Characterization of the Spontaneous and Gripping-Induced Immobility Episodes on *taiep* Rats

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ABSTRACT In 1989, we described a new autosomic-recessive myelin-mutant rat that develops a progressive motor syndrome characterized by tremor, ataxia, immobility episodes (IEs), epilepsy, and paralysis. *taiep* is the acronym of these symptoms. The rat developed a hypomyelination, followed by demyelination. At an age of 7–8 months, *taiep* rats developed IEs, characterized electroencephalographically by REM sleep-like cortical activity. In our study, we analyzed the ontogeny of gripping-induced IEs between 5 and 18 months, their dependence to light–dark changes, sexual dimorphism, and susceptibility to mild stress. Our results showed that IEs start at an age of 6.5 months, with a peak frequency between 8.5 and 9.5 months. IEs have two peaks, one in the morning (0800–1000 h) and a second peak in the middle of the night (2300–0100 h). Spontaneous IEs showed an even distribution with a mean of 3 IEs every 2 h. IEs are sexually dimorphic being more common in male rats. The IEs can be induced by gripping the rat by the tail or the thorax, but most of the IEs were produced by gripping the tail. Mild stress produced by i.p. injection of physiological saline significantly decreased IEs.

These results suggested that IEs are dependent on several biological variables, which are caused by hypomyelination, followed by demyelization, which causes alterations in the brainstem and hypothalamic mechanisms responsible for the sleep–wake cycle regulation, producing emergence of REM sleep-like behavior during awake periods. **Synapse 58:95–101, 2005.**

INTRODUCTION

Taiep rats were described in 1989 by Holmgren et al. The name of this myelin mutant is the acronym of tremor, ataxia, immobility episodes (IEs), epilepsy, and paralysis (Holmgren et al., 1989). The main anatomical finding is a progressive deterioration of the central myelin, but not the peripheral myelin (Duncan et al., 1992). At the ultrastructural level, *taiep* rats show an accumulation of microtubules in the cytoplasm and processes in the oligodendrocytes (Couve et al., 1997; Duncan et al., 1992). The accumulation of microtubules disrupts the normal transit of newly synthesized proteins and messenger RNA (mRNA) to form myelin. It was suggested by Song et al. (2003) that the impairment of two myelin-associated proteins (MAPs), kinesin and dynein, are responsible for the deficit in the transporting mechanisms of mRNA and proteins between the nucleus and the processes in olygodendrocytes when grown under in vitro conditions.

Biochemically, *taiep* rats showed a general decrease of all major myelin proteins; myelin basic protein (MBP), proteolipid protein (PLP), 2′,3′-cyclic nucleotide-3′-phosphodiesterase (CNP), and myelin-associated glycoprotein (MAG) (Möller et al., 1997), indicating a general impairment of all proteins that constitute myelin in this mutant. These low levels of myelin are not caused by decreased synthesis, because the

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transcriptional activity is similar for PLP and CNP. However, for MBP the mRNA transcripts decrease with age and hence their concentration within oligodendrocyte cell bodies, instead of their being uniformly distributed throughout processes, as shown by in situ hybridization (O'Connor et al., 2000). Not all the white tracts were equally affected; in *taiep* rats the demyelization affects the optic nerves, and the corticospinal and the gracilis pathways more than other white matter tracts in the spinal cord (Lunn et al., 1997). Song et al. (2001) showed that the anterior medullary velum of the cerebellum, which only has thinner axons, is more affected in its myelin sheath in 1-year-old *taiep* rats. These findings probably are correlated with the expression of SNS-PN3 sodium channels in cerebellar Purkinje cells in 1-year-old *taiep* rats (Black et al., 1999), probably caused by a change in the neuron–glia interactions. There are no alterations in this type of sodium voltage-gated channel expression before one year, which indicates that the alteration in the expression of sodium channels is probably related to later stages of demyelination and glial activation. In *taiep* rats this is probably caused by an additional mechanism, such as the activation of glia and the production of cytokines and its products in the CNS (León-Chavez et al., 2001, 2003).

In 1991, Prieto et al. described *taiep* rats as a model of narcolepsy-cataplexy because during IEs the electroencephalographic recordings (EEG) in the cerebral cortex show a desynchronized activity associated with theta rhythm in the hippocampus. Another EEG finding, obtained during short recording times (3 h) in the light phase, showed a disorganization of the sleep pattern, which was also correlated with a decrease in the eye movement density in *taiep* rats (Anch and Laposky, 2000; Prieto et al., 1991). All these findings indicated that *taiep* rats show EEG and sleep alterations similar to that observed in canine and human narcolepsy (Aldrich, 1992; Nishino and Mignot, 1997).

