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Role of $GABA_A$ receptors in the retrorubral field and ventral pallidum in rat jaw movements elicited by dopaminergic stimulation of the nucleus accumbens shell

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Abstract

The role of γ-aminobutyric acid $(GABA)_A$ receptors in the retrorubral field in the production of rat repetitive jaw movements was examined, as this nucleus receives a GABAergic, inhibitory input from the nucleus accumbens and is connected with the parvicellular reticular formation, a region that is directly connected with the orofacial motor nuclei. The $GABA_A$ receptor antagonist bicuculline (150 ng/0.2 μl per side) significantly produced repetitive jaw movements when injected bilaterally into the retrorubral field, but not the ventral pallidum. The effects of bicuculline were $GABA_A$ receptor specific, because the effects were abolished by muscimol, a $GABA_A$ receptor agonist, given into the same site. The bicuculline-induced jaw movements differed qualitatively from those elicited by injection of a mixture of (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol (SKF 82958; 5 μg) and quinpirole (10 μg), agonist at dopamine D1 and D2 receptors respectively, into the nucleus accumbens shell. Nevertheless, bilateral injections of muscimol (10 ng, 25 ng and 50 ng/0.2 μl per side) into the retrorubral field significantly inhibited jaw movements evoked by the dopamine D1/D2 receptor stimulation in the nucleus accumbens shell. Bilateral injections of bicuculline (50 ng and 150 ng/0.2 μl per side) also reduced the dopamine D1/D2 receptor-mediated jaw movements. Essentially similar effects were obtained when muscimol and bicuculline were given into the ventral pallidum, a region that is also known to receive GABAergic inhibitory inputs from the nucleus accumbens. In conclusion, $GABA_A$ receptor blockade in the retrorubral field elicits characteristic repetitive jaw movements, and the $GABA_A$ receptors in that region as well as in the ventral pallidum modulate the accumbens-specific, dopamine D1/D2 receptor-mediated jaw movements.

Keywords: Jaw movement; Nucleus accumbens shell; Retrorubral field; Ventral pallidum; $GABA_A$ receptor; Dopamine D1/D2 receptor stimulation; (Rat)

1. Introduction

It is well known that dopaminergic neurons in the retrorubral field primarily project to the striatum (Gerfen et al., 1987). This region also contains neural population that projects to the parvicellular reticular formation, a region that contains orofacial premotor nuclei and gives rise to neurones that converge onto neurones in the trigeminal motor nucleus (Fort et al., 1990; Travers and Norgren, 1983). The retrorubral field is known to receive γ-aminobutyric acid (GABA)ergic input from the nucleus accumbens (Zahm and Heimer, 1993). Activation of dopamine receptors in the nucleus accumbens has been found to elicit repetitive jaw

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movements in rats (Koshikawa et al., 1990a). Subsequently, it has been found that these dopamine receptor-mediated jaw movements are elicited predominantly by co-activation of dopamine D1 and D2 receptors in the shell, but not the core, of the nucleus accumbens (Cools et al., 1995; Koshikawa et al., 1996a).

Until now, it is not clear whether or not the retrorubral field plays any role in the transmission of these accumbens shell-specific, dopamine D1/D2 receptor-mediated jaw movements. Such a role can be expected in view of the fact that (1) it is known that the retrorubral field is involved in the control of oral behaviours in cats (Arts et al., 1998) and (2) the retrorubral field contains dopaminergic neurons projecting to the region of the striatum that encompasses its ventrolateral part (Gerfen et al., 1987), where repetitive jaw movements can be elicited by dopamine D1/D2 receptor stimulation (Koshikawa et al., 1989; Delfs and Kelley, 1990; Adachi et al., 2002, 2003).

In the first part of this study, like in our previous studies (Adachi et al., 2002, 2003), electromyography and a phototransduction system were used to characterise the pattern of jaw movements induced by injections of GABAergic drugs, muscimol and bicuculline to activate and inhibit $GABA_A$ receptors respectively, into the retrorubral field in order to compare these with those elicited by injections of dopamine receptor agonists into the nucleus accumbens shell (Cools et al., 1995). Once the nature of the behavioural response to injections into the retrorubral field of GABAergic drugs was established, we studied the specificity of the response using joint injections of the $GABA_A$ receptor agonist muscimol and the $GABA_A$ receptor antagonist bicuculline.

To analyse the role of the retrorubral field in the jaw movements that are elicited by stimulation of dopamine receptors in the nucleus accumbens shell, muscimol and bicuculline were injected bilaterally into the retrorubral field of rats treated with bilateral injections into the nucleus accumbens shell of a mixture of the dopamine D1 receptor agonist, (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol (SKF 82958; 5 μg), and the dopamine D2 receptor agonist, quinpirole (10 μg); the latter dopaminergic treatments have been found to be highly effective in eliciting the above-mentioned dopamine receptor-mediated jaw movements (Cools et al., 1995).

