ATYPICAL ANXIOLYTIC ACTIVITY OF PREGABALIN IN RODENTS

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INTRODUCTION

Pregabalin is occasionally used in the treatment of anxiety disorders. However, the anxiolytic-like activity of pregabalin is less extensively described in the literature compared with its reported anticonvulsant or analgesic activity. The present study aimed to characterize the effects of pregabalin in standard tests of anxiolytic-like activity in rodents.

MATERIAL & METHODS

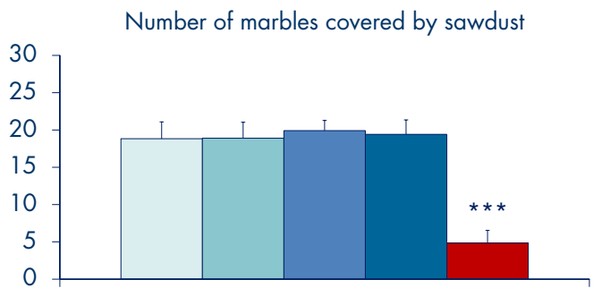
- **Treatment:** Pregabalin was dispersed in 0.2% hydroxypropylmethylcellulose in physiological saline and was administered intraperitoneally (i.p.), either immediately (Irwin test) or 30, 60, 90 and 120 minutes before the test (tests for anxiolytic-like efficacy). The administration volume was 5 or 10 ml/kg in the rat or in the mouse, respectively.
- **Experimental conditions:**
  - Irwin test: Behavioral symptoms in mice or rats were evaluated at different time-points (15, 30, 60, 120, 180 and 240 minutes) after administration.
  - Marble Burying test: Mice were placed in cages containing 25 marbles placed on a sawdust-covered floor. The number of marbles covered by sawdust was counted after a 30-minute period. Mice display digging behavior, this induces sinking of marbles below the surface of sawdust. Digging is decreased by anxiolytics.
  - Elevated Plus-Maze test: Mice or rats were placed in 4-arm mazes arranged in the form of a plus sign (+), two opposite arms were enclosed by walls and the two other arms were open and illuminated. The number of entries and the time spent in open arms was measured. Anxiolytics increase exploration of the open arms.
  - Vogel Conflict test: Rats deprived of water were placed in the presence of a water spout connected to an electric shock generator. Rats received electric shocks (1.7 mA) 2 seconds after they started to drink. The number of punished drinks was counted during a 3-minute test. Anxiolytics increase punished drinking.
  - Fear Potentiated Startle test: Rats were placed in plastic cylinders enclosed in startle chambers and the size of their movements was measured by a strain gauge. During the conditioning sessions (2 consecutive days), rats received electric shocks (0.4 mA) paired with a 3-second cue light. The day following conditioning, the startle reaction was measured with or without light. The FPS effect consists of an increase of startle reaction in presence of light and it is reversed by anxiolytics.
- **Statistical analysis:** Student's t tests, no indication = not significant; * = $p < 0.05$; ** $p < 0.001$ and *** = $p < 0.001$, as compared with vehicle control.

RESULTS

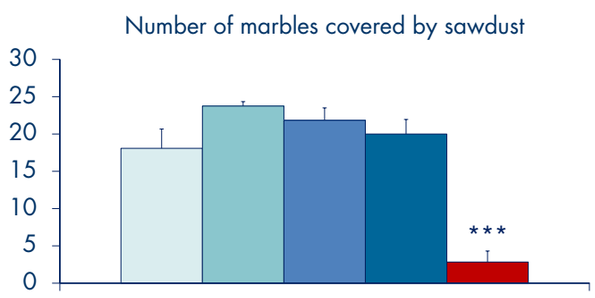
- In the Irwin test, pregabalin was devoid of effects in the mouse up to 60 mg/kg whereas it displayed weak sedative effects in the rat at 30 mg/kg i.p. starting 90 minutes after administration.
- Based on these data, the doses of 10, 30 and 60 and of 3, 10 and 30 mg/kg i.p. were chosen for the evaluation of anxiolytic-like activity in the mouse and in the rat, respectively.

Fig.1: MARBLE BURYING TEST

a) First experiment (pre-treatment 30 minutes)



b) Second experiment (pre-treatment 90 minutes)

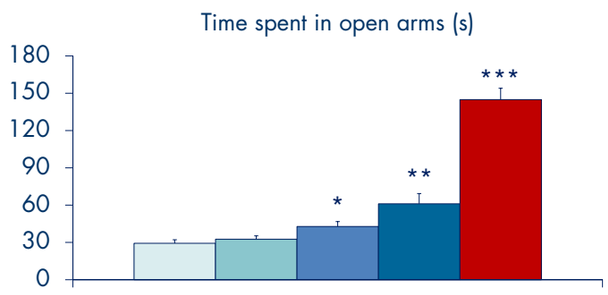


Vehicle (0.2% HPMC i.p.) control
Pregabalin 10 mg/kg i.p.
Pregabalin 30 mg/kg i.p.
Pregabalin 60 mg/kg i.p.
Clobazam 8 mg/kg i.p.

