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Neuroscience Letters 412 (2007) 159–162
Neuroscience Letters
www.elsevier.com/locate/neulet

Prazosin increases immobility episodes in *taiep* rats without changes in the properties of α_1 receptors

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Received 26 September 2006; received in revised form 31 October 2006; accepted 31 October 2006

Abstract

The *taiep* rat is a myelin mutant in which immobility episodes (IEs) can be induced in adult males by gripping. EEG recordings during gripping-induced IEs show a rapid eye movement (REM) sleep-like pattern, similar to that reported for narcolepsy-cataplexy suggesting that IEs represent a disorder of REM-sleep. An α_2 adrenoceptor agonist increases gripping-induced IEs, whereas α_2 antagonists decrease these. We have studied the effect of prazosin on IEs and the levels of α_1 adrenoceptors were evaluated in cerebro-cortical homogenates of *taiep* and control rats. Systemic administration of prazosin results in a significant increase in both the frequency and duration of gripping-induced IEs. Our results show that cerebro-cortical tissue is not an adequate candidate for the expression of cataplexy-like symptoms, but prazosin, an α_1 antagonist, is a potent inducer of gripping-induced immobility episodes in *taiep* rats.
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Keywords: Narcolepsy; Cataplexy; Noradrenaline; Myelin mutant; REM sleep; Monoamines

Taiep rats carry a hereditary autosomal, recessive myelin disorder that leads to the development of a progressive neurological syndrome, which is characterized by tremor, ataxia, immobility episodes (IEs), epilepsy, and finally paralysis of the hindlimbs [8]. The rats were named after the acronym (*taiep*) of the symptoms and morphologically show hypomyelination followed by progressive demyelination of the CNS axons [11]. Ultrastructurally, oligodendrocytes reveal an accumulation of microtubules leading to alterations in transport mechanisms [5,18].

At age 8–12 months, both spontaneous and gripping-induced IEs are observed in *taiep* rats, with males being more susceptible [4]. Electroencephalographic (EEG) recordings obtained during IEs resemble those characteristic of rapid eye movement (REM) sleep [4] suggesting that IEs represent a disorder of REM sleep generation similar to narcolepsy-cataplexy in canines [17].

Adrenergic transmission appears to be involved in gripping-induced IEs in *taiep* rats because systemic administration of α_2 agonists significantly increased their frequency and duration, whereas α_2 antagonists decrease these [6]. Prazosin, a well-known antihypertensive agent acting as selective antagonist at α_1 adrenoceptors, is also a potent inducer of cataplexy episodes in dogs and humans [1,7,14,15]. In this work, we tested the effect of systemic prazosin on gripping-induced IEs in *taiep* rats and searched for possible changes in the expression of brain α_1 adrenoceptors by analyzing the binding of [^{3}H]-prazosin to cerebro-cortical homogenates.

Taiep rats were supplied by our animal house facilities. Animals were under a 12:12 h light:dark cycle (lights on at 07:00 h), at 21 ± 2 °C and 30–45% relative humidity, with free access to water and food. Rats were tested at 08:00 h, at the peak in susceptibility to gripping-induced IEs [4].

Tests were done in acrylic cages. The IEs were induced by sequentially gripping the base of the rat's tail and 5 min later gripping around the thorax for 10 s. If an IE is not induced, the animal is put into the observation box [4]. The duration of the IE and the latency to the first IE were recorded.

Prazosin hydrochloride (25–800 μg/kg) and WB-4101 hydrochloride (1–1000 μg/kg) were purchased from Sigma–Aldrich. The drugs were freshly dissolved in sterile water, expressed as a free drug, and the dosage volume adjusted to 1 mL/kg weight of rat. Animals received an intraperitoneal injection of sterile water as a control and then prazosin in an increasing dose scheme every 48 h. Behavioral analysis was

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0304-3940/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2006.10.048

made by two observers, one of them blind to the drug tested. Analysis of data were done with a χ^2-test, followed by a Dunn's test with $P < 0.05$ considered statistically significant [20].

Before each gripping-induced IE, we measured the behavioral state of the rats as (0)-indicating somnolence, (1)-quiet rat, (2)-low activity such as sniffing and horizontal head movements, (3)-regular activity as grooming, scratching, and locomotion, and (4)-high activity indicating displacement and other motor activities such as grooming, scratching, or even jumping behavior [6]. Somnolence was characterized by closed eyes, no movement, and regular respiration.

The binding of [^{3}H]-prazosin to the cerebral cortex homogenates was determined in age-matched control and *taiep* rats. The animals were killed by decapitation, the brains were quickly removed, and the cerebral cortex was dissected out. Tissues were individually placed into plastic tubes, frozen by immersion in liquid nitrogen, and stored at −70 °C. On the day of the binding assay, tissues were individually homogenized in 20 volumes of 10 mM TRIS–HCl buffer, pH 7.4, containing 1 mM EGTA. The homogenates were centrifuged at 20,000 × *g* for 30 min and the pellets resuspended in 10 mM TRIS–HCl buffer and centrifuged again. Pellets thus formed were resuspended (∼4 mg protein/mL) [10] in incubation buffer (50 mM TRIS–HCl, 140 mM NaCl, 5 mM $MgCl_2$, pH 7.4).