Like the retrorubral field, the ventral pallidum is also known to receive a GABAergic input from the nucleus accumbens (Groenewegen and Russschen, 1984; Zahm and Brog, 1992). Although GABAergic manipulation of the ventral pallidum does not elicit repetitive jaw movements (Adachi et al., 2002), it has been found to modulate the jaw movements induced by bilateral injections of a mixture of SKF 82958 (5 μg) and quinpirole (10 μg) into the ventrolateral striatum (Adachi et al., 2002).

For that reason, it became of interest to compare the role of the retrorubral field with that of the ventral pallidum. The final part of this study therefore examined a role of $GABA_A$ receptors in the ventral pallidum by injecting muscimol and bicuculline bilaterally into this brain structure of rats treated with a mixture of SKF 82958 (5 μg) and quinpirole (10 μg) into the nucleus accumbens shell.

2. Materials and methods

2.1. Surgical procedures

Male Sprague–Dawley rats weighing 260–330 g were housed in cages (27×45×20 cm) that were kept at constant room temperature (23±2 °C) and relative humidity (55±5%) under a 12 h light/dark cycle (lights on at 0700 h), with free access to food and water.

Rats were anaesthetised with halothane (0.5–4.0% when appropriate) and supplemented with ketamine HCl (10.0 mg/kg, i.p.). The surgical and recording procedures were as described previously (Koshikawa et al., 1989, 1990a,b, 1991; Cools et al., 1995). After cannulation of the right external jugular vein, a small light-emitting diode was fixed to the mandible. The animal was placed in a stereotactic frame so that the head was kept in constant relation to a light-sensitive transducer, which detected the vertical movements of the diode. Bipolar electrodes were placed into the masseter and digastric muscles to record electromyographic activity. After surgery, the animals continuously received ketamine in a dose (10.0 mg/kg, i.v.) unable to influence either the jaw movements under study (Koshikawa et al., 1989) or the dopamine metabolism in the striatum (Koshikawa et al., 1988). Lignocaine HCl (2% gel) was applied to all incisions to ensure complete analgesia. Rectal temperature was maintained at 37.0 °C with a thermostatically controlled heating pad. Monitored concentrations of expired O_2 and CO_2 during the experiment were 19–21% and 2.0–2.5%, respectively. The jaw movements and electromyographic activity were recorded on an eight-channel tape recorder (RD-180T; TEAC) for off-line analyses according to previously described procedures (Adachi et al., 2002). Thus the recordings were analysed automatically, using a spike trigger that counted vertical jaw movements per 5 min, and the electromyographic data were full-wave rectified. Averaging of the vertical output of the movement transducer and jaw muscle electromyographic activity was performed with a computer system (signal processor 1000; NEC). The recording period lasted 120 min. The recorded electromyographic activity and movements of the mandible were averaged in order to establish the relationship between electromyographic activity and the movements more clearly.

Guide cannulas (0.5 mm o.d., 0.3 mm i.d. 6.0 mm length) were implanted bilaterally into the brain according to previously described procedures (Koshikawa et al., 1989). The coordinates based on the atlas of Paxinos and Watson (1998) were: anterior=10.6 mm, vertical=2.0 mm, lateral=0.7 mm (nucleus accumbens shell); anterior=8.7 mm,

vertical=2.6 mm, lateral=2.2 mm (ventral pallidum); anterior=2.7 mm, vertical=2.4 mm, lateral=2.0 mm (retrorubral field). Cannulas directed at the shell of the nucleus accumbens were angled 21° from the mid-sagittal plane to avoid the ventricular system (Cools et al., 1995). The injection was made slowly in a volume of 0.2 μl per side over 20 s, and the needle was left in situ for an additional 20 s period after completion of the injection. Damage to the target site was minimised by implanting the tips of the guide cannulas 2.0 mm (nucleus accumbens shell), 2.2 mm (retrorubral field) or 2.0 mm (ventral pallidum) above the desired injection site. Wire stylets were placed in the guide cannulas to prevent occlusion.

These experiments were approved by the Animal Experimentation Committee of Nihon University School of Dentistry, and were performed in accordance with Institutional guidelines for the care and welfare of experimental animals that were in compliance with the UK Animals Scientific Act 1986.

2.2. Drugs

The animals (n=5–10 per experiment) received bilateral injections of the full dopamine D1 receptor agonist, SKF 82958 (5 μg; (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol hydrobromide, Sigma, St. Louis, MO), and the dopamine D2 receptor agonist, quinpirole (10 μg; Sigma), combination (cocktail) into the nucleus accumbens shell. The $GABA_A$ receptor agonist, muscimol (10 ng, 25 ng or 50 ng; 5-aminomethyl-3-hydroxyisoxazole, Sigma), or the $GABA_A$ receptor antagonist, (−)-bicuculline methylbromide (50 ng or 150 ng; Sigma), was injected into the retrorubral field or ventral pallidum, immediately before the injection of the mixture of SKF 82958 and quinpirole into the nucleus accumbens shell. In co-administration experiments muscimol and bicuculline were given together in a single injection volume of 0.2 μl. All drugs were dissolved in saline immediately before use. Doses employed were based on previously published studies (Cools et al., 1995; Adachi et al., 2002, 2003). The animals were used only once.

