Dopaminergic D2-like agonists produce yawning in the myelin mutant \textit{taiep} and Sprague–Dawley rats

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Systemic administration of D2-like dopaminergic-receptor agonists increases yawning behavior. However, only a few studies have been done in animals with pathological conditions. The \textit{taiep} rat is a myelin mutant with an initial hypomyelination followed by progressive demyelination, being the brainstem one of the most affected areas. In our experiments, we analyzed the effects of systemic administration of the D2-family agonists and antagonists on yawning behavior, and correlated them with the lipid myelin content in the brainstem and other areas in the central nervous system (CNS) in 8 month old male \textit{taiep} and Sprague–Dawley rats. Subjects were maintained under standard conditions in Plexiglas cages with a 12:12 light–dark cycle, lights on at 0700 and free access to rodent pellets and tap water. Drugs were freshly prepared and injected i.p at 0800 and subjects were observed for 60 min. When antagonists were used it was administered 15 min before the agonist. Sprague–Dawley and \textit{taiep} rats significantly increased their yawning frequency after systemic injection of \textit{R}(+) -7-Hydroxy-2-(dipropylamino)tetralin hydrobromide (7-OH-DPAT) or \textit{R}(+) -3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3-b]-1,4-oxazin-9-ol hydrochloride ((±)-PD 128,907). Among D2-like agonists used higher effects were obtained with \textit{R}(+) -quinpirole. The effects caused by \textit{L}(+) -7-OH-DPAT or \textit{R}(+) -quinpirole hydrochloride, \textit{R}(+) -7-Hydroxy-2-(dipropylamino)tetralin hydrobromide (7-OH-DPAT) or \textit{R}(+) -7-OH-DPAT were decreased by tiapride only in \textit{taiep} rats. In Sprague–Dawley only \textit{L}(+) -sulpiride is able to decrease \textit{R}(+) -quinpirole-caused yawning. In conclusion, dopaminergic D2-like agonists are still able to cause yawning despite the severe myelin loss in \textit{taiep} rats. Similarly, patients with various CNS illnesses that affect myelin, such as stroke or multiple sclerosis, are able to yaw suggesting that trigger neurons are still able to command this innate behavior.

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1. Introduction

At the Institute of Physiology of the Benemérita Autonomous University of Puebla, México during a strict inbreeding process to obtain a high-yawning (HY) subline from Sprague–Dawley rats, we obtained a spontaneous mutation that affects myelin and it is called \textit{taiep}. The name is the acronym of a neurological motor syndrome characterized by tremor, ataxia, immobility episodes, epilepsy and paralysis during the first year of life (Holmgren \textit{et al.}, 1989). The illness is transmitted as an autosomal recessive trait (Duncan \textit{et al.}, 1992; Holmgren \textit{et al.}, 1989). These mutants show an initial hypomyelination followed by progressive demyelination in the central nervous system (CNS), but not in the peripheral one (Duncan \textit{et al.}, 1992; Lunn \textit{et al.}, 1997). At the ultrastructural level, the \textit{taiep} rat shows an abnormal accumulation of microtubules in the cytoplasm and its processes in the oligodendrocytes (Couve \textit{et al.}, 1997; Duncan \textit{et al.}, 1992). When the oligodendrocytes were cultured the polymerization of microtubules was greater than depolymerization, which produced an accumulation of these cytoskeleton proteins. This alteration was reversed by the use of nocodazole and colchicine that suppress the microtubule assembly and partially depolymerize the existing microtubules (Song \textit{et al.}, 2003). It has been proposed that the accumulation of microtubules disrupts the translocation of newly synthesized proteins from the endoplasmic reticulum to the cis-portions of the Golgi apparatus (Couve \textit{et al.}, 1997; O’Connor \textit{et al.}, 2000). The mutant shows a decrease of all major myelin proteins such as myelin basic protein (MBP), proteolipid protein (PLP), 2′,3′-cyclic nucleotide 3′–phosphodiesterase (CNP), and the myelin-associated glycoprotein (MAG) levels in different portions of the CNS (Möller \textit{et al.}, 1997). All the pathways that myelinate after birth, such as corticospinal, dorsal columns, and optic nerves are more affected than the pathways that were already myelinated at birth, such as ventral columns in the spinal cord, suggesting a nonhomogeneous alteration in the myelin pathways (Lunn \textit{et al.}, 1997).

