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Ana C. Barceló, Bárbara Filippini & Jorge H. Pazo

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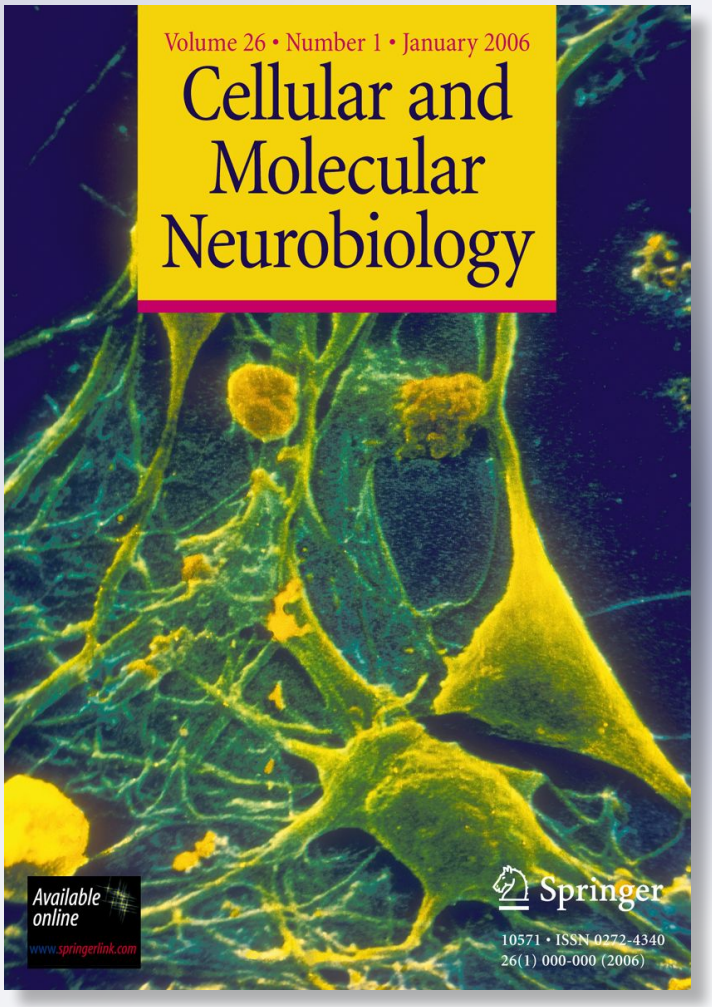

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REVIEW PAPER

The Striatum and Pain Modulation

Ana C. Barceló · Bárbara Filippini · Jorge H. Pazo

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Abstract The aim of this review was to give a general aspect of the sensorial function of the striatum related to pain modulation, which was intensively studied in our laboratory. We analyse the effect of electrical and chemical stimulation of the striatum on the orofacial pain, especially that produced by tooth pulp stimulation of the lower incisors. We demonstrated specific sites within the nucleus which electrical or chemical stimulation produced inhibition of the nociceptive jaw opening reflex. This analgesic action of the striatum was mediated by activation of its dopamine D_2 receptors and transmitted through the indirect pathways of the basal ganglia and the medullary dorsal reticular nucleus (RVM) to the sensorial nuclei of the trigeminal nerve. Its mechanism of action was by inhibition of the nociceptive response of the second order neurons of the nucleus caudalis of the V par.

Keywords Basal ganglia · Striatum · Orofacial pain · Jaw opening reflex · Sensorial trigeminal nuclei · Endogenous analgesic system · Indirect pathway · Electrical stimulation · Chemical stimulation

A. C. Barceló
Facultad de Odontología, Universidad de Buenos Aires, Cátedra de Fisiología, Buenos Aires, Argentina

B. Filippini · J. H. Pazo (✉)
Facultad de Medicina, Departamento de Fisiología, Laboratorio de Neurofisiología, Universidad de Buenos Aires, Paraguay 2155, Buenos Aires 1121, Argentina
e-mail: jpazo@fmed.uba.ar

Introduction

The basal ganglia are nuclei situated deep in the cerebral white matter in the diencephalon and midbrain. The term usually includes the caudate nucleus, putamen, globus pallidus, and related cell groups closely connected to them, the subthalamic nucleus and the substantia nigra (Brodal 1992). In rodents and other animals the caudate and putamen are collectively termed the striatum or neostriatum. For a long time, the basal ganglia have been related to motor functions since diseases affecting these structures lead to characteristic disturbances of movement and the muscles tone (Brooks 1995; Graybiel et al. 1994; Marsden and Obeso 1994; Wichmann and DeLong 2003; Jankovic 2008; Jeffery et al. 2007; Mahlon et al. 2007). However, there is growing evidence implicating the basal ganglia in autonomic, sensorial, and cognitive functions (Abbruzze and Berardelli 2003; Green et al. 2002; Packard and Knowlton 2002; Pazo and Belforte 2002).

The basal ganglia receive afferent inputs from nociceptive and non-noxious somatosensory information (Bernard et al. 1992; Chudler 1998; Schneider and Lidsky 1981). In anesthetized animals, a large proportion of the striatal, substantia nigra, and globus pallidus neurons are differentially or exclusively activated by noxious stimuli (Schneider and Lidsky 1981; Chudler et al. 1993; Richards and Taylor 1982). In human volunteers, thermal painful stimulation of the hand increases the blood flow in the contralateral striatum (Casey et al. 1996; Coghill et al. 2002; Svensson et al. 1997). Also, clinical studies show that approximately 40–50% of the patients with diagnosis of Parkinson's disease complain of sensory disturbances, being these complaints mostly painful sensations clinically unrelated to motor symptoms (Gardelat-Mas et al. 2007; Nolano et al. 2008).

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The basal ganglia and specifically the striatum are among the neural structures with highest concentrations of endogenous opiates and their receptors (Angulo and McEwen 1994; Hebert et al. 1990; McGeer and McGeer 1993; Parent et al. 1995), which could be relevant in the mechanisms of endogenous analgesia (Hebert et al. 1990; Kurumaji et al. 1988; Thorn-Gray and Levitt 1983).

The following review focuses on our results of the participation of the striatum in the endogenous analgesia. We also explored the possibility that the opioid receptors could be involved in the mediation of the analgesic action of the striatum, especially in the link with the sensorial trigeminal nucleus.

