THE ROLE OF CARBONIC ANHYDRASES IN EXTINCTION OF CONTEXTUAL FEAR MEMORY

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INTRODUCTION

Extinction consists of the learned inhibition of retrieval of a previously acquired memory. It is used in the psychotherapy of learned memory, often under the name of exposure therapy. As extinction does not erase the original memory, extinguished behaviors can return with the passage of time. Drugs promoting fear extinction could represent a novel therapeutic strategy. Carbonic anhydrases (CAs) are enzymes involved in physiological processes, including memory formation.

AIM

Evaluate the role of brain CAs in extinction of contextual fear memory.

METHODS

Male Wistar rats, submitted or not to stereotaxic surgery, were subjected to a contextual fear conditioning (CFC) training, in which three electrical foot shocks (0.5 mA, 2 s) were delivered at 30-s intervals. Twenty-four hours later, animals were subjected to extinction session. Immediately after, they received systemic administration (i.p.) of vehicle, CA inhibitor acetazolamide (ACTZ) or CA activadorD-phenylalanine (D-Phen). The animals with cannulae implanted bilaterally in the CA1 region of the dorsal hippocampus, basolateral amygdala (BLA), ventromedial prefrontal cortex (vmPFC) or substantia nigra pars compacta (SNpc) received infusions of vehicle, ACTZ or D-Phen. After 24 h, animals were subjected to a 3 min retention test. For c-Fos measurements, rats received i.p. injections of vehicle or ACTZ and were euthanized.

RESULTS

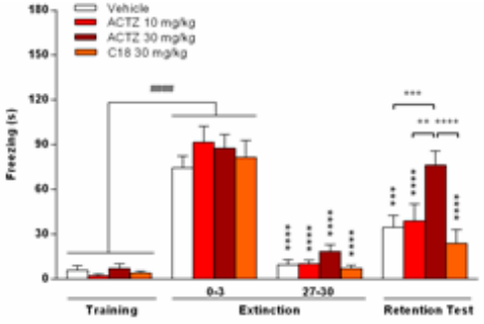

Fig. 1. Brain CA inhibition impaired the consolidation of extinction memory. Rats were trained in the CFC and after 24 h subjected to a 30-min extinction training session. Immediately after this session, they received an i.p. injection. A 3-min retention test was performed at 24 h after the extinction training session. Freezing time shown by rats given vehicle, ACTZ (10 mg/kg), ACTZ (30 mg/kg), or C18 (30 mg/kg) during training, extinction, and the retention test. Data are expressed as mean ± SEM of 6 to 10 rats for each group.

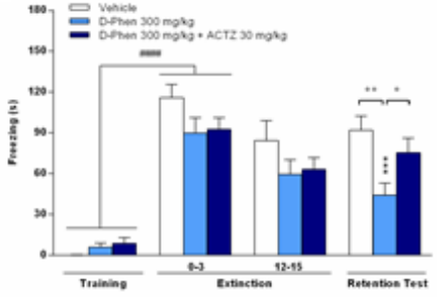

Fig. 2. CA activation enhanced the consolidation of extinction memory. Rats were trained in the CFC and after 24 h subjected to a 15-min extinction training session, then immediately given an i.p. injection of vehicle, D-phen or D-phen + ACTZ. A 3-min retention test was performed at 24 h after the extinction training session. Rats treated with D-phen showed fear extinction memory, as they spent significantly less time freezing than vehicle-treated rats in the retention test. ACTZ prevented the promnesic effect of D-phen. Data are expressed as mean ± SEM of eight or nine rats for each treated group.