The frequency of yawning is strongly dependent on dopaminergic neurotransmission (Holmgren and Urbá-Holmgren, 1980; Holmgren \textit{et al.}, 1982; Mogilnicka and Klimek, 1977; Yamada and Furukawa, 1997). The dopaminergic D2-like agonists are still able to cause yawning despite the severe myelin loss in \textit{taiep} rats. Similarly, patients with various CNS illnesses that affect myelin, such as stroke or multiple sclerosis, are able to yaw suggesting that trigger neurons are still able to command this innate behavior.

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Because the D2-like dopamine receptors are more involved in the regulation of this behavior, the D2 and D3 agonists have stronger effects on yawning in different strains of rats (Argiolas and Melis, 1998; Collins et al., 2005; Holmgren and Urbá-Holmgren, 1980; Holmgren et al., 1982; Eguibar et al., 2004); but until now there were no studies reporting yawning studies in animals with brain alterations and the taiep rats allow us to do this.

Taiep rats came from subjects with a higher incidence of spontaneous yawning with more than 20 yawns per hour (Urbá-Holmgren et al., 1990). Importantly, our research group showed a strong correlation among spontaneous- and dopaminergic-caused yawns and penile erections (Eguibar et al., 2003; Holmgren et al., 1985). The taiep rats are directly derived from a high-yawning subline which have different sensitivity to the D2-like dopaminergic agonists producing yawning (Urbá-Holmgren et al., 1993; Eguibar et al., 2003).

Later studies demonstrated that D2 agonists produced an increase in yawning and penile erection frequency in an inverted U-shape with the ascending limb caused by a D3 effect and the descending limb of the curve caused by an activation of D2 receptors (Baladi et al., 2010; Collins et al., 2005; Collins et al., 2009). In our present experiments, we analyzed the participation of the dopaminergic D2-like agonists and antagonists on yawning after systemic intraperitoneal administration of specific agonists and antagonists in normal outbred Sprague-Dawley and myelin mutant taiep 8 months old. We also analyzed the total protein and lipid content in the brainstem and other structures in the CNS of both groups of rats.

2. Material and methods

The experiments were done on 32 Sprague-Dawley and 32 taiep rats supplied by our animal room facilities. The animals were housed under a 12:12 light–dark cycle (with lights on at 0700), in controlled conditions 21±2 °C and 35% to 50% relative humidity. They were housed three rats per acrylic cage with free access to balanced rodent pellets (Zeigler, PA, USA) and tap water. The procedures described have been done in compliance with the Laws and Codes approved in the Seventh title of the Regulations of the General Law of Health regarding Health Research of the Mexican government (NOM-062-ZOO-1999), and also following the NIH guide for the Care and Use of Laboratory Animals (85–23, revised in 1985) that were followed throughout. All experimental procedures were approved by University of Puebla Animal Care and Use Committee.

2.1. Drugs

The compounds used in these studies were the D2-like agonists (−)-quinoiprole hydrochloride, R(+)-7-Hydroxy-2-(dipropylamino) tetralin hydrobromide (7-OH-DPAT), or trans-(−)-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyran-4,3-b-1,4-oxazin-9-ol hydrochloride (((−)-PD 128,907), and the D2 antagonists were (−)-sulpiride hydrochloride, 5,6-dimethoxy-2-(di-n-propylamino) indan maleate (U-99194), and tiapride hydrochloride. All drugs were purchased from Sigma-Aldrich (St. Louis, MO, USA) and tap water. All drugs were dissolved in sterile water and were freshly prepared at the beginning of each experimental session and administered by intraperitoneal injection (ip). The injection volume for all drugs was adjusted to 1 mL/kg. Sterile water served as the control injection.