Striatal Stimulation

The reflex evoked in the anterior belly of digastric muscles, the jaw opening reflex (JOR), produced by suprathreshold stimulation of the tooth pulp of the lower incisors of the rat (Pazo et al. 2001) was used as indicative of pain. The sensory innervations of the tooth pulp are considered to be nociceptive because it is provided almost exclusively from high threshold small myelinated and unmyelinated axons, fibers type Aδ and C, in humans and animals (Hildebrand et al. 1995). Tooth pulp stimulation, at intensities to evoke JOR, produces only painful sensations in humans (Sessle and Greenwood 1976; Tanaka and Toda 1982). The magnitude of this sensation is directly correlated with an increased activity of Aδ afferents fibers from dental pulp (Olgart et al. 1988). For these reasons the JOR evoked by high intensities tooth pulp stimulation was considered to be a nociceptive response and a good measurement of analgesic effects. In addition, the latency of the JOR 7.9 ± 0.25 ms (range 6–10 ms, $n = 60$) (Saunier-Rébori and Pazo 2006), is compatible with conduction velocity of tooth pulp Aδ nociceptors (range 10–20 m/s) and it is in agreement with previous articles from our and other laboratories (Belforte and Pazo 2005; Gear et al. 1999).

The electrical stimulation of the central-medial region of the striatum (Fig. 1a) with trains of 20 ms of duration and pulses of 0.5 ms width, at 333 Hz, preceding by 20 ms (conditioning test-interval) the stimuli to tooth pulp, produced a significant inhibition of the JOR (Fig. 1b) (Belforte et al. 2001). Similar results were observed by intrastriatal microinjections of glutamate, an excitatory amino acid (80 nmol dissolved in 0.5 µl of isotonic saline (Fig. 1c) in similar sites. Microinjection of glutamate into the sites of ineffective electrical stimuli of the striatum did not produce any effect on the JOR amplitude (Fig. 1d). However, excitatory responses of the JOR were eventually observed with electrical or glutamate stimulation in the striatum, and never with activation of the striatal dopamine receptors. For this reason, excitatory responses of the JOR were not considered in this review.

The above observations suggest that the effect obtained by electrical stimulation were mainly due to activation of striatal neurons rather than to fibers in passage (Belforte et al. 2001). Since, more than 90% of the striatal neurons send its axon out of the striatum and use GABA as neurotransmitter, we can assume that activation of these neurons should be responsible for inhibition of the JOR response.

To search about the mechanisms by which the striatum modifies the tooth pulp reflex, we studied the action of this nucleus on the responses of the sensory nuclei of the trigeminal nerve. We recorded with microelectrodes the neuronal activity of the trigeminal nucleus caudalis (NC) in anaesthetized rats. This nucleus was elected because clinical (Green et al. 2002; Morita and Hosobuchi 1992; Rosenkopf 1989), behavioral (Bohotin et al. 2003; Duale et al. 1996; Luccarini et al. 1998; Rosenfeld et al. 1983), anatomical (Clements et al. 1991; Coimbra and Coimbra 1994; Strassman and Vos 1993; Voisin et al. 2002), immunohistochemical (Strassman and Vos 1993; Bereiter et al. 1994; Lu et al. 1993; Meng and Bereiter 1996; Oakden and Boissonade 1998), and electrophysiological (Amano et al. 1984; Carstens et al. 1998; Chiang et al. 1991; Dallel et al. 1998; Hu et al. 1981; Tsai et al. 1999) evidence suggest that it is the most important site for relay of orofacial nociceptive information.

Extracellular single unit activity was recorded from a total of 42 neurons in the NC responding to dental pulp stimulation. These neurons were classified according to previously outlined criteria (Hu 1990; Meng et al. 2000; Sessle et al. 1986) as nociceptive specific (NS) when only responded to painful stimuli and as wide dynamic range (WDR) when responded to nociceptive and innocuous stimuli (e.g., hair movements or light pressure). The 60% of the neurons recorded were of the type NS and the 40% WDR. The neurons WDR were recorded in the deeper laminae of the caudalis nucleus while the NS were recorded in more superficial laminae (I/II). The neurons responded to dental pulp stimulation with a peak of short latency of 4.4 ± 0.23 ms, range 3.1–8.7 ms, $n = 42$, corresponding to activation of Aδ fibers (Fig. 2a), (Saunier-Rébori and Pazo 2006). In addition, the $\sim$33% of the units ($n = 14$) presented a second activation peak corresponding to C fibers, mean latency 41.9 ± 3.5 ms, range 32–84 ms (Fig. 2b), (Saunier-Rébori and Pazo 2006). The chemical activation of the striatum, with a microinjection of glutamate (80 nmol/0.5 µl of isotonic saline), produced inhibition of both nociceptive responses (Aδ and C) in the neurons of the NC to pulp stimulation (Fig. 2a, b). Simultaneously, there was an inhibition of the JOR (Fig. 2a, b). Maximal inhibition of the evoked neural