2.3. Histology

At the end of each experiment, the rats were deeply anaesthetised with sodium pentobarbitone (80 mg/kg, i.p.) and perfused transcardially with 10% formalin. The brains were removed, sectioned at 50 μm and stained with Cresyl violet to visualise the injection site; only data from animals in which the injections were correctly placed were included in subsequent analyses. Fig. 1 gives a survey of the injection sites located in the nucleus accumbens shell, retrorubral field and ventral pallidum.

2.4. Data analysis

All values are expressed as means±S.E.M. and analysed using one-way analysis of variance (ANOVA) or two-way ANOVA (group×time), followed by a post-hoc Dunnett's test where appropriate. A probability value of $P<0.05$ was considered statistically significant.

3. Results

3.1. Pattern of jaw movements elicited by bilateral injections of GABAergic drugs into the retrorubral field

Muscimol (50 ng) alone had no effect. In contrast, bicuculline (150 ng) was effective in eliciting jaw movements. Fig. 2 shows the results of the electromyographic activity recorded from digastric and masseter muscle together with the vertical component of jaw movements. Bilateral injections of bicuculline into the retrorubral field (Fig. 2, left parts) increased electromyographic activity in the digastric muscle that was associated with the movement of jaw opening, but did not change the stable moderate tone of the electromyographic activity in the masseter muscle during jaw movements (digastric type). This characteristic feature was unique in the sense that it did not match the pattern elicited by stimulation of dopamine D1/D2 receptors in the nucleus accumbens (Fig. 2, right parts). Thus, bilateral injections of the mixture of SKF 82958 (5 μg) and quinpirole (10

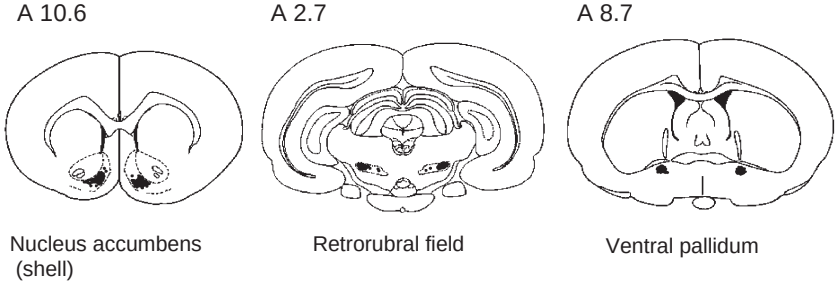

Fig. 1. Location of injection sites in the nucleus accumbens shell (left), retrorubral field (middle) and ventral pallidum (right). Planes are modified to a series of 2 or 3 sections for each brain area from the atlas of Paxinos and Watson (1998); approximate coordinates indicated are in mm anterior to the interaural line.

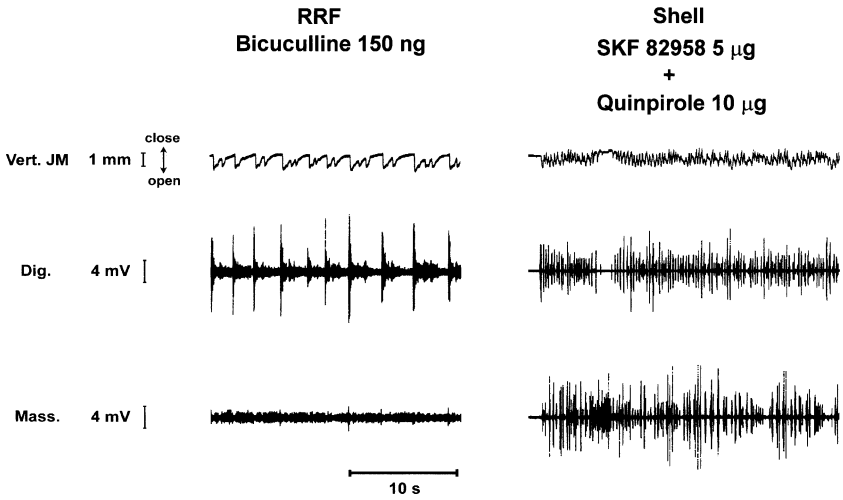

Fig. 2. Pattern of jaw movements elicited 10 min after bilateral injections of bicuculline (150 ng) into the retrorubral field (RRF, left part). For the sake of comparison, the pattern of jaw movements elicited 60 min after bilateral injections of the cocktail of SKF 82958 (5 μg) and quinpirole (10 μg) into the nucleus accumbens shell (right part) are included. Vertical component of jaw movements (Vert. JM) and associated electromyographic activity recorded from digastric (Dig.) and masseter (Mass.) muscles are shown.