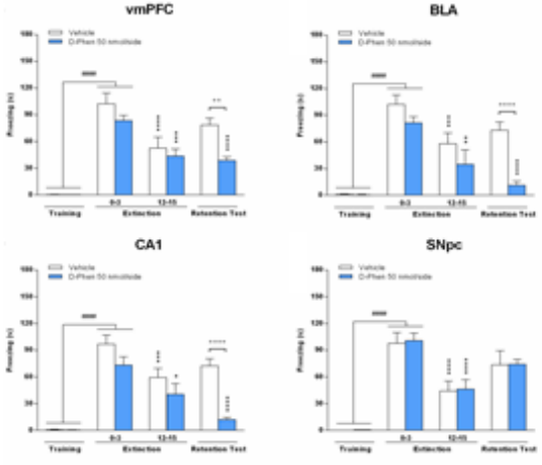

Fig. 3. CA inhibition in selected brain regions hindered the consolidation of extinction memory. Rats were trained in the CFC and after 24 h subjected to a 30-min extinction training session. Immediately after this session, the rats received bilateral infusions of vehicle or ACTZ into the vmPFC, BLA, CA1, or SNpc. A 3-min retention test was delivered at 24 h after the extinction training session. The freezing time observed in the retention test indicates that bilateral infusions of ACTZ into the vmPFC, BLA, and CA1, but not in the SNpc, impaired the consolidation of fear extinction memory. Data are expressed as mean ± SEM of 8 to 13 rats for each treated group.

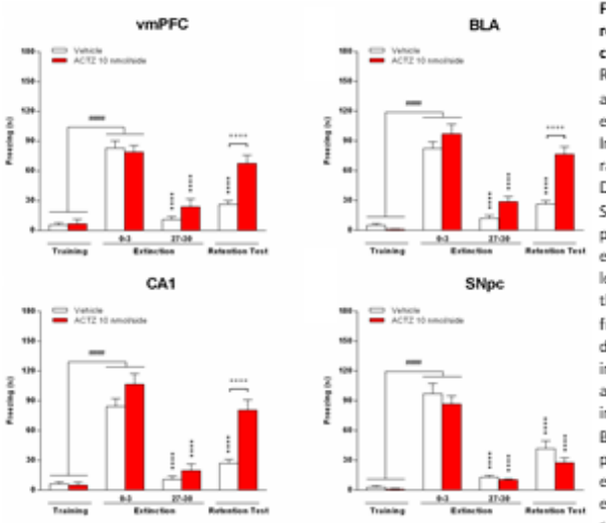

Fig. 4. CA activation in selected brain regions potentiated the consolidation of extinction memory. Rats were trained in the CFC and after 24 h subjected to a 15-min extinction training session. Immediately after this session, the rats received infusions of vehicle or D-phen into the vmPFC, BLA, CA1, or SNpc. A 3-min retention test was performed at 24 h after the extinction training session. All rats learned fear extinction memory, but this memory was short-lived, as the freezing time of vehicle treated rats did not differ significantly in the initial 3 min of the extinction session and in the retention test. Bilateral infusions of D-phen into the vmPFC, BLA, and CA1, but not in the SNpc, potentiated the consolidation of fear extinction memory. Data are expressed as mean ± SEM of 8 to 13 rats for each treated group.

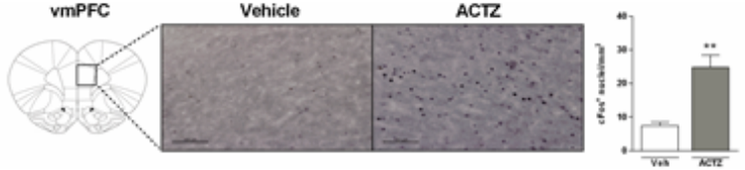

Fig. 5. Effect of systemic administration of ACTZ immediately after the extinction training session on c-Fos expression in the vmPFC. Rats were trained in the CFC and after 24 h subjected to a 30-min extinction training session. Immediately after this session, the rats received i.p. injections of vehicle or ACTZ (30 mg/kg). A 3-min retention test was performed at 24 h after the extinction training session. Rats were euthanized at 90 min after the retention test. Representative photomicrographs showing the effect of vehicle or ACTZ on c-Fos protein expression in the vmPFC.

CONCLUSION

The engagement of CAs in some brain regions is essential to ensure the consolidation of fear extinction memory.

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