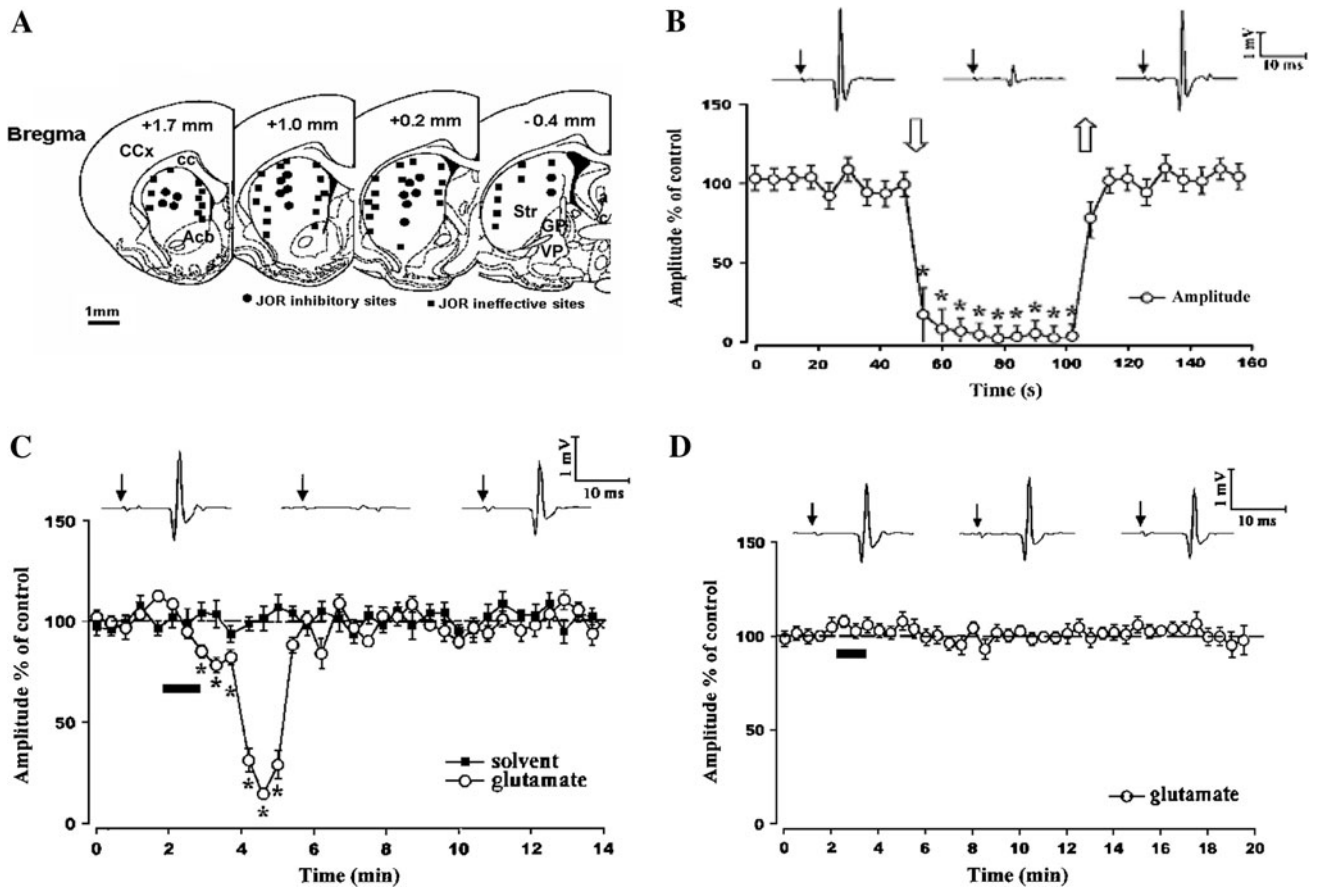


Fig. 1 **a** Histological reconstruction of the sites explored with electrical stimulation within the striatum in rats anaesthetized with urethane 1.2 mg/kg i.p. Outlines and levels were adopted from Paxinos and Watson (1997). *Acb* nucleus accumbens; *ac* anterior commissura; *CCx* cerebral cortex; *CC* corpus callosum; *GP* globus pallidus; *Str* striatum; *VP* ventral pallidum; **b** effect of electrical stimulation of the striatum at the effective sites. Each point is the mean ± SE of 50 consecutive responses expressed as percent of control values. $*P < 0.05$ when compared with control values (before striatal stimulation). Newman–Keuls post-hoc test after significant one way ANOVA for repeated measures ($F_{26,208} = 7.74$, $P < 0.0001$). **c** Effect of chemical stimulation of the striatum by microinjection of glutamate (80 nmol/0.5 µl of isotonic saline) at an effective site. **d** Microinjection of glutamate at an ineffective site. Each point is the mean ± SE amplitude of 25 consecutive JORs expressed as percent of control values. $*P < 0.05$ when compared with control values. Newman–Keuls post-hoc test after significant one way ANOVA for repeated measures ($F_{26,208} = 7.74$, $P < 0.0001$). *Insets* example of the JOR amplitude before, during, and after striatal stimulation. *Arrows* indicate stimulus artifact. *Empty arrows* in **b** indicate the start (*downward*) and the end (*upperward*) of striatal electrical stimulation. *Horizontal bars* in **c** and **d** indicate the period of glutamate microinjection. Modified from Belforte et al. (2001)

response appeared 1 min after the injection. This effect occurred before the maximal inhibition of the JOR in ~53% of cases (Fig. 2c) and simultaneously in ~47% of cases (Fig. 2d).

To search whether the inhibitory action of the striatum on the nociceptive reflex is exerted on the afferent sensorial branch (analgesic effect) or on the motor branch (motor effect), simultaneous recording of the neuronal activity of the NC, the motor neurons of the anterior belly of the digastric muscle, located in the ipsilateral ventromedial part of trigeminal motor nucleus (Fay and Norgren 1997; Mizuno et al. 1975) and the JOR, was made. The dental pulp stimulation evoked an excitatory response of the digastric motor neurons followed by the JOR and all was temporally preceded by sensorial activation of the NC neuron (Fig. 3a).

The microinjection of glutamate into the striatum did not modify the spontaneous activity of the neurons of the NC or the motor neurons (Fig. 3b). However, a significant decrease in the evoked responses in the NC, digastric motor neurons, and the JOR was observed after the glutamate activation of the striatum (Fig. 4a, b). The time course of the inhibition of the motoneurons of the digastric muscle paralleled the neurons of the NC. From these results, we can assume that striatal inhibition in the tooth pulp-evoked responses in digastric motoneurons may be the consequence of a decrease in the sensorial input arriving from the sensory nucleus rather than a direct inhibition of the