In our study, we analyzed the influence of several variables on gripping-induced IEs, such as development, light–dark cycle, sexual dimorphism, and the role of mild stress produced by i.p. injection and a sequence to induce IEs. Part of these data was presented in abstract form (Eguibar et al., 2000).

MATERIALS AND METHODS

General procedures

The experiments were made on *taiep* rats supplied by our animal room facilities. The animals were under a 12:12 light–dark cycle, with the lights on at 0700 h, and with a controlled temperature (21 ± 2)°C and relative humidity of 40–60%. The animals were maintained in collective acrylic cages, with free access to balanced rodent pellets (5008, PMI Laboratories) and tap water. The procedures described here have been done in compliance with the policies of the Society for the Neuroscience for scientific research and also with the guidelines of the Laws and Codes of the Mexican government approved in the Seventh title of the Regulations of the General Law of Health regarding Health Research.

Procedures

The immobility was induced by an alternate method of gripping *taiep* rats every 5 min. We started all the experiments by gripping the rat at the base of the tail (1–2 cm from the base), followed by gripping it around the thorax. The test was done in acrylic cages (21 × 24.5 × 35 cm) with the bottom covered with wood shavings (Beta chip). The total duration of the tests was 120 min, and so the maximum score of gripping-induced immobility is 24. We also recorded the total duration in seconds of each IE and the absolute latency to the first IE. The IE was characterized by immobility, i.e., there is a loss of support associated with an increase in muscle tone and Straub tail. In some IEs, the rat shows mioclonic movements.

EEG recording

The spontaneous IEs were recorded over a 24-h EEG on male *taiep* rats, using a video EEG recording system (Stellate System, Canada). Two stainless steel electrodes were implanted in the cortex, two in the neck muscles, one in the eye's orbit, and one bipolar electrode in the hippocampus in rats under choral hydrate anesthesia.

RESULTS

Behavioral and EEG characterization of IEs in *taiep* rats

The gripping-induced IEs are characterized by a sudden loss of the antigravitatory reflexes, contracture of the facial musculature, with the ears flattening behind the cranium of the rats so that a characteristic facies is expressed as shown in Figure 1A. During an IE, the EEG shows desynchronized activity with low theta rhythm in the hippocampus (5.73 ± 0.05 Hz), see Figure 1B, with or without Straub tail. At the end of each IE, the animal recovers the normal facial expression and begins vertical movements of the head and the body. Fast Fourier transform of the signal obtained in the hippocampus shows a peak of 5.8 ± 0.05 Hz during 43 gripping-induced IEs, suggesting REM-like sleep characteristics during IEs.

Development of gripping-induced IEs in male and female *taiep* rats

To characterize the ontogeny of gripping-induced IEs, we analyzed 13 male and 13 female rats between ages 5 and 18 months. Figure 2 showed that