The radioligand assays were done simultaneously and contained 1 mL buffer, 2 nM [^{3}H]-prazosin (77.2 Ci/mmol, New England Nuclear), ∼400 μg protein, and increasing concentrations (10^{-10} M–10^{-6} M) of unlabelled prazosin. Equilibration was for 45 min at 25 °C and termination of the reaction was by filtration through Whatman GF/B glass fiber paper presoaked in 0.3% polyethylenimine. Nonspecific binding was determined as that insensitive to 10 μM phentolamine (Sigma) and accounted for 25–30% of total binding. Radioactivity was measured by scintillation counting. Inhibition curves were fitted by a nonlinear regression to a logistic (Hill) equation using the program Prism 4.03 (GraphPad). Values for the dissociation constant (K_d) were calculated according to the equation $K_d = IC_{50} - (\text{concentration of } [^3\text{H}]\text{-prazosin})$. The maximum binding ($B_{max}$) was estimated by correcting for fractional occupancy (α) by using the equation $\alpha = K_a\,[D]/\{K_a\,[D] + 1\}$, where K_a is the affinity constant ($1/K_d$) and [D] is the concentration of [^{3}H]-prazosin (2 nM).

All procedures described in this study were in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Mexican Council for Animal Care as approved by the BUAP Animal Care Committee and are also in accordance with guide for the care and use of laboratory animals [3].

The prazosin dose range was 25–800 μg/kg in increasing successive doses at 48 h intervals. No signs of behavioral alteration or discomfort were observed with this dose scheme.

Fig. 1A shows that whereas prazosin doses between 25 and 200 μg/kg had no effect on gripping-induced IEs, the two highest doses tested (400 and 800 μg/kg) did induce a statistically significant increase in the analyzed behavior (χ^2-test = 29.9, d.f. = 6, $P < 0.001$, followed by Dunn's test, $P < 0.05$) with a maximum effect of 216 ± 22% of control (8.2 ± 0.6 versus 3.8 ± 0.7 IEs, mean ± S.E.M., $n = 7$).

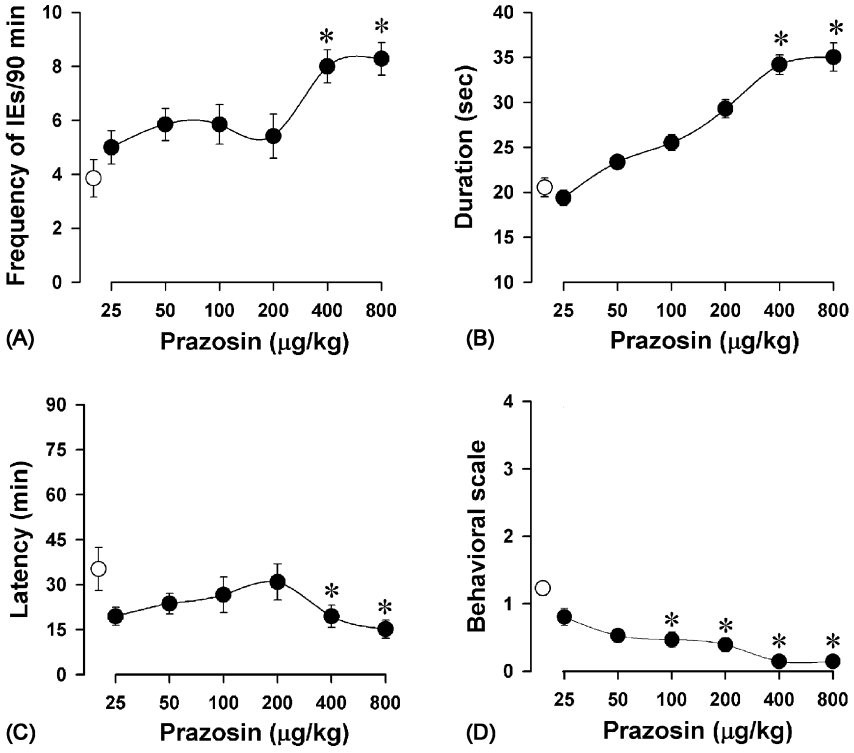

Fig. 1. Effect of prazosin on the frequency and duration of gripping-induced immobility episodes in *taiep* rats. Values are expressed as means ± S.E.M. A) At 400 and 800 μg/kg prazosin induces a significant increase in the frequency of gripping-induced IEs ($^*P < 0.05$, χ^2-test = 29.9, d.f. = 6, $P < 0.001$, followed by Dunn's test $P < 0.05$). B) The same prazosin doses produced a significant increase in the mean IE duration ($^*P < 0.05$, χ^2-test = 36.8, d.f. = 6, $P < 0.001$, followed by Dunn's test).

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