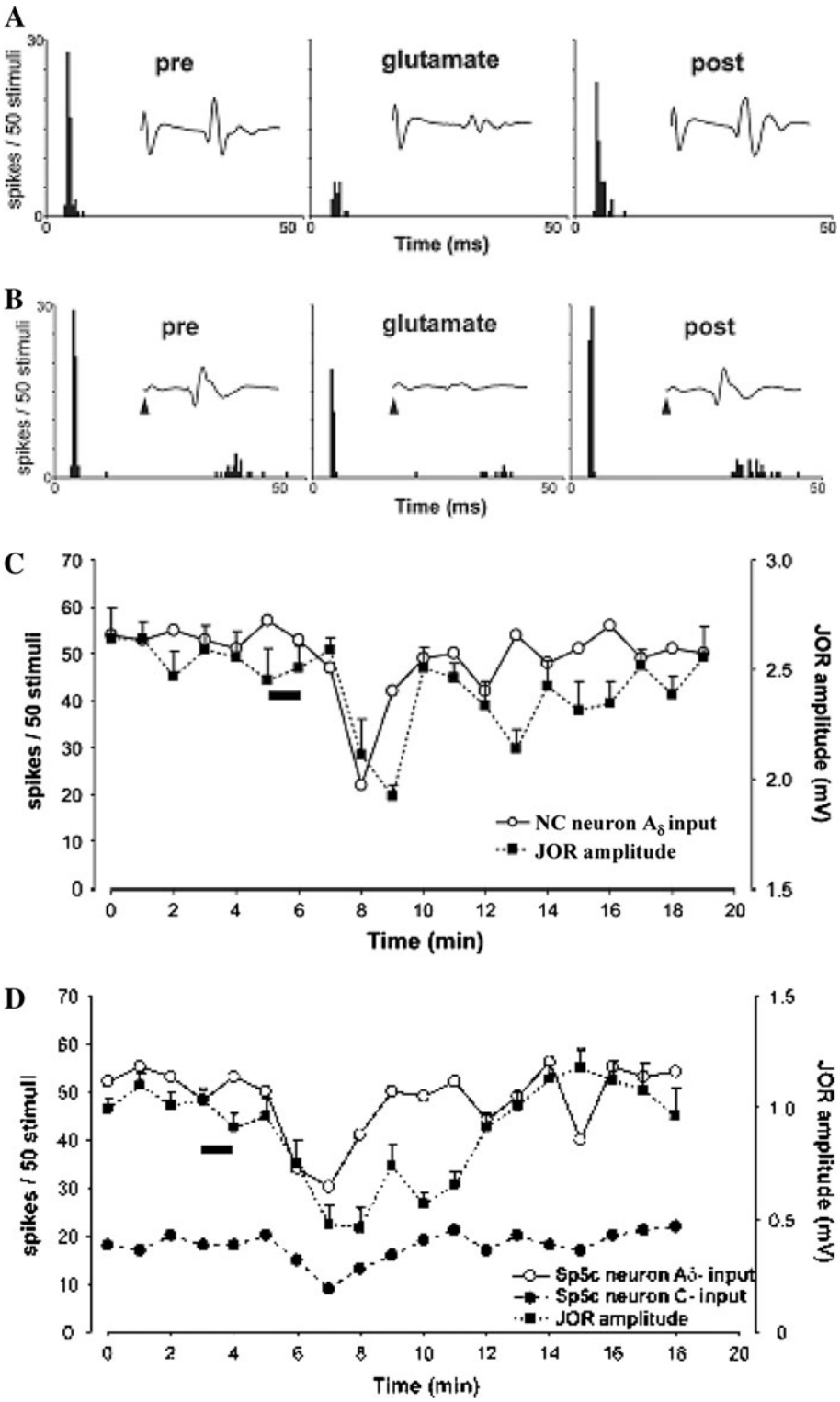


Fig. 2 In **a** and **b**, representative post-stimulus time histograms (PSTHs) of nociceptive response of the neurons of the NC evoked by dental pulp stimulation before, during, and after intrastriatal microinjection of glutamate (80 nmol/0.5 µl of isotonic saline) are shown. In **a**, an example of the response of nociceptive specific (NS) neuron and in **b**, an example of wide dynamic range (WDR) neuron are shown. Time 0 corresponds to stimulation onset. Bin width 0.5 ms, 50 sweeps. Note the inhibitory action exerted by the striatum on the noxious-evoked responses of both type of neurons. *Insets* representative 25 ms traces of digastrics EMG (JOR) recorded during the same period of neuronal recording. In **c** and **d**, representative examples of the time course of intrastriatal effect of the microinjection of glutamate on the evoked responses in the digastric muscle (JOR) and in nociceptive neurons are shown. In **c**, NC neuron with Aδ input and in **d**, neuron with Aδ and C inputs plotted separately are shown. Each point represents mean ± SE of 50 consecutive responses (JOR) or amplitude of evoked response of the neurons measured from the PSTHs. The *horizontal bar* beneath the graphics indicates duration of intrastriatal microinjection of glutamate. Modified from Belforte and Pazo (2005)

motoneurons. The region of the striatum which stimulation produced rhythmical jaw movements (Hashimoto and Amano 1998; Kelley et al. 1989; Kolomiets et al. 2001; Koshikawa et al. 1989; Nakamura et al. 1990) was not involved in the inhibition of the tooth pulp-evoked nociceptive responses.

Striatal Dopamine Receptors

The dopaminergic nigrostriatal projection arises from the substantia nigra pars compacta (SNc) modulates the activity of the striatum in both normal and pathological conditions. The lesion of this pathway in animals and in

