in N2a cells and hippocampal slices, the vardenafil-induced enhancement of Aβ42 production occurred in the absence of changes in APP expression. Apparently, vardenafil did not affect also the activity of BACE-1, the APP-cleaving enzyme that is necessary for Aβ42 formation. However, using the OptiCAB assay (Optical Convergence of APP and BACE-1)6, we observed that vardenafil treatment was able to significantly increase the approximation of APP and BACE-1 and their co-localization into the endo-lysosomal compartment of cultured hippocampal neurons, a cellular district where APP cleavage preferably occurs.

As for hippocampal LTP, we confirmed that vardenafil (10 Nm) was able to convert early LTP into late LTP. However, this effect of the PDE5 inhibitor was not observed when hippocampal slices were pretreated with an anti-Aβ antibody (M3.2 mAb; 2μg/ml) for 20 minutes before the tetanus, but it was rescued by the addition of human Aβ42 (200 pM). In addition, the LTP potentiating effect of vardenafil was absent in hippocampal slices obtained from APP knock out mice.

Finally, Vardenafil (1 mg/kg) was able to enhance wild type mice memory in the object location task, whereas it was ineffective in APP knock out mice.

In conclusion, we have discovered a new functional relationship between cGMP and Aβ, which is necessary for LTP and memory to work in physiological conditions. These findings could represent the mechanism of action of PDE5 inhibitors that might exert their cognitive-enhancing effects via a positive modulation of Aβ in the healthy brain. Moreover, our data highlight the importance of fully understanding the physiological role(s) of Aβ to design effective and safe AD therapies, since Aβ lowering treatments could worsen memory instead of ameliorating it.

References

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