2.2. Experimental conditions

To habituate the animals to the test environment, the Sprague-Dawley and taiep rats were transferred in Plexiglas cages (21×24.5×35 cm) 30 min before testing to an experimental room in which behavioral tests were done. All animals were injected ip at 0800 and all yawns were then recorded for the next 60 min by two trained observers, one of them was blind to the experimental conditions. Each drug was tested with a different group of rats and using an increasing dose scheme with at least a 48-h drug washout period between sessions.

For the antagonists, another group of rats was used and the experiments were also made with an increasing dose scheme. In a third group of rats we used a Latin-square design with the antagonist injected ip 15 min before the corresponding agonist to allow a diffusion and binding of the antagonist to receptors before the agonist administration, which was injected 5 min before the start of yawning counts. The agonist was also administered ip. We used the maximum dose of antagonist and for the agonist the dose that produced the highest increase of yawning frequency in each group of rats.

2.3. Yawning recordings

Yawning was characterized as a wide opening of the mouth accompanied by deep inspiration. Sometimes a tongue protrusion is associated with this behavior (Ushijima et al., 1984). The yawn ends when subjects close their mouth and return to normal breathing (Argiolas and Melis, 2005; Holmgren et al., 1985).

2.4. Biochemical measurements

For biochemical analysis, the rats were killed with an overdose of sodium pentobarbital (60 mg/kg) and decapitated using a guillotine. The cranium was opened and the brain and brainstem removed to the first cervical level where a cut was made using a scalpel. The tissue was transferred to a Petri dish over crushed ice. The brainstem was obtained in less than 3 min, and the tissue was homogenized for 3 min using a Potter–Elvehjem in a solution of 2:1 chloroform–methanol with a constant proportion of 20 mL/g of tissue (Folch et al., 1957). All samples were stored at −70 °C in polypropylene tubes until measurements were made. The biochemical determinations were made using the homogenate filtered through a filter paper to extract the lipids and collect the insoluble proteins (Folch et al., 1957). The lipids were determined using the Chavrol and Charonnat method (Aiquel et al., 1952) for unsaturated lipids, which first have a reaction with sulfuric acid and then with phosphovanillin with the intensity of the rose color proportional to the lipid content. We used as a reference a solution of 1 mg of cholesterol in 1 mL of chloroform. All samples were measured in a LKB Ultrospec II spectrophotometer at 535 nm (Aiquel, 1997).

The proteins were measured with the micromethod of Lowry using the Folin phenol method and the Ciocalteu reaction. Bovine albumin was used as a reference. The products were measured in a spectrophotometer at 620 nm (Lowry et al., 1951).

2.5. Statistical analysis

We used Sigma Stat v 3.5 under Windows 7.0 software to analyze all data using the Friedman repeated-measures analysis of variance (ANOVA). The significance between treatments was obtained by Dunn’s test comparing versus control or by Tukey test when we compared among all treatments and a Student’s t-test for comparison between two groups of rats.

3. Results

3.1. Dopaminergic D2-like agonists produced yawning

The participation of the D2-like dopaminergic receptor agonists on yawning frequency was evaluated by systemic administration of agonists and antagonists. In taiep rats the injection of ((−)-PD 128,907 produced the greatest increase of yawning with 200 and 400 µg/kg, significantly different from rats treated with sterile water (χ² = 17.2, df = 4, P=0.002; followed by Dunn’s test P<0.05). Similar effects were
obtained in normal Sprague–Dawley rats, with the total amount of yawns lower in Sprague–Dawley than in taeip rats, and only 400 μg/kg (±)-PD 128,907 dose was significantly different compared to the water-treated subjects ($\chi^2 = 14.6$, $df = 4$, $P < 0.006$; followed by Dunn’s test $P < 0.05$) (Fig. 1).