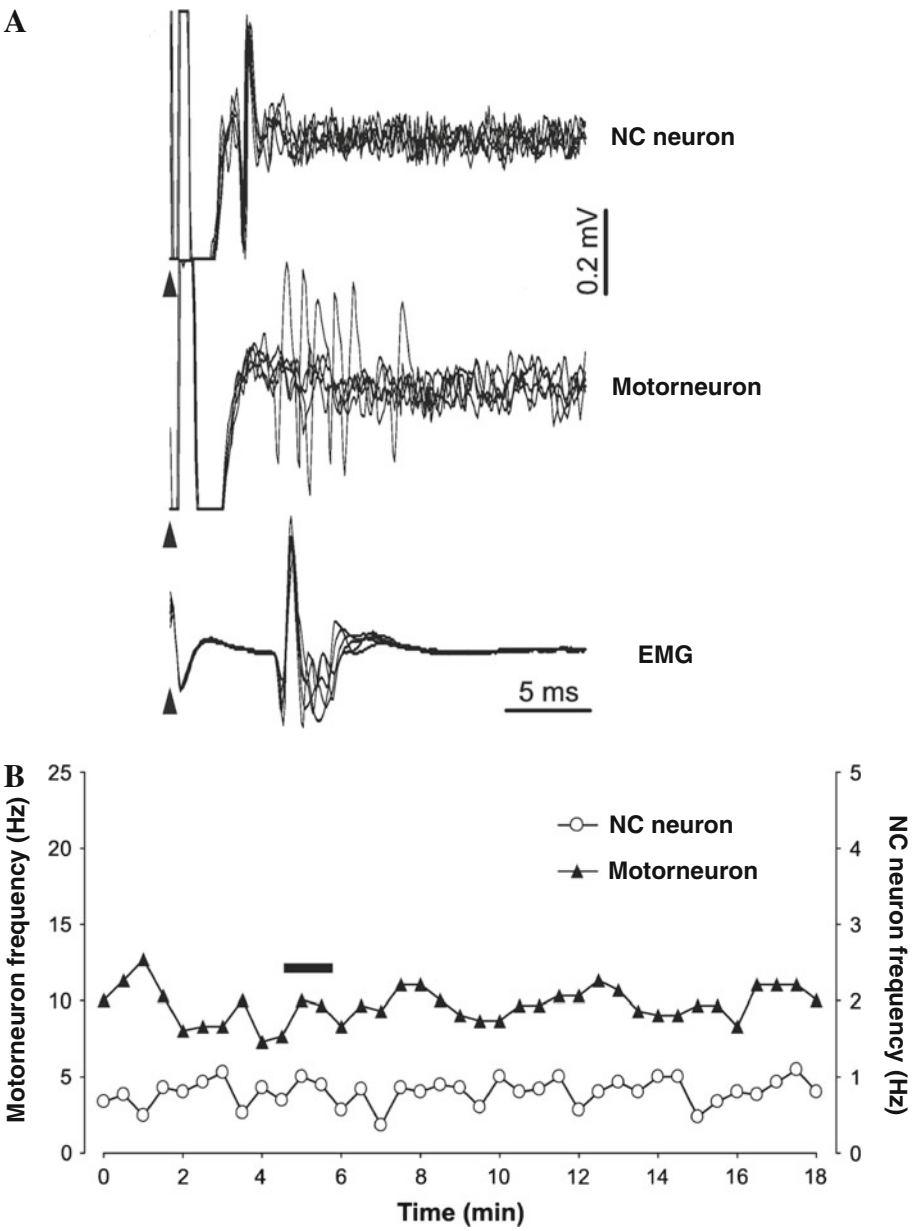


Fig. 3 Representative example of a pair of neurons recorded simultaneously within the NC and motor digastric muscle. **a** Five superpose responses of a neuron of the NC and a motor neuron of the digastric nucleus and the JOR (EMG) evoked by tooth pulp stimulation. Note the temporal relationship of each activity. **b** Time course of the spontaneous neuronal activity of the NC and digastric motor neuron before, during, and after an intrastriatal microinjection of the glutamate (80 nmol/0.5 µl of isotonic saline). Each point represents mean discharge frequency during 30 s. Note the absence of effect of the drug. The *arrow heads* indicate the stimulus artifact. *Horizontal bar* indicates duration of intrastriatal microinjection. Modified from Belforte and Pazo (2005)

Parkinson patients leads to a reduction of movements as well as other motor deficits. However, different evidences have also involved striatal dopamine in pain control. Clinical studies have shown that approximately 40% of the patients of Parkinson's disease complain sensory abnormalities that could not be attributed to motor manifestations of the disease. Pain is the most common sensory complain in these patients. Similar results were reported in animal models of the disease (Carey 1986; Saade et al. 1997). Also, the nigrostriatal dopaminergic system have been recently associated to the burning mouth syndrome, an intense chronic oral mucosal pain condition of unknown etiology, as well as in atypical facial pain (Hagelberg et al. 2003, 2004). Furthermore, studies in healthy volunteers have indicated that striatal dopamine D2 receptors may play a significant role in tonic and dynamic regulation of pain in humans (Hagelberg et al. 2002). Electrophysiological experiments have shown that electrical or natural stimulation of the skin nociceptors modifies the spontaneous activity of the dopamine neurons of the SNc (Gao et al. 1990; Schultz and Romo 1987). Studies with microdialysis demonstrated that noxious stimuli produce release of dopamine in the striatum of the rats (Gao et al. 1990). The analgesic effect of the nigrostriatal pathway was also observed in some studies with intrastriatal microinjections of dopaminergic drugs (Lin et al. 1981). We studied the participation of the striatal dopamine receptors in the effect of the striatum on the

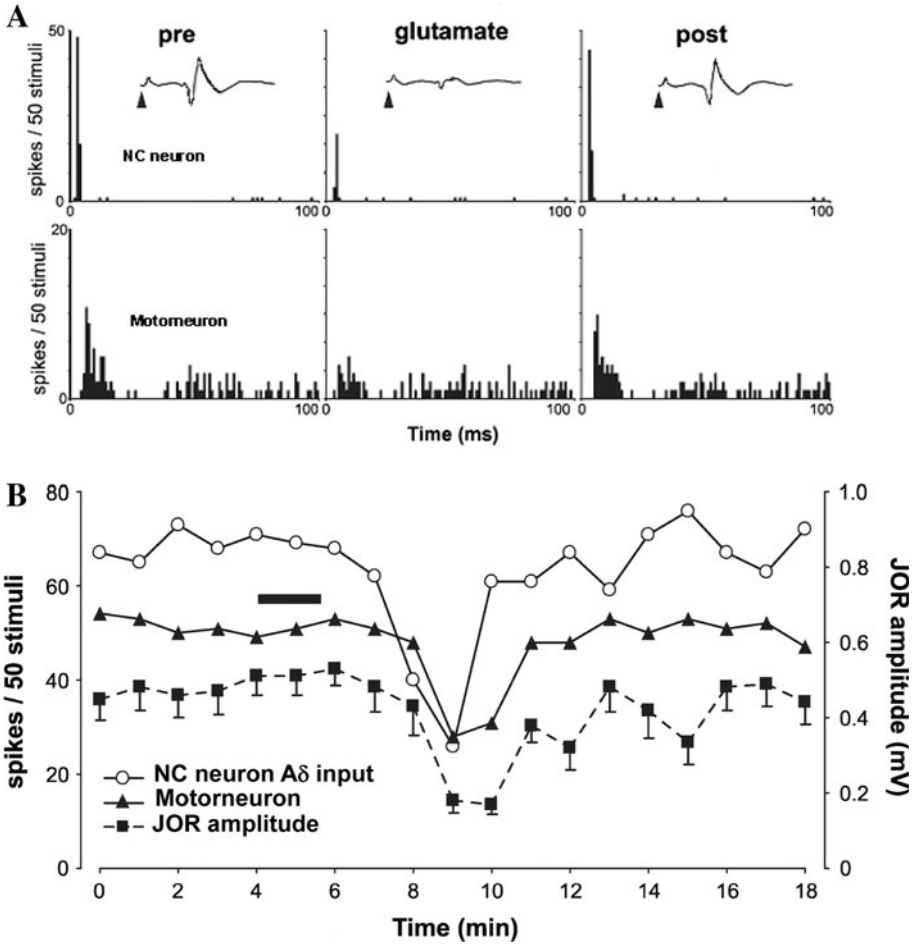
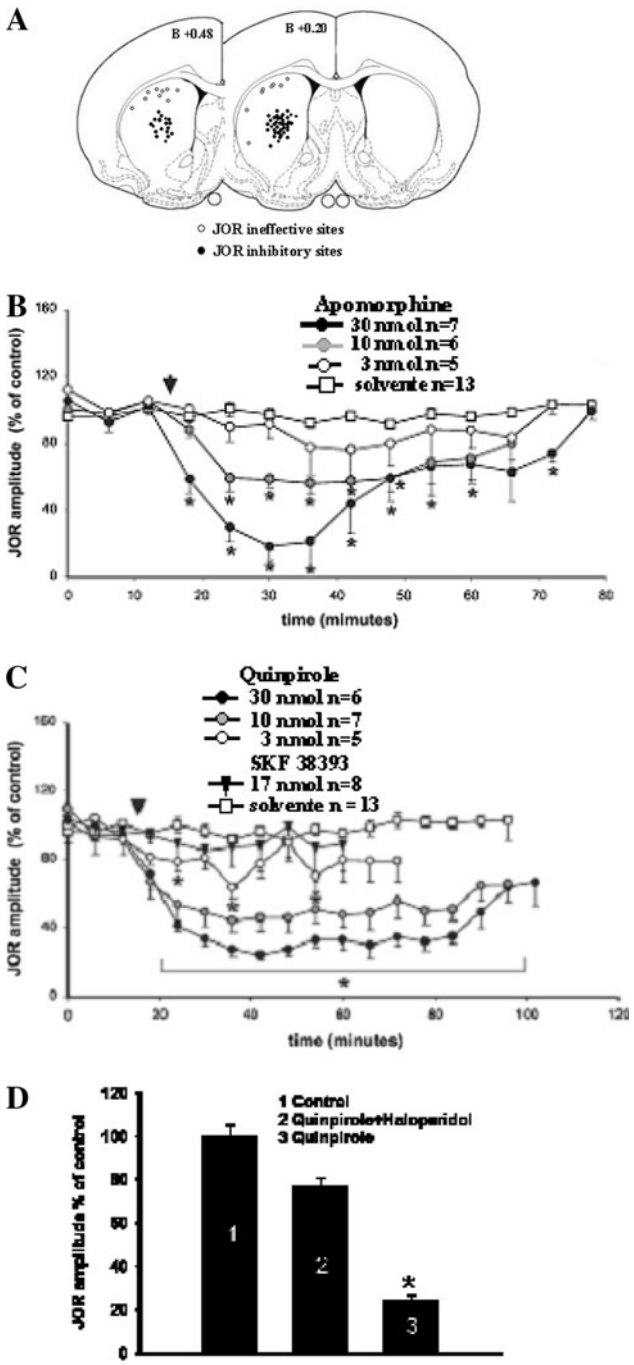