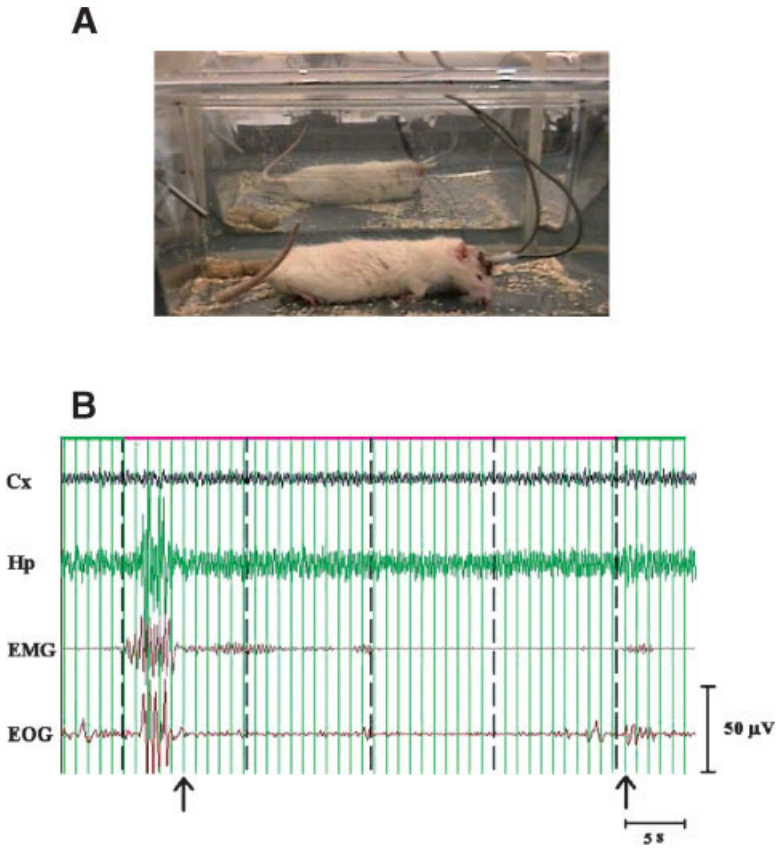

Fig. 1. A *taiep* rat during an immobility episode and simultaneous polysomnographic EEG recordings. (**A**) A *taiep* rat during an IE. See the increase in muscle tone, Straub tail, and characteristic facies produced by the retraction of facial musculature. (**B**) During IE the cerebral cortex is desynchronized (black trace) and low theta rhythm in the hippocampus is recorded (green trace). Note that when the IE starts (left arrowhead) there is an increase of EMG (brown trace) followed by a progressive decrease to reach the same amplitude as before the initiation of the immobility reflex response (right arrowhead).

gripping-induced IEs started at 6.5 months and increased gradually until they reach a maximum frequency between 8.5 and 9.5 months, decreasing gradually to 12 months and then maintaining a low frequency between 12 and 18 months. In general, male IE frequencies are greater than those in female *taiep* rats (MANOVA, $F_{(1,\ 19)} = 6.21$, $P < 0.02$). The age factor was statistically significant (MANOVA, $F_{(12,8)} = 4.59$, $P < 0.02$). A two-way analysis of variance shows differences caused by gender ($F_{(1,\ 67)} = 30.22$, $P < 0.001$) and age ($F_{(12,\ 25)} = 11.29$, $P < 0.001$) and an interaction between factors ($F_{(12,\ 4.53)} = 2.04$, $P < 0.02$). A post hoc Tukey test ($P < 0.05$) shows statistical differences from 8 to 9.5 months between genders. There are also statistical differences between 5, 5.5, 6, and 6.5 months compared with IE frequencies shown at 8, 8.5, 9, 9.5, 10, 10.5, and 11 months in *taiep* male rats.

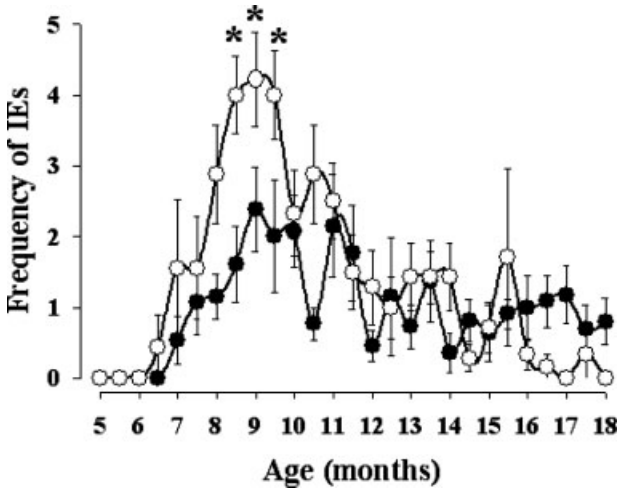

Fig. 2. Ontogenetical development of gripping-induced IEs in male and female *taiep* rats. The mean frequency ± standard deviation of gripping-induced IEs in male *taiep* rats. Male *taiep* rats (empty circle) start early immobilities at 6.5 months that increase with age to reach statistically significant peaks between 8.5 and 9.5 months and a reduction afterwards. Female *taiep* rats show a similar pattern but with lower mean scores than males.