μg) into the nucleus accumbens shell increased the electromyographic activity in both the digastric and the masseter muscles, a phenomenon that was associated with movements of both jaw opening and closing: digastric activity was dominant during jaw opening, and masseter activity was dominant during jaw closing (digastric/masseter type).

3.2. GABA-specific effects of bicuculline within the retrorubral field

Bilateral injections of bicuculline (150 ng; n=7) into the retrorubral field elicited jaw movements (150 ng vs. saline: $F(1,264)=4.03$, $P<0.05$). The time-dependent effect of bicuculline, shown in Fig. 4, clearly illustrates that the effect started nearly immediately after injection, reached its peak around 10 min and vanished about 30 min after injection. Injections of saline (n=6) into the retrorubral field did not elicit any repetitive jaw movement (Fig. 3).

The effects of bicuculline (n=7) were completely abolished by muscimol (50 ng; n=7; $F(1,288)=23.18$, $P<0.001$) injected into the same site: muscimol (50 ng; n=7) alone did not elicit any jaw movement (Fig. 3).

3.3. Effects of bilateral injections of muscimol into the retrorubral field on jaw movements elicited by administration of SKF 82958 and quinpirole mixture into the nucleus accumbens shell

The time-dependent effect of the mixture of SKF 82958 and quinpirole is shown in Fig. 4. This figure illustrates that the jaw movements occurred initially at low levels but subsequently increased markedly and then declined over the 120-min observation period. When given into the retrorubral field, muscimol produced a dose-dependent inhibition of the number of jaw movements elicited by the mixture of SKF 82958 and quinpirole injected into the nucleus accumbens shell [overall: $F(3,28)=16.41$, $P<0.0001$; 10 ng (n=10) vs. control (n=8): $P<0.01$; 25 ng (n=7) vs. control (n=8): $P<0.001$; 50 ng (n=7) vs. control (n=8): $P<0.001$, Dunnett's test] (Fig. 4). However, the pattern of jaw movements and the associated muscle activity (digastric/masseter type) were not altered by muscimol.

3.4. Effects of bilateral injections of bicuculline into the retrorubral field on jaw movements elicited by administration of SKF 82958 and quinpirole mixture into the nucleus accumbens shell

Injections of bicuculline into the retrorubral field suppressed the number of jaw movements elicited by the mixture of SKF 82958 and quinpirole injected into the nucleus accumbens shell [overall: $F(2,19)=7.21$, $P<0.01$; 50 ng (n=7) vs. control (n=8): $P<0.01$; 150 ng (n=7) vs. control (n=8): $P<0.01$, Dunnett's test] (Fig. 5). However, the pattern of jaw movements and the associated muscle activity (digastric/masseter type) were not altered by bicuculline.

3.5. Effects of bilateral injections of muscimol or bicuculline into the ventral pallidum on jaw movements elicited by administration of SKF 82958 and quinpirole mixture into the nucleus accumbens shell

When given into the ventral pallidum, muscimol produced a dose-dependent inhibition of the number of jaw movements elicited by the mixture of SKF 82958 and quinpirole injected into the nucleus accumbens shell [overall: $F(3,23)=13.81$, $P<0.0001$; 10 ng (n=10) vs. control