Fig. 4 **a** Representative PSTH of neuronal responses evoked by tooth dental pulp stimulation in a nociceptive neuron and a digastric motor neuron, before, during, and after intrastriatal microinjection of glutamate (80 nmol/0.5 µl of isotonic saline). Time zero corresponds to stimulation onset. Bin width 1 ms, 50 sweeps. *Insets* representative 25 ms traces of digastric EMG recorded simultaneously with the neuronal responses. The *arrow heads* indicate dental pulp stimulation. Note the inhibitory effect produced by the intrastriatal microinjection of glutamate on noxious-evoked responses in both neurons. **b** Time course of the striatal activation by a microinjection of glutamate on the nociceptive-evoked responses in the digastric muscle (JOR), in a neuron of the NC and a motor neuron of the digastric muscle. Each point represents mean ± SE of 50 consecutive responses (JOR) or amplitude of the evoked response (neuron) measured from PSTHs. *Bar* indicates duration of the intrastriatal microinjection of glutamate. Modified from Belforte and Pazo (2005)

JOR and on the evoked responses of the neurons of the trigeminal NC to tooth pulp stimulation.

The microinjection of unspecific agonist of the dopamine receptors apomorphine (APO) (0.5 µl) into the striatum, at sites that produced inhibition of the JOR (effective sites; Fig. 5a), also decreases the amplitude of the nociceptive reflex in a dose-dependent relationship (Fig. 5b). The maximal inhibition was observed at dose of 30 nmol/0.5 µl of isotonic saline. The duration of the effect ranged from 30 to 80 min. When the specific agonist of dopamine D_2 receptors, quinpirole, was microinjected into the striatum inhibit the JOR evoked by tooth pulp stimulation in a dose-response relationship (Fig. 5c). However, the administration intrastriatal of the selective dopamine agonist of the D_1 receptors, SKF 38393, left unaffected the JOR amplitude. Intrastriatal administration at the effective sites of 7 nmol/0.5 µl of commercial solution of haloperidol, a D_2 receptor antagonist, followed after 20 min by a microinjection of 30 nmol/0.5 µl of quinpirole blocked the effect of D_2 agonist on the JOR amplitude (Fig. 5d). However, the administration into the striatum of haloperidol alone did not modify the amplitude of the JOR evoked by tooth pulp stimulation. These results demonstrated that the D_2 striatal dopamine receptors are involved in the analgesic action of the striatum.

To analyse the sensory nature of the dopamine-induced JOR attenuation, the response to dental pulp stimulation of the neurons of the NC of the trigeminal nerve were recorded simultaneously with the JOR. Intrastriatal microinjection of the 30 nmol/0.5 µl of quinpirole significantly reduced the early response (Aδ fibers) to dental pulp stimulation in 77% (10/13) of the neurons studied (Fig. 6a).



◀ **Fig. 5** Time course of dose response curves to unspecific and specific agonists of the striatal dopamine receptors. In **a**, reconstructions of the microinjected sites in the striatum are shown. Diagrams and levels were adopted from Paxinos and Watson (1997). In **b**, time course of the dose–response curves of the effect of microinjections of unspecific dopamine agonist APO are shown. Each point is the mean ± SE of *n* microinjections (one per animal) expressed as percent of control. $*P < 0.05$ when compared with the respective control or with the solvent, Newman–Keuls, after a significant two way ANOVA for repeated measured. Note that the highest concentration of APO (30 nmol) induced the maximal inhibition of the JOR amplitude and the largest duration of action. In **c**, time course of dose–response curves of the specific agonist for D_2 dopamine receptors quinpirole and the specific agonist for D_1 dopamine receptors SKF38393 are shown. Note that the maximal inhibition of the JOR was observed with 30 nmol/0.5 µl of quinpirole, while the stimulation of the D_1 receptors was ineffective. Each point is the mean ± SE of *n* microinjections (one per animal) as percent of control values (before injection). $*P < 0.05$, when compared with the respective control or the solvent, Newman–Keuls after two ways ANOVA for repeated measures. The *arrow heads* indicate the onset of the microinjections. **d** Histogram shows the effect of a microinjection of D_2 dopamine receptor antagonist haloperidol (7 nmol/0.5 µl), injected 20 min before the microinjection of 30 nmol/0.5 µl of quinpirole. The inhibitory effect on the JOR amplitude of the quinpirole was blocked significantly by the haloperidol. $*P < 0.05$ Newman–Keuls, one way ANOVA, $F_{2,15} = 83.39$, $P < 0.001$, $n = 6$ animals per group. Modified from Saunier-Rébori and Pazo (2006)

Similar results were observed in the responses of the C fibers input (Fig. 6a). This effect of quinpirole was associated to an inhibition of the JOR (Fig. 6a, b).