Spontaneous and gripping-induced IEs in male *taiep* rats vary during the light–dark cycle

Figure 3A shows a light–dark oscillation in the susceptibility to gripping-induced IEs in male *taiep* rats at an age of 8 months (Kruskal-Wallis one-way ANOVA, $H = 43.6$, $n = 7$, $P < 0.0002$). A post hoc Dunn's test ($P < 0.05$) shows differences between the 8–10 h periods compared with the 3–5 h or 15–17 h periods. However, spontaneous IEs are evenly distributed throughout the dark–light cycle with a mean frequency of 3 IEs every 2 h (Fig. 3B). The mean duration of 177 spontaneous IEs was 53.1 ± 1.9 s, which was statistically greater than 24.2 ± 0.3 s, the mean

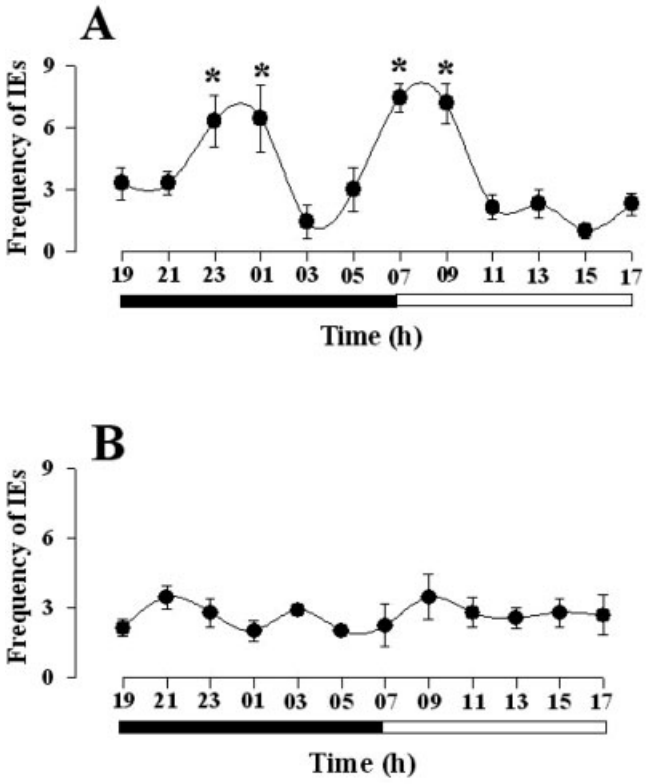

Fig. 3. Changes in the frequency of gripping-induced IEs during the circadian cycle. (**A**) Male *taiep* rats at 8 months show two statistically different peaks in their susceptibility to exhibit gripping-induced IEs, one at midnight (2300–0100 h) and the second at the beginning of the light phase (0700–0900 h). (**B**) Spontaneous IEs during 24-h EEG recording on 8-month *taiep* rats. Note that the frequency of IEs does not show any oscillation during the 24 h of the light–dark cycle. On average, IEs occurred 3 times every 2 h, which contrasts with the frequency of gripping-induced IEs that oscillate during the light–dark phase with two peaks of susceptibility.

duration of 321 gripping-induced IEs analyzed (Student's t-test, $t = 19.01$, $df = 496$, $P < 0.001$).

Gripping-induced IEs on male and female *taiep* rats show sexual dimorphism

To further characterize the differences between genders, Figure 4 shows the frequency and mean duration of IEs in male and female rats at ages 7 and 8 months. Male rats have higher IE frequencies at 7 months (6.5 ± 0.4 IEs ($n = 13$)) and 8 months (4.0 ± 0.6 IEs ($n = 9$)) than female rats with 3.2 ± 0.3 ($n = 11$) and 2.0 ± 0.8 ($n = 11$) at 7 and 8 months. These frequencies are statistically different between genders at both the ages tested (Mann-Whitney U test; $U = 195.5$, $P < 0.001$ at 7 months and $U = 106.5$, $P < 0.001$ at 8 months).

The mean durations of gripping-induced IEs are statistically different in male *taiep* rats at 27.6 ± 0.8 s ($n = 14$) and female *taiep* rats at 22.5 ± 0.1 s ($n = 11$) at 7 months (Student's t-test; $t = 5.12$, $df = 10$, $P < 0.001$). This is also true at 8 months with a mean duration of IEs in males at 26.7 ± 0.1 s ($n = 13$) compared with 23.5 ± 0.2 s ($n = 11$) for female rats (Student's t-test; $t = 14.25$, $df = 22$, $P < 0.001$).

Middle stress significantly reduces IE frequency

We explored the effects of stress on the induction of IEs. For this, we used an i.p. injection of saline solution because we are interested in the effects produced by the systemic administration of drugs on IEs. The i.p. injection produced a significant reduction in the mean frequency of gripping-induced IEs from 5.5 ± 0.4 ($n = 35$) to 4.3 ± 0.3 ($n = 36$) after the injection (Mann-Whitney U test; $U = 2.41$, $df = 114$, $P < 0.02$); see Figure 5.