The systemic administration of 7-(OH)-DPAT, a preferential D3 agonist, also produced a significant increase of yawning frequency in taeip rats with the lower doses tested of 200, 400, and 800 μg/kg ($\chi^2 = 14.4$, $df = 4$, $P < 0.006$; followed by the Dunn’s test $P < 0.05$), which decreased with the highest doses tested (see Fig. 2A). In normal Sprague–Dawley rats only the 200 μg/kg dose was significantly different from the control group ($\chi^2 = 16.3$, $df = 4$, $P < 0.003$; followed by the Dunn’s test, $P < 0.05$).

In Fig. 3A it is shown that the systemic administration of (−)-quinpirole to taeip rats produced a significant increase in yawning frequency only with the 32 μg/kg dose and decreased yawning frequency with the higher doses tested ($\chi^2 = 21.4$, $df = 5$, $P < 0.001$; followed by the Dunn’s test, $P < 0.05$). For Sprague–Dawley rats there was a significant increase on yawning frequency with 32 μg/kg and 100 μg/kg doses ($\chi^2 = 25.5$, $df = 5$, $P < 0.001$; followed by the Dunn’s test, $P < 0.05$) (Fig. 3B).

3.2. Dopaminergic D2-like antagonists do not change yawning frequency but are able to reduce agonist-produced yawning

Systemic administration of (−)-sulpiride, tiapride, or U-99194 did not produce any significant changes of yawning frequency in both groups of rats (data not shown).

![Fig. 1. D2-like dopaminergic agonist (±)-PD 128,907 increased yawning frequency in male taeip and outbred Sprague–Dawley rats. A) Systemic injections in taeip rats of (±)-PD 128,907 produced a significant increase in yawning frequency ($\chi^2 = 17.2$, $df = 4$, $P < 0.002$) with the 200 and 400 μg/kg doses significantly different from the control ($* P < 0.05$, Dunn’s test). B) In Sprague–Dawley rats (±)-PD 128,907 also produced a significant increase of yawning ($\chi^2 = 14.6$, $df = 4$, $P < 0.006$), with the 400 μg/kg dose significantly different from the control ($* P < 0.05$, Dunn’s test). Data are the mean ± SE of 6 rats in each group.]

![Fig. 2. Systemic administration of 7-OH-DPAT, a specific D3 agonist, increased yawning frequency in taeip and outbred Sprague–Dawley rats. A) On taeip rats 7-OH-DPAT increased yawning frequency with 200, 400, and 800 μg/kg doses ($\chi^2 = 14.4$, $df = 4$, $P < 0.006$; followed by Dunn’s test $* P < 0.05$). B) For the injection of 7-OH-DPAT in Sprague–Dawley rats only the 200 μg/kg dose increased yawning ($\chi^2 = 16.3$, $df = 4$, $P < 0.003$, followed by Dunn’s test $* P < 0.05$). Data are the mean ± SE of 6 rats per group.]

By using a Latin-square design, we are able to show that 7-OH-DPAT at 200 μg/kg increased yawning in both groups of rats, being greater in taeip than Sprague–Dawley animals (see Table 1). Previous administration of tiapride, a D3 antagonist, produced a significant decrease of the effect produced by 7-OH-DPAT in taeip rats ($\chi^2 = 22.8$, $df = 3$, $P < 0.001$, followed by Tukey test $P < 0.05$; see Table 1); but not in the Sprague–Dawley rats in which a potentiation was obtained. Systemic administration of 32 μg/kg of (−)-quinpirole significantly increased yawning frequency in both groups of rats and this effect was significantly blocked by the previous administration of the antagonist (−)-sulpiride ($\chi^2 = 22.8$, $df = 3$, $P < 0.001$, followed by Tukey test $P < 0.05$; see Table 1).

