Blockade of aversive and appetitive memory reconsolidation by systemic administration of beta-noradrenergic and NMDA-receptors antagonists

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It is well known that consolidated long-term memory can under certain conditions revert to a labile state and then reconsolidate (Lewis et al., 1972; Nader et al., 2000; Dudai, 2004). The main condition for the transition of memory to a labile state is the process of reactivation. Reactivation of memory is carried out by a reminder, i.e. placing the subject (animal) in the same environment where primary training was conducted, or by isolated single presentation of the same conditional stimulus on the basis of which the primary training was developed, or presentation of both at the same time (Muravieva and Alberini, 2010). The discovery of memory labilization at its retrieval and repeated consolidation allows intervening into a "bad" memory and coping with the post traumatic stress disorder or relapse of drug addiction (Nader et al., 2000; Torregrossa, Taylor, 2013; Grigoryan, Markevich, 2015).

The aim of this study was to investigate whether the disruption of noradrenergic and glutamatergic synaptic transmissions will erase or make substantially weaker a memory about aversive or rewarding events.

Three experiments have been done in rats.

Experimental groups

PrR+/ MK801R+ – receiving a reminder (placing onto the same context) and intraperitoneal injection of propranolol (0.5 mg/kg) or MK-801(0.1 mg/kg) immediately after a trial

SalR+ – receiving a reminder and injection of saline,

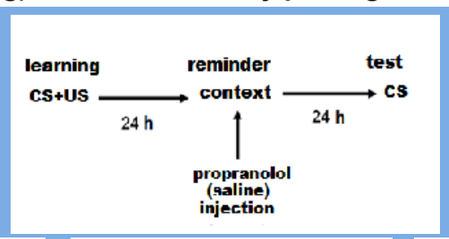
PrR-/ MK801R- – not receiving a reminder, but injection of propranolol or MK-801 in a home cage

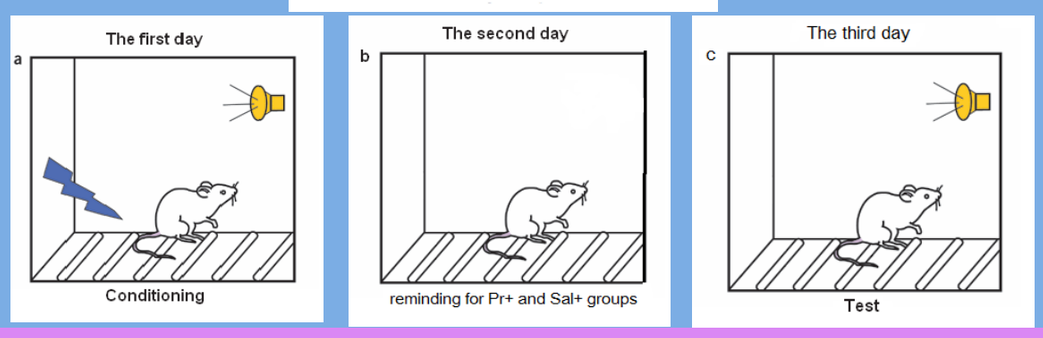
SalR- – not receiving a reminder, but injection of saline in a home cage.

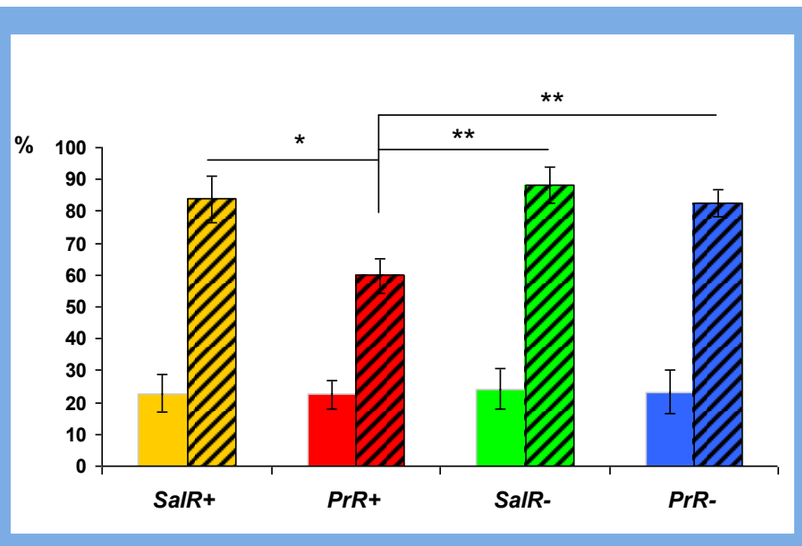
background test

Experiment 1.