Manipulation sequence is important for the susceptibility of gripping-induced IEs in male *taiep* rats

IEs can be induced when the rat was gripped from the base of the tail or when it is gripped around the thorax. We analyzed their dependence on the sequence of manipulation: tail–tail (T–T), body–body (B–B), tail–body (T–B), and body–tail (B–T) with a random sequence used on 13 male rats at 8 months. The results show a strong dependence on the sequence with the T–T to be the most effective (ANOVA of ranks $H = 26.4$, $df = 3$, $P < 0.001$). A post hoc comparison using Dunn's test showed statistical differences between the B–B maneuver compared with the other sequences used to induce IEs ($P < 0.05$; see Fig. 6).

DISCUSSION

Our study focused on the dependence of some environmental and biological variables that could influence the susceptibility of *taiep* rats to express gripping-induced IEs. Our results showed that the light–dark cycle has an influence on the susceptibility with two peaks; one early in the morning after the active period of the rat, probably caused by the accumulation of the homeostatic influences that control REM sleep (Franken et al., 1991). The second peak was in the middle of the night probably caused by the disorganization of the REM sleep that produces an increase in the susceptibility to show REM during the active period in *taiep* rats. Narcoleptic dogs show a unorganized rhythm of their activity cycle during the light–dark phases (Nishino et al., 1997), and it is also true with the *taiep* rat (Cortés et al., 2004). Unpublished results suggest some alteration in the circadian pacemaker mechanisms caused, at least in part, by demyelination.

For the ontogeny of gripping-induced IEs, we demonstrated that it is a temporal window in which the susceptibility to exhibit IEs is maximum between age

