Experimental panel 16.2 The involvement of NMDA[1] receptors in memory formation

Background to the study

In order to establish that NMDA receptors and long-term potentiation (LTP)[2] of synapses play a role in learning and memory formation, various types of behavioural studies were performed on living animals. Rats trained in a water maze provided clear-cut evidence about involvement of NMDA receptors and LTP in spatial memory formation.

Experimental approach

A water maze consisting of a round pool (2.14 m diameter) was filled with water made opaque by the addition of powdered milk such that a swimming rat could not see a small platform (0.10 m diameter) placed under the surface of the water. The platform was placed in the centre of quadrant 2 of the pool as shown diagrammatically in Figure A and rats were subjected to various spatial memory formation-related training protocols to help them find the platform and escape based on cues located around the circumference of the maze. Shortly after the rat located the platform and climbed on it, the rat was removed from the pool.

After 15 training sessions the escape platform was removed and the rats were allowed to move freely for 60 s through the water maze while their swimming path was recorded by a computerized tracking system.

One group of rats had their NMDA receptors blocked with a drug (D,L-2-amino-5-phosphonopentanoic acid, or D,L-AP5), which does not affect synaptic transmission but prevents hippocampal[3] LTP after brief high frequency stimulation. LTP formation after brief frequency stimulation was also assessed in the hippocampus of control and drug-treated rats.

Results

The average time spent by the normal and drug-treated rats in each of the four quadrants of the pool after the training sessions is shown in Figure A. The normal rats spent most of the time (~35 s out of 60 s) in the vicinity of the place where the platform was during the training sessions, indicating that after the training sessions they learned and remembered where the escape platform was located. In contrast, the D,L-AP5-treated rats spent about the same length of time in each of the four quadrants of the pool, showing that they have either not learned during the training sessions about the platform's location in the first instance, or they could not remember the platform's initial location. Electrophysiological tests on LTP induction after brief high frequency stimulation showed normal LTP induction in hippocampal regions of control rats and a complete block of LTP induction in the same regions of the D,L-AP5-treated rats.

Other experiments using the water maze showed that L,D-AP5 did not affect retention of previously acquired spatial information. Therefore, the inability of the L,D-AP5-treated rats to know where the escape platform was located during the training sessions was due to impairment of spatial memory formation rather than to impairment of information retrieval.

Interestingly, blocking the NMDA receptors with L,D-AP5 did not affect the ability of rats subjected to visual discrimination tasks, such as distinguishing between two platforms painted differently and placed just above the water surface. One platform was fixed and allowed the rats to escape, while the other was unstable, causing the rats to fall back into the water when the rats attempted to climb on it.

Conclusions reached

Taken together, these results provided strong evidence that LTP associated with NMDA receptors is necessary for some types of learning and memory formation. Spatial learning was impaired when the NMDA receptors in the hippocampus were fully blocked and LTP induction was prevented without affecting fast synaptic transmission. However, visual discrimination and retention of previously acquired spatial information were not affected when LTP induction in the hippocampus was blocked. These re-

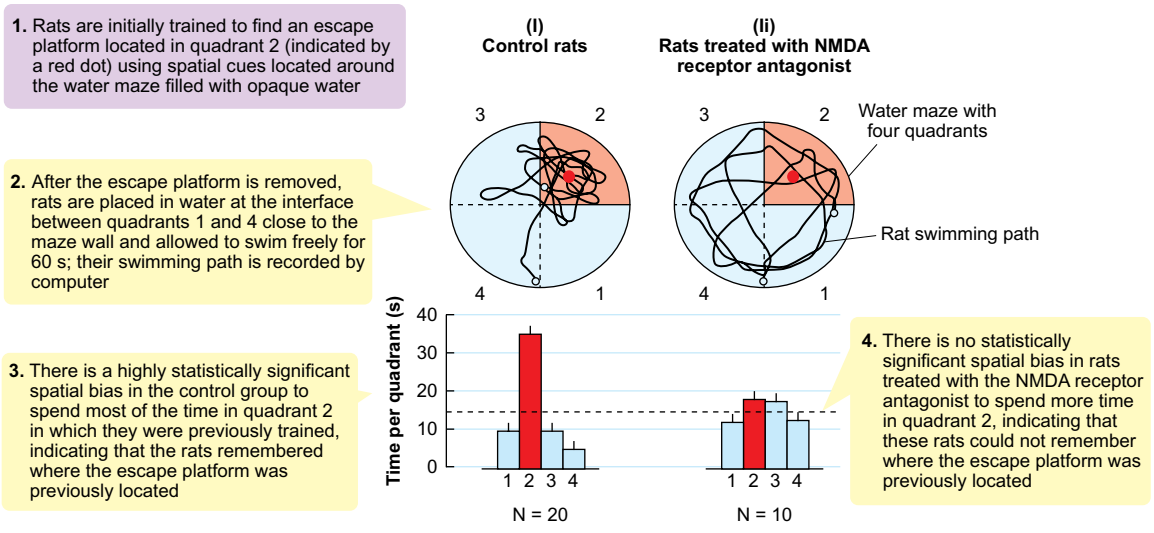

Figure A Source: Morris RGM et al (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319: 774–776.

sults showed that NMDA-associated LTP formation in hippocampus is likely involved in some types, but not all types of learning; when this was the case, LTP is involved in the initial phases of learning and memory formation and not in retrieval processes.

Arguably the strongest evidence of NMDA receptor-dependent LTP in memory formation was provided by more recent experiments in which rats were trained to avoid a dark chamber, in which they received an electric shock upon entry. This inhibitory avoidance type of learning produced a rapid phosphorylation of the NMDA receptor, delivery of NMDA receptor subunits to the synapse, and increased amplitude of excitatory postsynaptic potentials in specific regions of the hippocampus. These effects were qualitatively and quantitatively similar to changes observed in LTP induced by high frequency stimulation. Importantly, the changes induced by this type of inhibitory avoidance learning significantly reduced the LTP and its associated changes induced by high frequency stimulation *in vivo*. Thus, inhibitory avoidance learning produces the same changes at synapse as the induction of NMDA receptor-dependent LTP by high frequency stimulation. By implication, these observations strengthen the case for NMDA receptor and LTP involvement in at least some types of memory formation.

Find out more

Morris RGM, Anderson E, Lynch G, Baudry M (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319: 774–776.

Morris RGM (1989). Synaptic plasticity and learning: Selective impairment of learning in rats and blockade of long-term potentiation in vivo by an N-methyl-D-aspartate receptor antagonist AP5. Journal of Neuroscience 9: 3040–3057.

Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006). Learning induces long-term potentiation in the hippocampus. Science 313: 1093–1097.

[1] We discuss NMDA receptors in Section 16.3.4.

[2] We discuss LTP in Section 16.3.6.

[3] The hippocampus is a brain structure, which is involved in spatial learning.