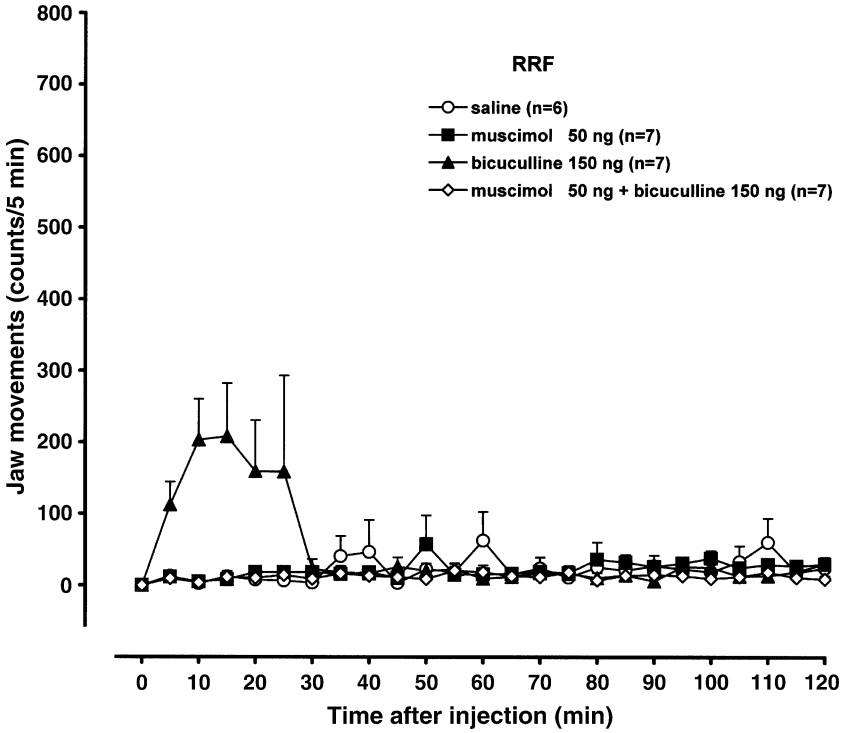

Fig. 3. The time-dependent effects of bilateral injections of saline (0.2 μl/side), bicuculline (150 ng/side), muscimol (50 ng/side) or the mixture of bicuculline (150 ng/side) and muscimol (50 ng/side) into the retrorubral field on production of jaw movements. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n=6–7). Vertical bars indicate S.E.M.

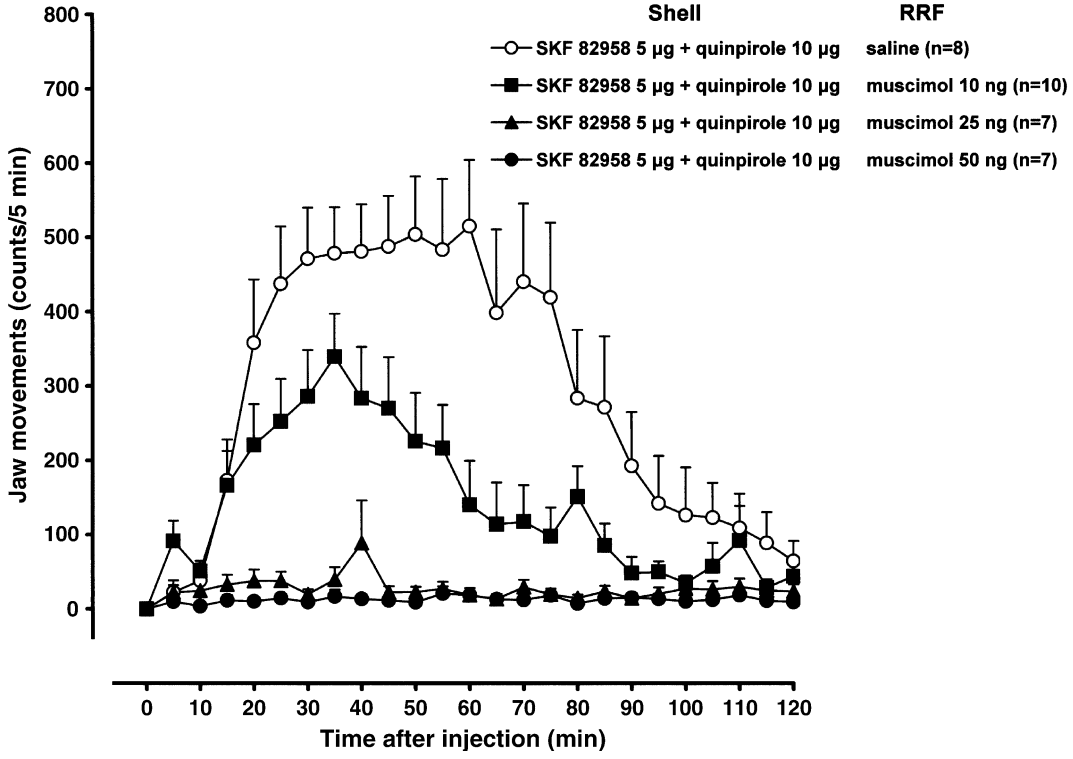

Fig. 4. Effects of muscimol (10, 25 and 50 ng/side) injection into the retrorubral field on production of jaw movements induced by the mixture of SKF 82958 (5 μg) and quinpirole (10 μg) given into the nucleus accumbens shell. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n=7–10). Vertical bars indicate S.E.M.