The participation of the analgesic opiate system in the inhibition of the nociceptive JOR was studied using the naloxone an antagonist of the opiate receptors. Naloxone was systemically administrated (1 mg/kg in 0.2 ml, i.v.) at the peak of the inhibition of the JOR induced by intrastriatal microinjection of quinpirole (30 nmol/0.5 µl). Naloxone reverted partially the inhibition of the JOR and the neuron response, of the NC, to activation of the striatal D_2 receptors (Fig. 6c). The duration of this effect was about 7 min. The above result provides inconclusive evidence of a possible involvement of opiate receptors in the analgesic action of the striatum.

Neural Basis

We also search the neural basis of the effect of activation of the striatal dopamine receptors on the inhibition of the nociceptive reflex (JOR) and the response of the neurons of the trigeminal NC to stimulation of the dental pulp.

The striatum has not direct connections with neural structures related to the endogenous analgesic system. However, two pathways: the striopallidal and the strionigral could mediate its analgesic effect. The lesion (electrolytic or with kainic acid) of the GP suppressed the inhibition of nociceptive JOR by striatal stimulation (Fig. 7a). This evidence suggests that the strionigral pathway was not involved (Barceló et al. 2010). Since the STN is an important target of the GP projection, we lesion that structure. The lesion of STN suppressed the JOR inhibition by striatal stimulation (Fig. 7b). Similar result was observed with lesion of the SNr (Fig. 7c). On the basis of

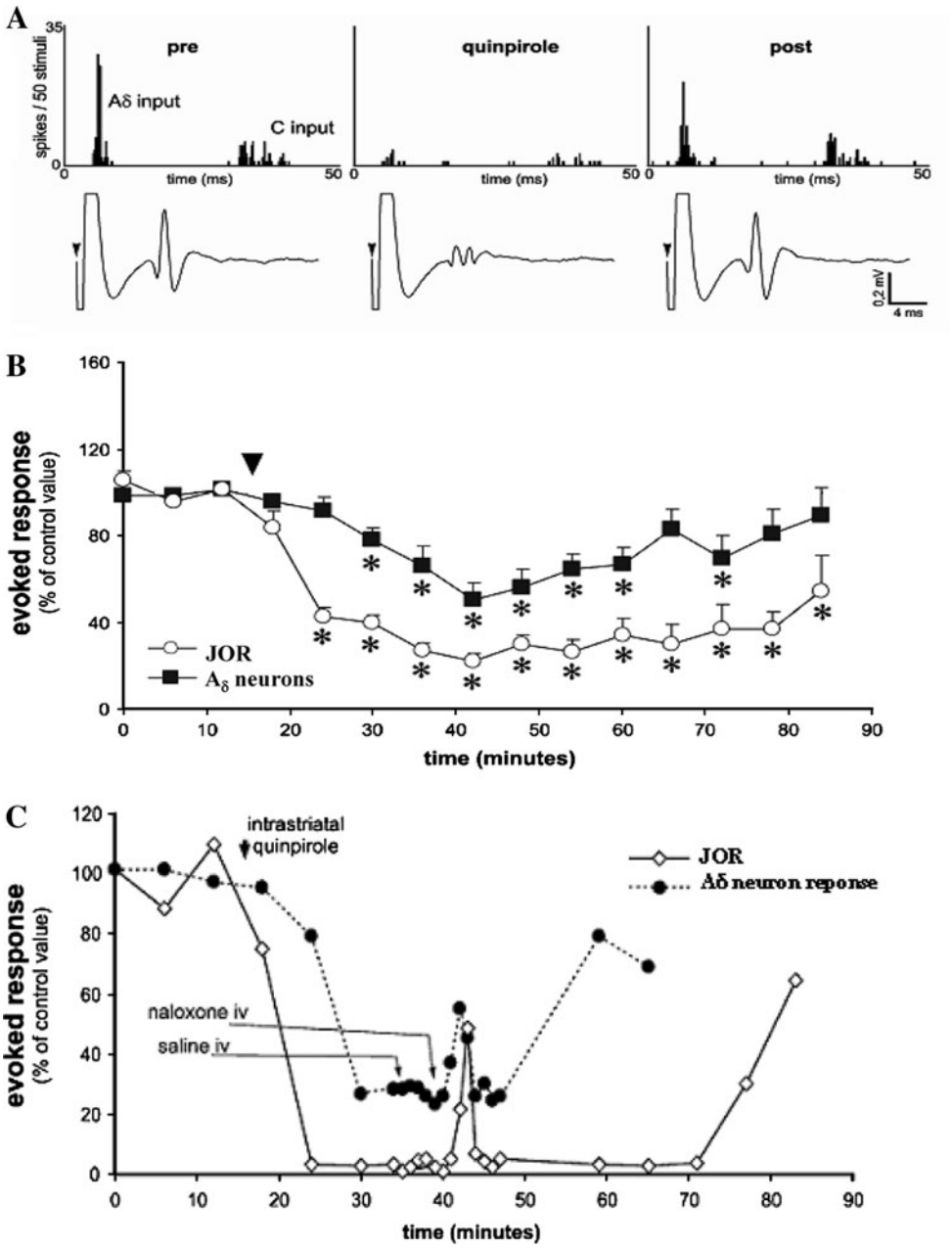


Fig. 6 Effect of intrastriatal microinjection of quinpirole (30 nmol/0.5 µl) on the evoked responses of a neuron of the NC of trigeminal nerve and digastric muscle (JOR), recorded during tooth pulp stimulation. In **a**, a representative PSTH of a neuron of the NC, in response to Aδ and C fibers activated by dental pulp stimulation before, during, and after quinpirole microinjection into the striatum is shown. PSTH bin width 1 ms, 50 sweeps. Dental stimulus onset was at time zero. *Lower row* JOR responses before, during, and after quinpirole administration recorded simultaneously with the neuron. The *arrow heads* indicate dental stimulation. Note the inhibitory action of quinpirole on both responses of Aδ and C afferents and on the JOR. In **b**, time course of neuron's response of the NC to Aδ inputs and the JOR induced by tooth pulp stimulation, before, during, and after intrastriatal microinjection of quinpirole (30 nmol/0.5 µl) is shown. Each point is the mean ± SE of 8–13 experiments as percent of control values. The values of neuronal responses were obtained from PSTHs and JOR amplitude from the mean ± SE of 50 consecutive individual responses. $^*P < 0.05$ Newman–Keuls after one way ANOVA for repeated measures, $F_{10,20} = 11.4$, $P < 0.0001$ (neurons Aδ inputs); $F_{10,120} = 8.9$, $P < 0.0001$ (JOR), when compared with the values before injection. *Arrowhead* indicates the onset of the microinjection. In **c**, effect of intravenous administration of naloxone (1 mg/kg in 0.2 ml of saline) on the inhibition of Aδ responses of the NC and of the JOR, induced by intrastriatal quinpirole (30 nmol/0.5 µl) is shown. Each point is mean of the evoked neuronal activity and the JOR mean amplitude of 50 consecutive responses expressed as percent of control values. Note the brief duration of the effect of naloxone. The solvent of naloxone was ineffective. Modified from Saunier-Rébori and Pazo (2006)