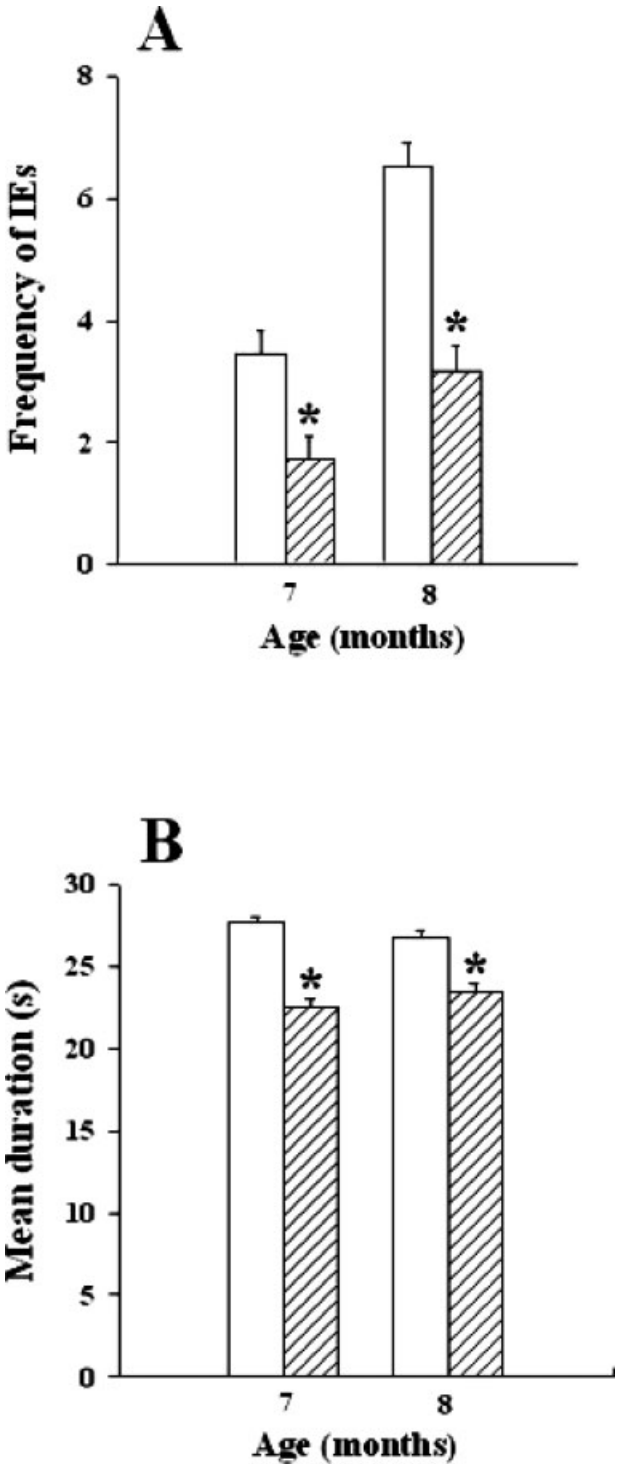

Fig. 4. Sexual dimorphism in gripping-induced IEs at two different ages. Panel (**A**) shows mean scores ± SEM of gripping-induced IEs in male (empty bars) and female *taiep* rats (hatched bars) at 7 and 8 months. The mean ± s scores are shown and they are statistically different between genders (Mann-Whitney U test; $U = 195.5$, $P < 0.0001$ at 7 months; $U = 106.5$, $P < 0.001$ at 8 months). Panel (**B**) shows the mean duration ± SEM of gripping-induced IEs in male (empty bars) and female (hatched bars) *taiep* rats.

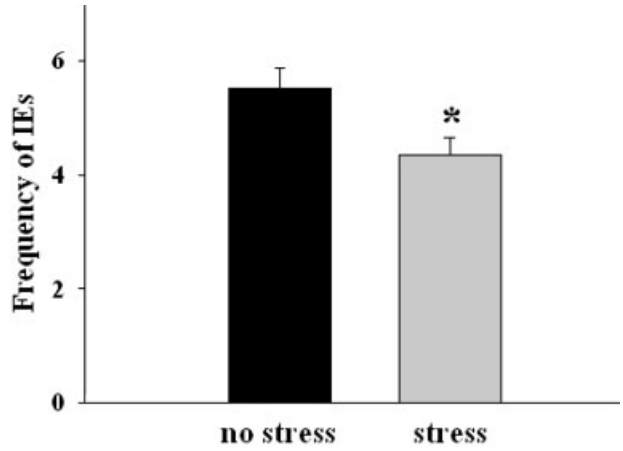

Fig. 5. Stress produced by i.p. injection diminished gripping-induced IEs. The i.p. injection (1 ml/kg) produced a statistically significant reduction of the gripping-induced IEs (Mann-Whitney U test: $U = 2.41$, $P < 0.02$) caused by stress mechanisms.

8 and 10 months. After that, a decrease of IEs is obtained, probably as a result of the plastic changes that took place in the CNS of *taiep* rats caused by the progressive demyelination and by glial activation during the rat's development (León-Chavez et al., 2001, 2003; Lunn et al., 1997). For the narcoleptic dog, it has been shown that axonal degeneration occurs in several parts of the CNS; the amygdala, septum, diagonal band of Broca, and the adjacent forebrain areas, which are progressive during development (Siegel et al., 1999). In canine narcoleptics and *taiep* rats, a progressive axonal degeneration occurs in the CNS and subsequent activation of glial cells occurs, which apparently disrupts the sleep–wake cycle (Krsulovic et al., 1999; Lunn et al., 1997; Siegel et al., 1999) and could be responsible for the alteration in the brainstem mechanisms that regulate muscle tone.

In Doberman puppies, Riehl et al. (1998) demonstrated that the median age of onset of cataplexy was at 7 weeks. The severity of cataplexy increased with the age of the dog and reached a plateau between 16 and 24 weeks (Riehl et al., 1998). This progression is correlated with the progressive gliosis in the CNS of the narcoleptic dog (Siegel et al., 1999). The *taiep* rat also shows a progression with age (see Fig. 3) and this is associated with progressive gliosis in the CNS (Krsulovic et al., 1999; León-Chavez et al., 2001). It is also true with the variation in the rest–activity cycle, which is disorganized in narcoleptic dogs (Nishino et al., 1997) and in narcoleptic humans (Middelkoop et al., 1995). Unpublished data from our laboratory also show that *taiep* rats also have an alteration in the organization of the sleep–wake cycle (Cortés et al., 2004).