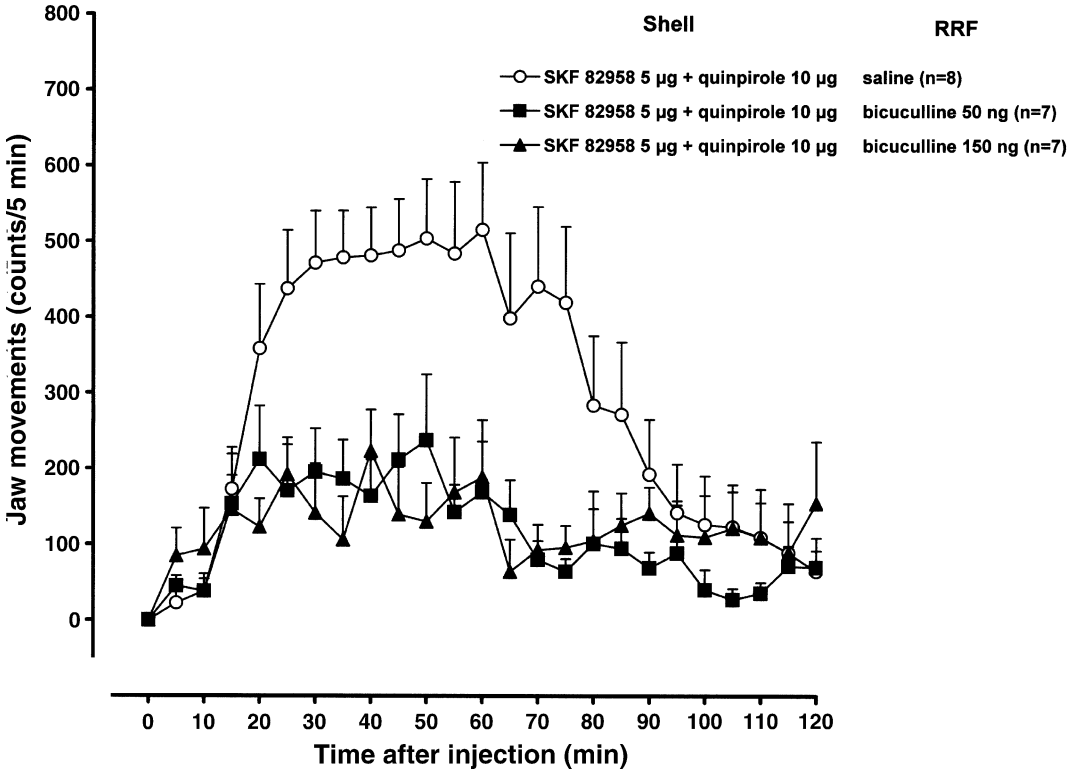

Fig. 5. Effects of bicuculline (50 and 150 ng/side) injection into the retrorubral field on production of jaw movements induced by the mixture of SKF 82958 (5 μg) and quinpirole (10 μg) given into the nucleus accumbens shell. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n=7–8). Vertical bars indicate S.E.M.

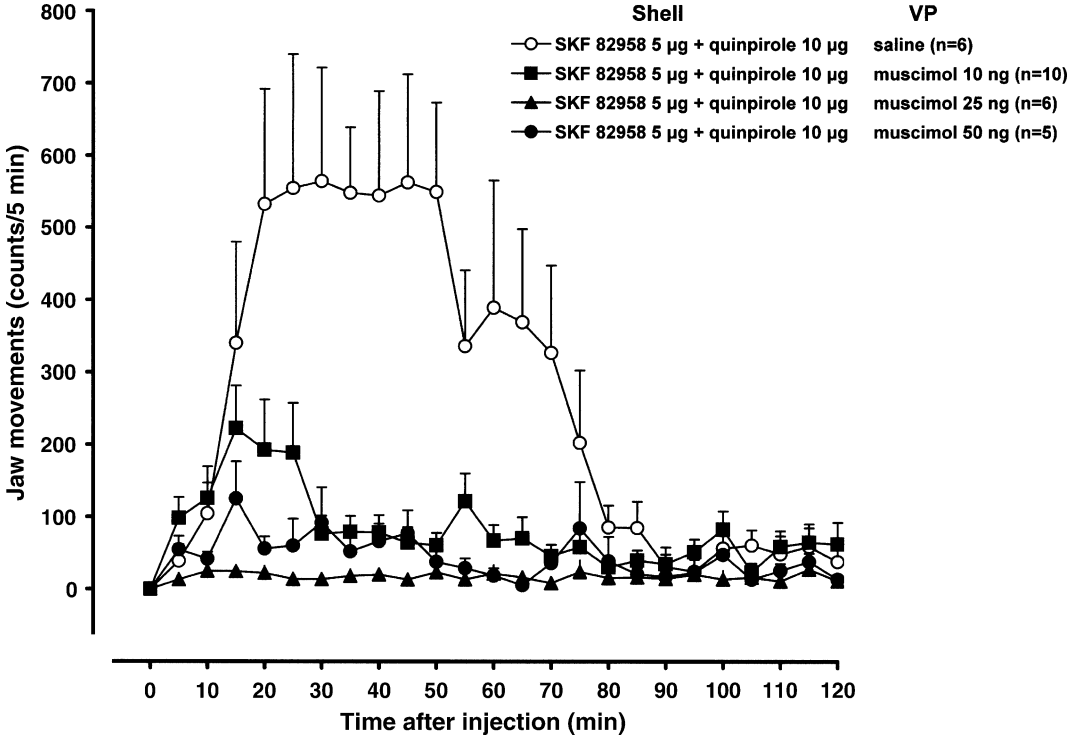

Fig. 6. Effects of muscimol (10, 25 and 50 ng/side) injection into the ventral pallidum on production of jaw movements induced by the mixture of SKF 82958 (5 μg) and quinpirole (10 μg) given into the nucleus accumbens shell. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n=5–10). Vertical bars indicate S.E.M.

