SPIRONOLACTONE ENHANCES EXTINCTION OF CONTEXTUAL FEAR: A POTENTIAL THERAPEUTIC FOR POST-TRAUMATIC STRESS DISORDER?

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INTRODUCTION

- Patients with post-traumatic stress disorder (PTSD) exhibit a combination of memory intensification (or extinction impairment) and memory deficits.
- Glucocorticoids have a role in memory formation, and they may contribute to memory changes in PTSD.
- Glucocorticoids have an important role in aversive memory (Roozendal et al., 2006)
- Small pilot study (n=3 patients with PTSD) showed that a small daily dose of cortisol could reduce the frequency or intensity of feelings associated with a traumatic event (Aerni et al., 2004)
- Cortisol acts through mineralocorticoid (MRs) or glucocorticoid receptors (GRs)

OBJECTIVES

Thus, the objective of the present study was to evaluate the effect of

- Spironolactone (an MR antagonist)
- Mifepristone (a GR antagonist)
- Dexamethasone (a GR agonist)

on the extinction of contextually conditioned fear, an animal model of PTSD. Propranolol was used as a positive control

METHODS

- **Adult male Wistar rats**, from our own breeding colony, under controlled conditions

GENERAL PROCEDURE

day 1 Conditioning → *24h* → day 2 Test 1 → *24h* → day 3 Test 2 → *24h* → day 4 Test 3

CONDITIONING PROCEDURE day 1

Contextual fear conditioning (training session)

Habituation in the conditioning chamber for 3 min => foot shock (1 seg 1.5 mA) => remain in the chamber + 1min after shock
Pamplona et al. 2006

EXTINCTION (TEST) PROCEDURE day 2 => day 4

Memory index => freezing behaviour in non-reinforced re-exposures to the context (test sessions). An animal was considered frozen when it presented a stereotypical crouching position with complete immobility, except for breathing movements.

STATISTICAL ANALYSIS: two-way ANOVA with treatment type as the independent factor and session number as the dependent factor. After establishing significant differences by ANOVA, differences between groups were evaluated by post hoc Student's t-test or one-way ANOVA followed by the Newman-Keuls test. The accepted level of significance for the tests was p≤0.05.

RESULTS

PRE-TEST: PROPRANOLOL

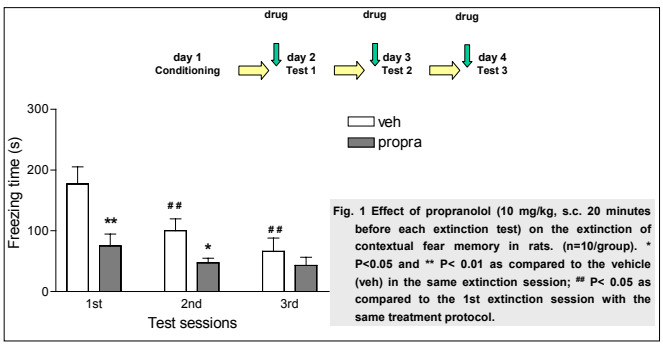


Fig. 1 Effect of propranolol (10 mg/kg, s.c. 20 minutes before each extinction test) on the extinction of contextual fear memory in rats. (n=10/group). * P<0.05 and ** P< 0.01 as compared to the vehicle (veh) in the same extinction session; ## P< 0.05 as compared to the 1st extinction session with the same treatment protocol.

RESULTS

PRE-TEST: (A) SPIRONOLACTONE; (B) MIFEPRISTONE; (C) DEXAMETHASONE

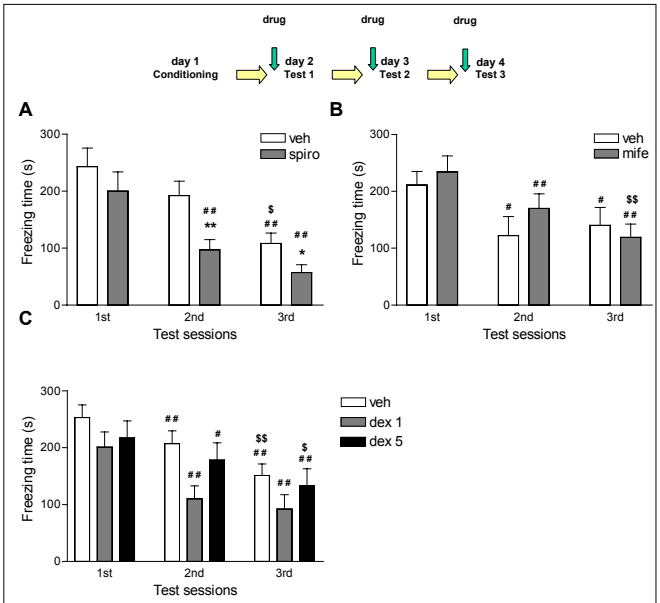
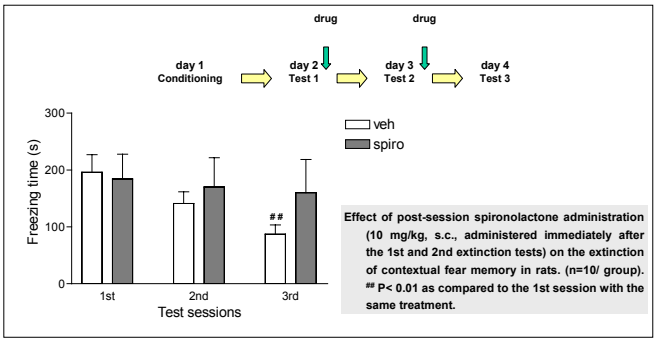


Fig. 2 - Effect of (A) spironolactone (10 mg/kg, s.c.), (B) mifepristone (10 mg/kg, s.c.), or (C) dexamethasone (1 and 5 mg/kg, i.p.) 20 minutes before each extinction test on the extinction of contextual fear memory in rats (n=10-20/ group).
* P<0.05 and ** P< 0.01 as compared to the vehicle (veh) in the same test session.
# P < 0.05 and ## P< 0.01 as compared to the 1st extinction session with the same treatment;
$ P < 0.05 and $$ P< 0.01 as compared to the 2nd extinction session with the same treatment.

POST-TEST: SPIRONOLACTONE



Effect of post-session spironolactone administration (10 mg/kg, s.c., administered immediately after the 1st and 2nd extinction tests) on the extinction of contextual fear memory in rats. (n=10/ group).
P< 0.01 as compared to the 1st session with the same treatment.

CONCLUSIONS

The results showed that:

- Spironolactone increased the extinction of an aversive memory (but only when administered before extinction sessions) => this can indicate an impairment in memory retrieval and not an increase of a new learning (association between context and shock absence).
- neither Dexamethasone nor Mifepristone treatment had any effect.
- as expected, Propranolol (positive control) administered before a test session increased memory extinction.

These results indicate that MR antagonists may be an option for the treatment of PTSD.

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There is no conflict of interest