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Role of cGMP in learning: alterations in pathological situations and therapeutic implications

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Activation of NMDA receptors is involved in some forms of learning. However, the molecular events by which NMDA receptors modulate learning remain unclear. Activation of NMDA receptors leads to increased intracellular calcium which binds to calmodulin and activates neuronal nitric oxide synthase, increasing the formation of nitric oxide (NO) which, in turn, activates soluble guanylate cyclase. This leads to increased formation and release to the extracellular space of cGMP. We propose that activation of this glutamate-NO-cGMP pathway and the release of cGMP to the extracellular space are involved in the process of learning a Y maze conditional discrimination task.

We analyzed by in vivo brain microdialysis the function of the glutamate-NO-cGMP pathway in cerebellum in vivo in different animal models and found that there is an excellent correlation between the function of the pathway and the ability of rats to learn the Y maze conditional discrimination task.

Patients with hepatic encephalopathy show impaired intellectual capacity. The underlying molecular mechanism remains unknown. Rats with portacaval anastomosis or with hyperammonemia without liver failure (animal models of hepatic encephalopathy) show impaired learning ability and impaired function of the glutamate-NO-cGMP pathway. We hypothesised that impairment of learning in liver failure and hyperammonemia would be due to the impairment of the function of the pathway and that its pharmacological manipulation to increase cGMP content could restore learning ability. It is shown, by in vivo brain microdialysis, that chronic intracerebral administration of zaprinast, or oral administration of sildenafil, two inhibitors of the phosphodiesterase that degrades cGMP, normalizes the glutamate-NO-cGMP pathway function and extracellular cGMP in brain in vivo in rats with portacaval anastomosis or with hyperammonemia. Moreover, zaprinast and sildenafil restored the ability of these rats to learn the conditional discrimination task.

Intracerebral administration of cGMP, that does not enter into the cells, also restores learning, indicating that extracellular cGMP modulates learning of this task. In conclusion, the results reported indicate that impairment of learning ability in rats with chronic liver failure or with hyperammonemia is due to impairment of the glutamate-NO-cGMP pathway and that pharmacological manipulation of the pathway maybe useful for the clinical treatment of the impairment in intellectual function in patients with hepatic encephalopathy.