3.3. Myelin content in the central nervous system of taeip and Sprague–Dawley rats

Table 2 showed that taeip rats had a significant decrease in the lipid and protein/lipid ratio contents in the brainstem of 82% and 83% compared to control Sprague–Dawley rats (Student’s t-test, $P < 0.001$). Similar decreases were seen in the spinal cord (72%, $P < 0.001$), but a lesser decrease of myelin was obtained in the cerebral cortex and cerebellum with only 50% reduction, although this is still significant compared to the data obtained from Sprague–Dawley rats (Student t-test, $P < 0.01$).

4. Discussion

The 8 month old male taeip rats showed a severe demyelination with just 18% of lipids in the brainstem compared to the control group. Similar decreases were obtained in the spinal cord (21%), but the cortex and cerebellum were less affected with just a 50% decrease on the lipid content compared to the Sprague–Dawley animals at
myelin decrease, the D2-like dopaminergic receptors are still "jumpy", shivering, and quaking (Ganser et al., 1988). Instead of a content were reported in several myelin-mutant mice, such as myelin mutants (Norton, 1981). Similar decreases in the lipid 70%, measurements of the total myelin content have been believed to falls on the ascending limb of the dose curve in the Sprague–Dawley rats (Collins et al., 2005, 2007; Baladi et al., 2010, 2011). Because of the higher doses used in this study, only the descending limb of the curve mediated by D2 receptors was obtained with the ascending limb of the curve mediated by D3 receptors and the descending limb mediated by the D2 receptors (Collins et al., 2005, 2007; Baladi et al., 2010, 2011). Because of the higher doses used in this study, only the descending limb of the curve was explored because at these doses there was a significant increase in the gripping-produced tonic-immobility episodes, a cardinal sign of this myelin-mutant rat (Eguibar et al., 2010), suggesting that myelin is not the fundamental component to obtain maximum effects caused by dopaminergic-generated yawning with these higher doses.

Binding experiments clearly demonstrated that (±)-PD 128,907 has a similar affinity for D3 receptors as 7-OH-DPAT. These D3 receptors are more abundant in the islands of Calleja followed by the nucleus accumbens, nucleus of the horizontal limb of the diagonal band, and the ventral caudate-putamen (Bancroft et al., 1998). Taiep rats show higher levels of D1 receptors in the ventral subregions of the basal ganglia compared to normal Sprague–Dawley rats, with these differences greater in rats older than 9 months. However D2-like dopamine receptor levels are similar in both groups of rats (Flores et al., 2002). For yawning, it has been shown that dopaminergic pathways from mesocortical, mesostriatal, and local dopaminergic pathways in the paraventricular nucleus of the hypothalamus (PVN) are involved in the regulation of yawning (Argiolas and Melis, 1998; Collins and Eguibar, 2010; Dourish and Cooper, 1990). Dopaminergic drugs acting on the PVN and through magnocellular nucleus axons project to the brainstem in which the central ensemble of neurons that generated and coordinated the musculature in the pharynx, larynx, and facial musculature are involved in the yawn reflex pattern.

The dopamine exerts a tonic inhibitory control over cholinergic neurons that produced yawning (Holmgren and Urbá-Holmgren, 1980; Holmgren et al., 1982; Yamada and Furukawa, 1981). It is clearly established that an inverted U-shape dose–response curve was obtained with the ascending limb of the curve mediated by D3 receptors and the descending limb mediated by the D2 receptors (Collins et al., 2005, 2007; Baladi et al., 2010, 2011). Because of the higher doses used in this study, only the descending limb of the curve was explored because at these doses there was a significant increase in the gripping-produced tonic-immobility episodes, a cardinal sign of this myelin-mutant rat (Eguibar et al., 2010), suggesting that taiep rats are less sensitive to D3 and D2 effects on yawning. For the D2-family antagonist used, the lack of effect is probably caused by the low spontaneous yawning frequency. However, tiapride is able to antagonize the increase of yawning frequency produced by 7-OH-DPAT in taiep rats because the myelin mutants had different sensitivity in D3 receptors and so this dose in Sprague–Dawley rats is on the descending limb of the dose–response curve, as previously suggested (Baladi et al., 2010, 2011; Collins et al., 2007, 2009). Under free access to chow taiep and Sprague–Dawley rats showed different sensitivities to the action of the D2-like dopaminergic agonists, which could explain the differences obtained when antagonists were administered before the agonist, because at that dose the 7-OH-DPAT falls on the ascending limb of the dose–effect curve on taiep rats, but it could be on the descending limb in the Sprague–Dawley rats. The agonist is acting at D3 receptors in the former and quite probably in the D2 receptors in the latter (see Table 1 and Fig. 2). These differences in response to dopaminergic drugs can be because of

