PREGABALIN HAS AN ATYPICAL PROFILE OF ANXIOLYTIC-LIKE ACTIVITY 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 as compared to 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.

METHODS

- **Treatment**: Pregabalin was prepared 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.
- **Irwin test**: Behavioral symptoms in mice or rats were evaluated at different time-points (15, 30, 60, 120, 180 and 240 minutes) after administration of pregabalin.
- **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 the 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 over a 3-minute test. Anxiolytics increase punished drinking.
- **Fear Potentiated Startle (FPS) test**: Rats were placed in plastic cylinders enclosed in startle chambers and the magnitude 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 in an increase of startle reaction in presence of light and it is reversed by anxiolytics.

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 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)

### 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)

### Fig. 3: Vogel conflict test

- **a)** First experiment (pre-treatment 60 minutes)
- **b)** Second experiment (pre-treatment 30, 90 or 120 minutes)

**Statistics**: Student’s t tests, no indication = not significant; * = p < 0.05; ** p < 0.001 and *** = p < 0.001, as compared with vehicle control.

**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.

**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.

**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 increase with longer pre-treatment times.

N = 10 rats/group.

CONCLUSION

The present data confirm 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 of pregabalin when compared with benzodiazepines.