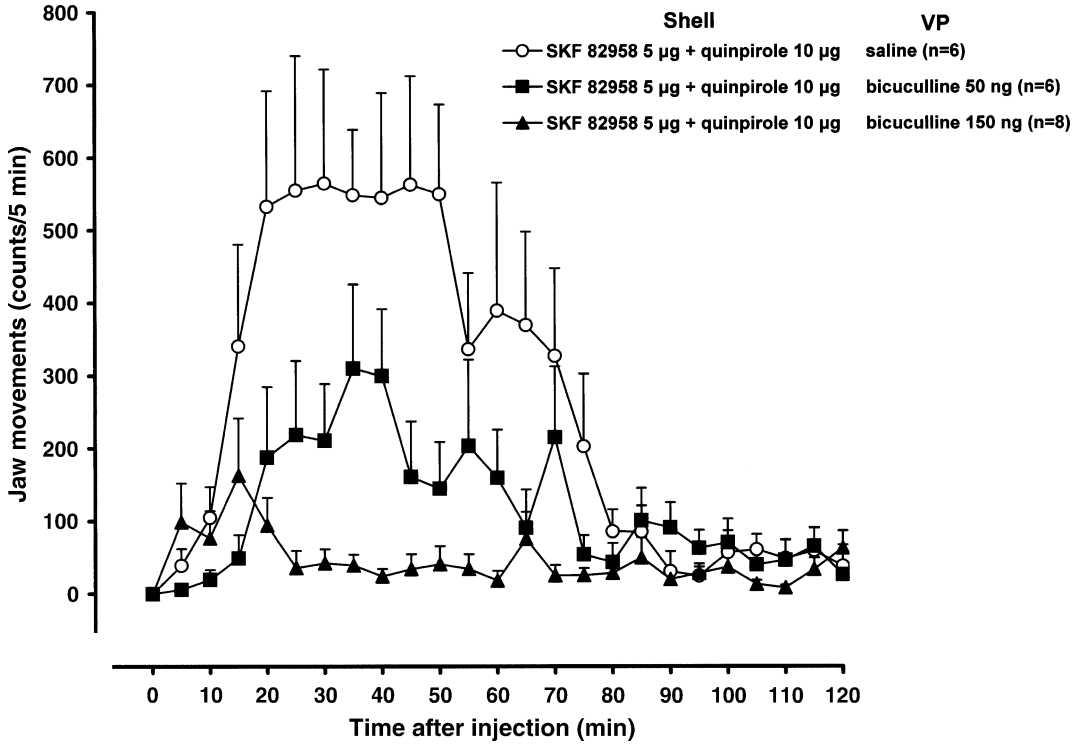

Fig. 7. Effects of bicuculline (50 and 150 ng/side) injection into the ventral pallidum on production of jaw movements induced by the mixture of SKF 82958 (5 μg) and quinpirole (10 μg) given into the nucleus accumbens shell. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n=6–8). Vertical bars indicate S.E.M.

(n=6): P<0.001; 25 ng (n=6) vs. control (n=6): P<0.001; 50 ng (n=5) vs. control (n=6): P<0.001, Dunnett's test] (Fig. 6). Injections of bicuculline into the ventral pallidum dose-dependently inhibited the number of jaw movements elicited by the mixture of SKF 82958 and quinpirole [overall: F(2,17)=9.55, P<0.01; 50 ng (n=6) vs. control (n=6): P<0.05; 150 ng (n=8) vs. control (n=6): P<0.001, Dunnett's test] (Fig. 7). However, the pattern of jaw movements and the associated muscle activity (digastric/masseter type) were not altered by muscimol or bicuculline.

4. Discussion

The present study demonstrates that bilateral injections of the $GABA_A$ receptor antagonist bicuculline produced characteristic repetitive jaw movements when injected into the retrorubral field. The behavioural response to bicuculline was specific for $GABA_A$ receptors, because the $GABA_A$ receptor agonist muscimol well inhibited this response (Fig. 3). Using an identical experimental set up (Adachi et al., 2002), we have previously shown that none of the GABAergic drugs, injected into the ventral pallidum, namely a region that also receives a GABAergic input from the nucleus accumbens, elicit any jaw movement. The results therefore allow the conclusion that the accumbens-specific, dopamine receptor-mediated jaw movements are not funnelled via the ventral pallidum towards brain stem nuclei.