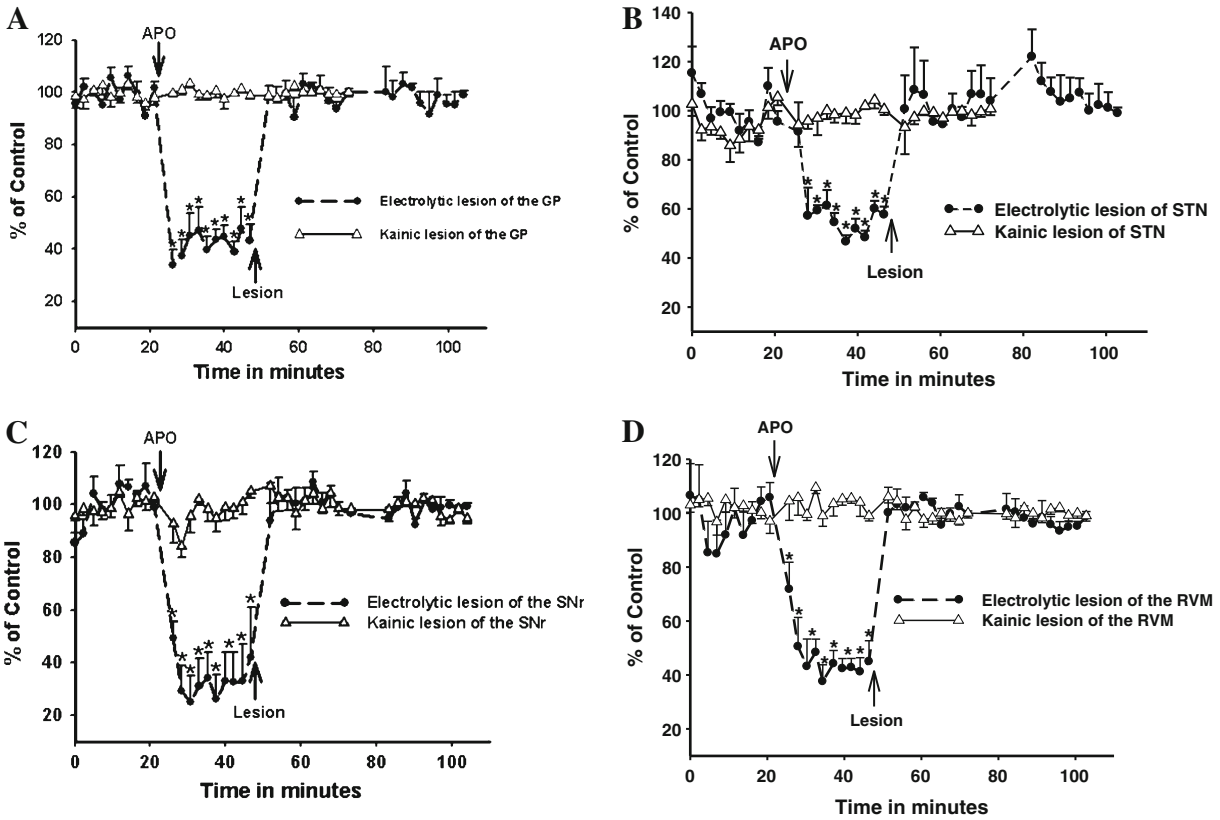


Fig. 7 Time course of the effect of microinjection of APO (30 nmol/0.5 µl) into the striatum of animals (5–6 per group) with acute electrolytic or chronic kainic acid lesions, ipsilateral to the striatum stimulated. In **a**, with lesion of the globus pallidus, in **b** of the subthalamic nucleus, in **c** of the substantia nigra pars reticulata, and in **d** of the rostral ventromedial medulla bilaterally are shown. The *arrows* indicate the microinjection of APO and the electrolytic lesion (lesion). $*P < 0.05$ Dunnett test after a significant one way ANOVA for repeated measures. Modified from Barceló et al. (2010)

these results, we concluded that the indirect pathway of the basal ganglia could mediate the analgesic action of the striatum.

Previous studies demonstrated that stimulation of the nuclei of rostral ventromedial medulla (RVM) inhibits the responses of neurons of the NC to tooth pulp stimulation and the nociceptive reflex, JOR (Tanaka and Toda 1982; Chiang et al. 1991, 1995; Dostrovsky 1984; Sasa et al. 1975; Sessle and Hu 1981). In addition, the RVM projects bilaterally to the sensory trigeminal nuclei (Basbaum and Fields 1979; Hental and Fields 1988; Li et al. 1995; Watkins et al. 1980). These evidences suggest that RVM could mediate the action of the striatum. Bilateral electrolytic or kainic acid lesion of RVM blocked the inhibition of the JOR produced by striatal activation (Fig. 7d). Although, the lesion of the RVM suppressed the inhibitory action of the striatum, it is not clear what projections from the basal ganglia arrived to the RVM. However, afferents from the GP and the SNr to medullary dorsal reticular nucleus in the rat has been reported, which in turn is connected with the RVM (Leite-Almeida et al. 2006).

Conclusions

The activation of the striatum inhibits the JOR, a nociceptive reflex, induced by suprathreshold stimulation of the dental pulp. In this analgesic action, the activation of the striatal dopamine D_2 receptors is involved, which is associated with inhibition of the painful responses of second order neurons of the trigeminal NC. Thus, inhibitions of sensorial afferent branch suppressed the activation of the digastric motor neurons with consequent inhibition of the JOR.

Neuronal pathways underlying the analgesic effect of the striatum implicated the indirect pathway (GPe–STN–SNr) of the basal ganglia. The lesion of any component of this pathway suppresses the inhibitory effect of the striatum on the nociceptive reflex, JOR. The final link of this projection is the RVM that innervates the sensorial trigeminal nuclei. The lesion of the RVM suppressed the inhibition of the JOR produced by striatal stimulation.

The participation of the opiate system in the analgesic action of the striatum is uncertain. The effectiveness of

naloxone to reduce the analgesic effect of the striatum on the JOR, it is in contraposition to the fact that systemic administration of naloxone increases by itself the JOR amplitude, possibly by inactivation of other analgesic systems.

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