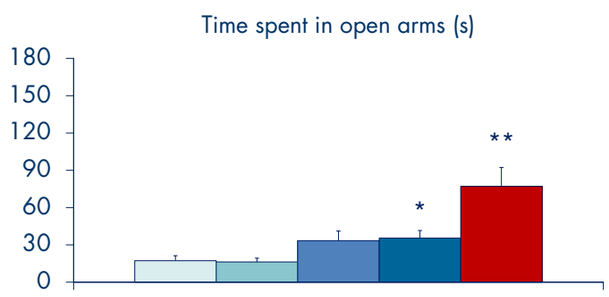
➢ **Figure 1**: pregabalin was devoid of anxiolytic-like activity at 10, 30 and 60 mg/kg i.p. This was confirmed in two separate experiments, conducted either 30 or 90 minutes after administration.
N=12 mice/group.

Fig.2: ELEVATED PLUS-MAZE TEST

a) Test performed in the mouse (pre-treatment 90 minutes)



b) Test performed in the rat (pre-treatment 120 minutes)

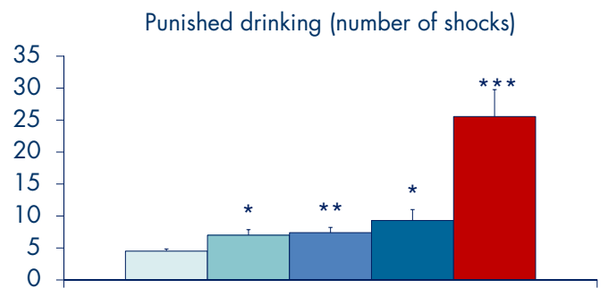


Vehicle (0.2% HPMC i.p.) control
Pregabalin 10 (mouse) or 3 mg/kg i.p. (rat)
Pregabalin 30 (mouse) or 10 mg/kg i.p. (rat)
Pregabalin 60 (mouse) or 30 mg/kg i.p. (rat)
Clobazam 8 (mouse) or 16 mg/kg i.p. (rat)

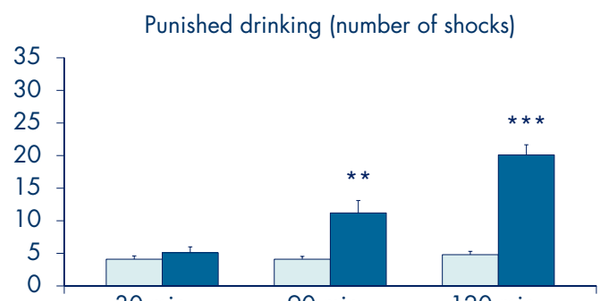
➢ **Figure 2**: a) in the mouse, pregabalin significantly and dose-dependently increased the time spent in the open arms at 30 and 60 mg/kg i.p.
b) in the rat, pregabalin weakly increased the exploration of open arms at 30 mg/kg i.p.
N = 10 animals/group.

Fig.3: VOGEL CONFLICT TEST

a) First experiment (pre-treatment 60 minutes)



b) Second experiment (pre-treatment 30, 90 or 120 minutes)



Vehicle (0.2% HPMC i.p.) control
Pregabalin 3 mg/kg i.p.
Pregabalin 10 mg/kg i.p.
Pregabalin 30 mg/kg i.p.
Clobazam 32 mg/kg i.p.

➢ **Figure 3**: a) pregabalin significantly and dose-dependently increased punished drinking at 3, 10 and 30 mg/kg i.p.
b) pregabalin at 30 mg/kg i.p. increased punished drinking and its efficacy increased with longer pre-treatment times.
N = 10 rats/group.

- Pregabalin at 3, 10 and 30 mg/kg i.p. was devoid of effects in the fear-potentiated test in the rat.

CONCLUSION

The present data confirm the presence of dose-dependent anxiolytic-like effects of pregabalin in the Elevated Plus-Maze and the Vogel Conflict tests in rodents. Nevertheless, the absence of activity in the marble burying test at doses observed to be active in other tests in the mouse or in the rat, suggests an atypical anxiolytic profile when compared with benzodiazepines.

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