As illustrated in Fig. 2, the site-specific and $GABA_A$ receptor-mediated jaw movements are characterised by a dominant digastric activity during jaw opening without any significant change in masseter activity during jaw closing (digastric type), namely a pattern that fully differs from the pattern elicited by stimulation of dopamine D1/D2 receptors in the nucleus accumbens shell (digastric/masseter type). In view of this data, it is concluded that the retrorubral field, like the ventral pallidum (cf. Adachi et al., 2002), is not a station that transmits jaw movements elicited by stimulation of dopamine D1/D2 receptors in the nucleus accumbens shell. Although the mechanism that gives rise to the bicuculline-induced jaw movements is unknown, it is evident that removal of the GABAergic inhibitory tone can disinhibit neurons that ultimately terminate in the reticular region around the trigeminal motor nucleus and parvicellular reticular formation of the medulla oblongata (von Krosigk et al., 1992), where many premotor neurons for the orofacial motor nuclei are present.

The retrorubral field is known as A8 area that contains dopaminergic neurones projecting primarily to the ventrolateral part of the striatum (Gerfen et al., 1987), namely a region that itself is the origin of striato-entopedunculo-bulbar and striato-nigro-bulbar fibres (von Krosigk et al., 1992; Takada et al., 1994; Iwata et al., 1996). The dopaminergic activity in the ventrolateral striatum is known to be under accumbal dopaminergic control (Koshikawa et al., 1996b; Kitamura et al., 1999). It is therefore hypothesised that the GABAergic mechanisms in the retrorubral field

play a modulatory role in jaw movements elicited by stimulation of dopamine D1/D2 receptors in the nucleus accumbens shell. Since neurones of the ventral pallidum are known to exert an inhibitory effect on cells in the dorsolateral part of the substantia nigra pars reticulata (Maurice et al., 1997), the GABAergic mechanisms in the ventral pallidum may also have a modulatory role in this respect (see below).

As shown in the Results section, both injections of the $GABA_A$ receptor agonist, muscimol, and the $GABA_A$ receptor antagonist, bicuculline, into the retrorubral field and ventral pallidum inhibited to various degrees the dopamine D1/D2 receptor-mediated jaw movements that were elicited from the nucleus accumbens shell. These effects were not aspecific, because injections of the solvent of these drugs into the regions under study did not produce any inhibition. As suggested in our previous study (see Adachi et al., 2002), the most likely explanation is that the regions under study are heterogeneous, encompassing an area sensitive to the $GABA_A$ receptor agonist because the tonus of its GABAergic input is low, and an area sensitive to the $GABA_A$ receptor antagonist because the tonus of its GABAergic input is high. Although such heterogeneity has not been described for regions such as the retrorubral field, it is well known for pallidal regions such as the ventral pallidum and the entopeduncular nucleus (Filion et al., 1994; Matsumura et al., 1995). According to the latter authors, pallidal segments are marked by a centre-surround organisation, with hypoactivity in the peripheral outer part and hyperactivity in the central inner part. In fact, they have demonstrated that there is a topological antagonistic centre-surround organization, providing a topological arrangement that allows an informational convergence on a limited number of pallidal neurons in the centre. Such an organisation implies that the GABAergic input is high in the peripheral outer part, but low in the central inner part, or vice versa. Considering our above-mentioned data in the context of these findings, it is suggested that the dopaminergic treatment reduced the tonus of the GABAergic input of the peripheral outer parts of the two regions examined with the consequence that it indirectly enhanced the GABAergic tonus at the level of the output neurons in the central inner part, resulting in a hypoactive output of the region under study. In this manner, the terminal structures of striato-entopedunculo-bulbar and/or striato-nigro-bulbar systems, namely the orofacial motor nuclei, are ultimately released from tonic inhibition and can, accordingly, give rise to the initiation of jaw movements (cf. Hikosaka and Wurtz, 1985). According to this model, bicuculline inhibited the dopamine D1/D2 receptor-mediated jaw movements because it inhibited the high GABAergic input of the inner part, and muscimol inhibited these jaw movements because it enhanced the GABAergic input in the peripheral outer part.

It is evident that the above-mentioned explanation of the present findings is open for discussion. Despite this, the data available clearly suggest that the two regions examined are heterogeneous as far as concerns the GABAergic input, and that the regions indirectly modulate dopamine D1/D2 receptor-mediated jaw movements that are elicited from the nucleus accumbens shell. Future studies are required to provide direct evidence in favour of this hypothesis.

In conclusion, the present study demonstrates that a $GABA_A$ receptor blockade in the retrorubral field elicits a characteristic type of repetitive jaw movements that fully differs from those elicited by stimulation of dopamine D1/D2 receptors in the nucleus accumbens shell. Furthermore, evidence is provided that $GABA_A$ receptors in the retrorubral field control accumbens shell-specific dopamine D1/D2 receptor-mediated jaw movements in a manner essentially similar to that of the $GABA_A$ receptors in the ventral pallidum.

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