![Graph A: Effects of tiapride and (-)-quinpirole on yawning frequency in Sprague–Dawley rats.](image)

**Table 2.** Total amounts of lipids and lipids/mg of proteins in a total different brain area homogenates.

<table>
<thead>
<tr>
<th>Lipids/mg of tissue</th>
<th>Brainstem</th>
<th>Cerebral cortex</th>
<th>Cerebellum</th>
<th>Spinal cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-PD 128,907 (32 μg/kg)</td>
<td>142.5±11</td>
<td>42.7±2.8</td>
<td>69.9±6.7</td>
<td>142.4±13.6</td>
</tr>
<tr>
<td>Tiapride (32 μg/kg)</td>
<td>25.7±1.8</td>
<td>21.3±1.2</td>
<td>25.7±2.9</td>
<td>30.5±3.6</td>
</tr>
<tr>
<td>(-)-Quinpirole (32 μg/kg)</td>
<td>15.5±1.2</td>
<td>5.4±0.4</td>
<td>8.1±0.8</td>
<td>20.7±2.3</td>
</tr>
</tbody>
</table>

**Table 1.** Effects of antagonists on dopaminergic agonists-induced yawning on taiep rats.

<table>
<thead>
<tr>
<th>Doses (μg/kg)</th>
<th>Sprague–Dawley</th>
<th>taiep</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-OH-DPAT (400 μg/kg)/tiapride (3200 μg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water/water</td>
<td>0.0±0.0</td>
<td>0.2±0.2</td>
</tr>
<tr>
<td>Tiapride/water</td>
<td>0.0±0.0</td>
<td>0.2±0.2</td>
</tr>
<tr>
<td>Water/7-OH-DPAT</td>
<td>3.7±1.9</td>
<td>13.3±2.7</td>
</tr>
<tr>
<td>Tiapride/7-OH-DPAT</td>
<td>17.7±5.4</td>
<td>4.0±0.6</td>
</tr>
</tbody>
</table>

| (-)-Quinpirole (32 μg/kg)/(-)-sulpiride (800 μg/kg) | | |
| Water/water | 0.2±0.2 | 0.7±0.7 |
| Sulpiride/water | 0.0±0.0 | 1.8±0.7 |
| Water/quinpirole | 34.5±8.4 | 28.2±3.5 |
| Sulpiride/quinpirole | 18.0±8.8 | 16.2±2.9 |

**Friedman ANOVA, P<0.01; followed by Tukey test P<0.05.**

Sprague–Dawley: Tiapride, 3200 μg/kg; 7-OH-DPAT, 200 μg/kg.
Sulpiride, 1600 μg/kg; Quinpirole, 32 μg/kg.
taiep: tiapride, 3200 μg/kg; 7-OH-DPAT, 400 μg/kg.
Sulpiride, 800 μg/kg; quinpirole, 32 μg/kg.

* Significantly different from water/water treatment.

** Student’s t-test P<0.01.
*** Student’s t-test P<0.001 in male taiep respect to control Sprague–Dawley rats at 8-months-old.

8 months. Detailed microscopic studies showed a general decrease of the myelin thickness with age in taiep rats, particularly in all myelin tracts that mature after birth (Lunn et al., 1997).