Experiment 1. The effect of beta-noradrenergic antagonist, propranolol (0.5 mg/kg) on reconsolidation of aversive memory acquired in a classical *fear conditioning paradigm* was studied. Reactivation (reminding) was carried out by placing the animals into the same context



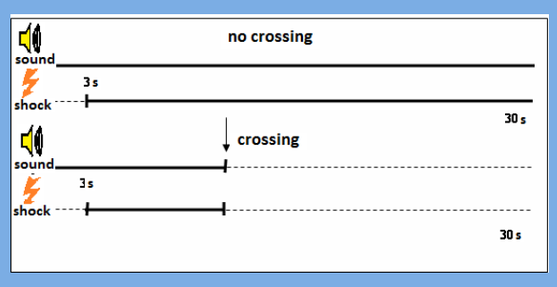


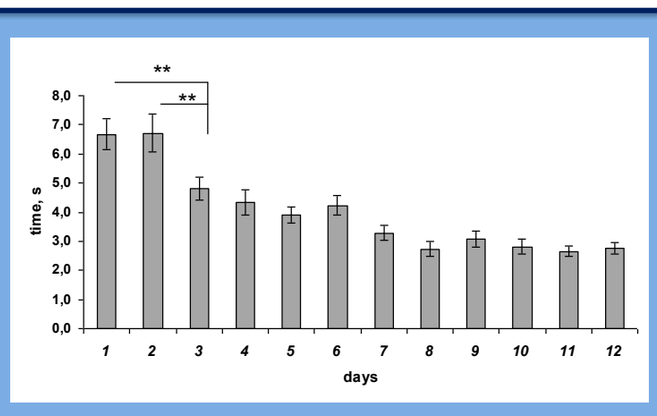


A single pairing of tone (CS) with electrocutaneous painful stimulation (US) led to a significant increase of freezing reaction during a repeated test of animals after 48 hours. Propranolol given immediately after memory reactivation reduced the intensity of freezing on 25% from the baseline at the fear conditioning

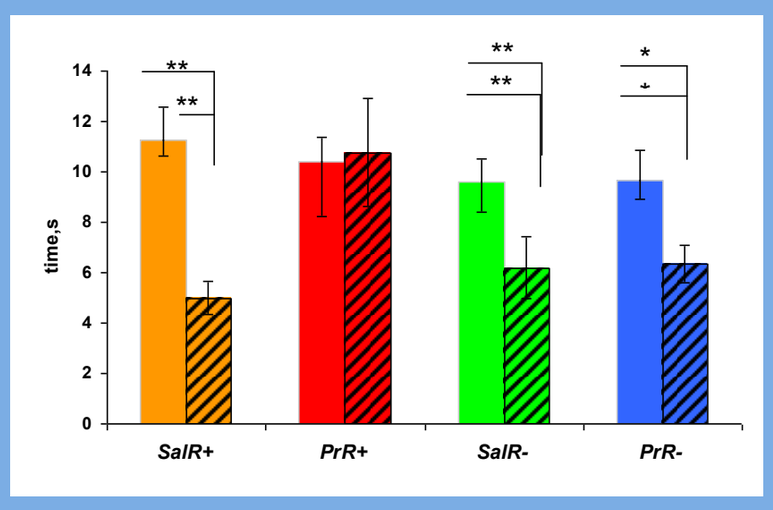
Experiment 2.

Experiment 2. The aversive state was elaborated during the two-ways escape learning. Reactivation (reminding) was carried out by applying the same amount of pairings of conditional and unconditional stimuli as at initial learning.





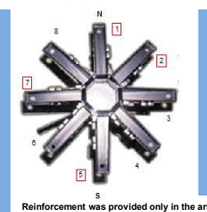
A significant decrease in the latency of escape response on the third day of the two-way avoidance reaction training was revealed.



Propranolol given immediately after memory reactivation on the second day resulted in a complete regress of the two-ways escape reaction compared to the other groups of rats.

Experiment 3.