Narcoleptic female dogs are more susceptible than male dogs to the food-elicited cataplexy test (FECT) and the play-elicited cataplexy test (PECT), and also to the cumulative time that dogs spent in cataplexy

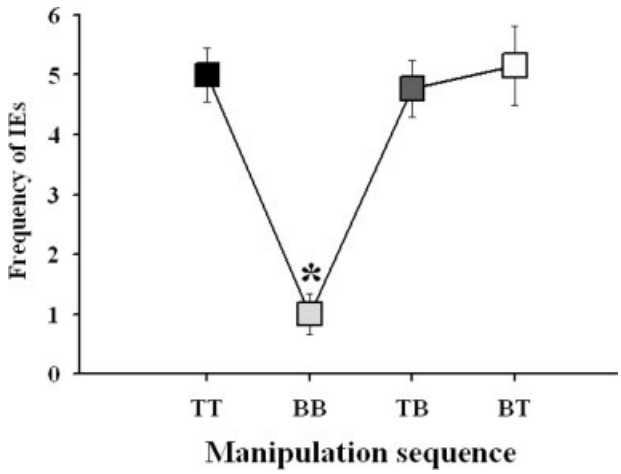

Fig. 6. Manipulation from the tail is better to induce IE than the body. The tail manipulation (T) sequence is more effective in inducing IEs than the thorax (B). Note that body–body sequence is statistically different ($P < 0.05$) than the rest of sequences (T–T, T–B, and B–T) in inducing IEs.

during these tests. For *taiep* rats, the incidence of gripping-induced IEs is greater in male than in female *taiep* rats (see Fig. 2), but there is a progressive decrease in the susceptibility of gripping-induced IEs in older *taiep* male rats, indicating that the deterioration of myelin probably disrupts the mechanisms that control muscle tone. The mesopontine area and the medial reticular formation in the medulla are involved in the regulation of atonia during REM sleep and also during cataplexy in narcoleptic dogs (Lai and Siegel, 1999).

Electrical and chemical stimulations of the medial medulla produced a complete suppression of muscle tone. The neurons and pathways in this region are responsible for mediating the muscle-tone suppression that occurs during REM sleep and during cataplexy episodes in narcoleptic dogs (Lai et al., 1987; Morrison, 1983; Siegel et al., 1989). An important area is the pontomesencephalic zone including the midbrain retrorubral (RRN), ventral paralemniscal tegmental field (vTFP), reticular tegmental nucleus (TRN), and the pedunculo pontine nucleus (PPN), which are able to produce bilateral suppression of muscle tone in decerebrated cats and rats particularly in the pontine reticular formation (Lai and Siegel, 1990). Further, electrophysiological studies are necessary to elucidate which brainstem areas are involved in the gripping-induced IEs in the *taiep* rat and also those brain areas that participate in the disorganization of REM sleep. In general, all active immobility responses involve the aforementioned brainstem areas (Klemm, 1990). Our results show that *taiep* rats are a suitable model to analyze the effects of several drugs on immobility, which is similar to cataplexy shown by narcoleptic dogs. We have some evidence that dopaminergic D_2 and α adrenergic systems are similarly involved in the inmobility responses in narcoleptic dogs and *taiep* rats (Eguibar et al., 1998; Nishino and Mignot, 1997).

The IEs of *taiep* rats are similar to the behavioral arrest that is produced after specific stimuli, such as an awkward restriction position. This behavioral arrest has been described in various natural and experimental contexts, ranging from "*freeze*" behavior to catalepsy and "death feint." The common denominator in these is that the immobility is active and is active in the sense that it is induced by a stimulus and requires a degree of muscle tone (Klemm, 1990). The tonic immobility is cited either as an immobility response or immobility reflex. The conventional way to produce an immobility reflex is by inversion and manual restrait of the subject, but it is also possible to induce it by applying paper clips along the midline on the skin of the back of the neck. All these immobility responses caused similar development of high voltage, slow activity in the EEG, a reduced frequency and amount of hippocampal theta activity, and depressed spinal polysynaptic reflexes (Klemm, 1990).

In *taiep* rats, we tested several ways to produce IEs; palatable foods, olfactory stimuli, stroboscopic light, and different intensities and frequencies of sounds that are not able to induce them in a regular and predictable way. The gripping-induced IE is easy, predictable, and controllable. The minimum intertrial is about 3 min, and so 5 min between tests are sufficient to analyze the effects of environmental variables and also the effects of several drugs on gripping-induced IEs.

Because the pontine reticular formation (pontis oralis nucleus) and medial reticular formation in the medulla (magnocellularis, gigantocellularis, and paramedian nucleus) are all involved in the mediation of behavioral arrest in cataplexy, catalepsy, and active immobility reflex, future experiments will help to dilucidate the participation of the reticular formation in the IEs of *taiep* rats.

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