Because lipids are the major solid component in the CNS, about 70%, measurements of the total myelin content have been believed to be an adequate way to evaluate the degree of demyelination in myelin mutants (Norton, 1981). Similar decreases in the lipid content were reported in several myelin-mutant mice, such as ‘jimpy’, shivering, and quaking (Ganser et al., 1988). Instead of a myelin decrease, the D2-like dopaminergic receptors are still functional to produce a significant increase of yawning frequency. In this study we showed that (−)-quinpirole increases yawning frequency in both strains of rats, being more potent than (±)-PD 128,907 and 7-OH-DPAT. Similar results were obtained by Collins and his group in outbred Sprague–Dawley rats (Collins et al., 2005, 2007, 2009), suggesting that myelin is not the fundamental component to obtain maximum effects caused by dopaminergic-generated yawning with these higher doses.

**Fig. 3.** D2-like dopaminergic agonist (−)-quinpirole increased yawning frequency in male Sprague–Dawley and taiep rats. A) Systemic administration of (−)-quinpirole in taiep rats increased yawning frequency ($\chi^2=214.4, df=5, P<0.001$) with the 32 μg/kg dose significantly different from sterile water-treated rats ($P<0.05$, Dunn’s test). B) Sprague–Dawley rats, also significantly increased yawning frequency with 32 and 100 μg/kg doses ($\chi^2=25.5, df=5, P<0.001$; followed by Dunn’s test $P<0.05$). Data are the mean±SE of 6 rats per group.
age, gender, genetics, and nutritional status, as previously suggested (Baladi et al., 2011; Sevak et al., 2008). In our results it is quite clear that the differences in the response to tiapride and 7-OH-DPAT are caused by the genetic background of taiep rats and why yawning frequency differs in both groups of rats.

In stroke patients the voluntary contractions of paralyzed arms are impossible, however during yawning this paralyzed arm is stretched. In the case of taiep rats the progressive demyelination produced, at 8–9 months old, a large reduction in the myelin sheath reaching 100%, 70%, and 70% in the corticospinal tract, ventral column, and the optic nerve (Lunn et al., 1997), but they are still able to respond to the D2-like dopaminergic agonists as also for hemiplegic patients in which apomorphine in low doses increased yawning and concomitantly the stretching of the paralyzed arm (Blin et al., 1994). It is quite remarkable that in humans there are only a few clinical reports in which neurological stroke patients are able to move their paralyzed arm during yawning (Wimalaratna and Capildeo, 1988). This movement is strictly concomitant with the yawn and the arm persists in being inert once the yawn ends (Blin et al., 1994; Walusinski et al., 2005, 2010). For most of these patients the lesions, which are located on the internal capsule affecting cortical and subcortical areas, are with the loss of myelin one cardinal sign after a stroke (Walusinski et al., 2005; Walusinski, 2009; Cattaneo et al., 2005).

It is quite probable that a set of motoneurons that produces yawning is located in the brainstem, near the nerve centers that control the respiratory, laryngeal, and pharyngeal musculature (Barbizet, 1958; Heusner, 1946). These sets of motoneurons respond reflexively to the changes of dopaminergic transmission, as demonstrated in hemiplegic patients and now in the myelin mutant taiep rats. The upper parts of the CNS are able to modulate the threshold of motoneurons that are responsible for the control of facial musculature involved in yawning and also the musculature that stretches the paralyzed arm in stroke patients, the so called Parakinesia brachialis oscillans (Walusinski et al., 2005). There is a strong correlation of yawning and stretching to increase awakening when light–dark changes happen (Provine et al., 1987), another circumstance in which both the motor acts are expressed together probably to increase the awakening state.

5. Conclusion

In conclusion, it is possible to cause yawning in the myelin mutant taiep rat through systemic injection of the D2-like dopaminergic agonists. The taiep is a myelin mutant with a progressive demyelination, and this response correlates with clinical observations of the presence of yawning behavior in hemiplegic patients in which the myelin is altered, but this reflex response commanded by dopaminergic neurons happens suggesting that it is wired in a coordinated way to produce that motor sequence.

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