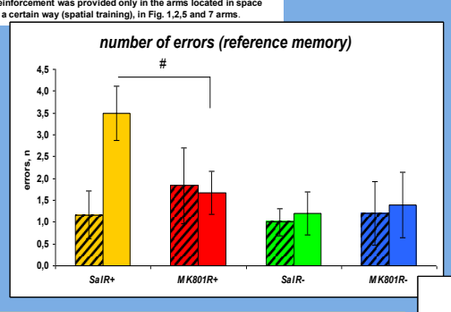
The reconsolidation of the appetitive memory was investigated. The initial learning was carried out in an 8-arm radial maze with one trial (5 min) a day for 25 days continuously. 4 arms of the maze were constantly rewarded, while another 4 arms were non-reinforced. The entries into non-rewarded arms were considered as the long-term memory errors, while the repeated entries into rewarded arms as the short-term memory errors. Three ways of a memory reactivation were used: a) with one non-reinforced trial, b) with three consecutive non-reinforced trials, c) with three more intensive than usual reinforced trials. 24 hours after reactivation the memory was retested.

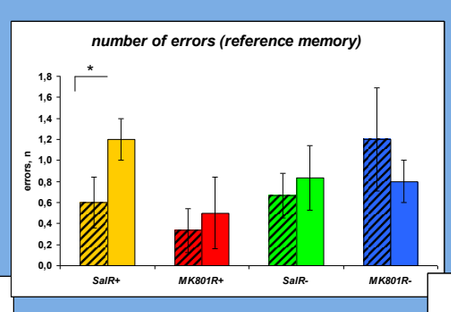


single unreinforced trial

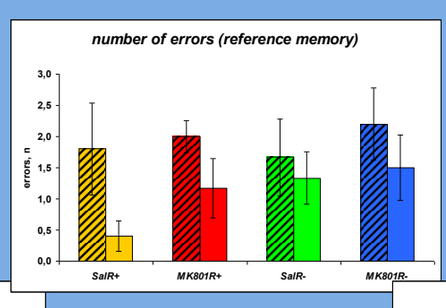
three consecutive unreinforced trials

three consecutive reinforced trials

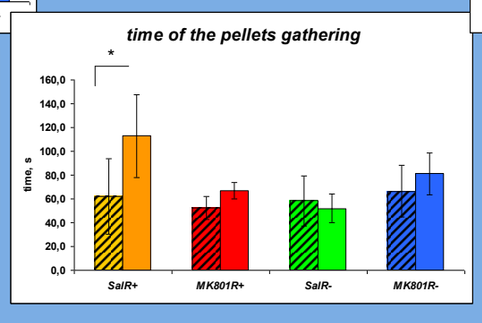


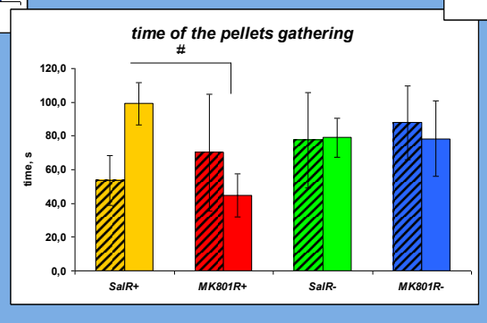


The memory did not reconsolidate by reactivation with three consecutive unreinforced trials

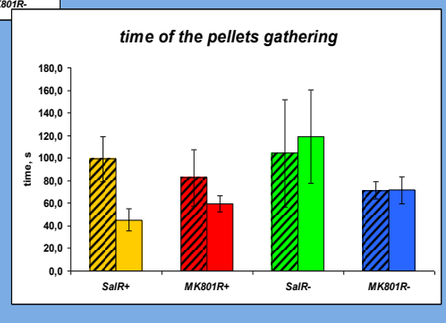


Blockade of NMDA receptors by MK-801 administration prevented for memory reconsolidation after a single unreinforced trial.





Three trials with more intensive and tasty reinforcement at the reactivation phase did not lead to the changes of memory during testing phase.



Conclusion

Propranolol given immediately after memory reactivation reduced intensity of freezing at the fear conditioning and practically led to disappearance of memory and complete regress of the two-ways escape reflex. MK-801 prevented for memory reconsolidation in the experiments with food reinforcement. Tested 24 hours later the memory underwent reconsolidation by reactivation with one unreinforced trial, but not by reactivation with three unreinforced trials or with three reinforced trials. The data suggest that the mechanisms of noradrenergic influence on memory loss during reconsolidation are different in the used models of aversive learning and could be explained in the light of a role of memory update and reinforcement prediction error in the processes of memory reconsolidation.