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Research report

Topographical connections of the substantia nigra pars reticulata to higher-order thalamic nuclei in the rat

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ABSTRACT

The substantia nigra pars reticulata (SNR) is the ventral subdivision of the substantia nigra and contains mostly GABAergic neurons. The present study explores whether the SNR relates to all dorsal thalamic nuclei equally or just to a particular group of nuclei, such as first or higher-order nuclei.

Injections of biotinylated dextran amine (BDA) were made into the SNR of 10 male adult rats. The distribution of anterogradely labelled axon terminals in the thalamic nuclei was documented. The projections of the SNR to the thalamic nuclei were exclusively to some motor higher-order, but not to first-order thalamic relays. There were bilateral projections to the ventromedial (VM), parafascicular (PF), centromedian (CM) and paracentral (PC) nuclei and unilateral projections to the centrolateral (CL), mediodorsal (MD) and thalamic reticular nucleus (Rt). Labelled axon terminals in the thalamic nuclei ranged from numerous to sparse in VM, PF, CM, CL, PC, MD and Rt. Further, injections into the SNR along its rostral-caudal axis showed specific topographical connections with the thalamic nuclei. The rostral SNR injections showed labelled axon terminals of VM, PF, CL, PC, CM, MD and Rt. Caudal SNR injections showed labelling of VM, PF, PC, CM and MD. All injections showed labelled axons and terminals in the zona incerta.

The nigrothalamic GABAergic neurons can be regarded as an important system for the regulation of motor activities. The SNR is in a position to influence large areas of the neocortex by modulating some of the motor higher-order thalamic nuclei directly or indirectly via Rt.

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1. Introduction

The substantia nigra pars reticulata (SNR) is an important processing center of the basal ganglia. The GABAergic neurons convey some of the output of the basal ganglia to the thalamus and superior colliculus. The inputs to the SNR neurons are GABAergic inhibitory inputs from the striatum and external globus pallidus and glutamatergic excitatory inputs from the subthalamic nucleus [7]. The major output targets of the SNR include the thalamus, midbrain reticular formation (pedunculopontine nucleus) and superior colliculus [12,13,15,41,53]. Cebrián et al. [12], classified the projecting neurons of the SNR into 4 type as: type I (project to the thalamus), type II (project to thalamus, superior colliculus and pedunculopontine tegmental nucleus), type III (project to thalamus and periaquaductal gray) and type IV (deep mesencephalic nucleus and superior colliculus). Extensive studies on the nigrothalamic axons have shown that these originate from multipolar neurons located throughout at the lateral and central part of the SNR and terminate in the ventral medial (VM), ventral lateral (VL), ventral anterior (VA), centrolateral (CL), centromedial (CM), mediodorsal (MD), paracentral (PC) and parafascicular (PF) thalamic nuclei in the rat, cat and monkey [4,12,13,17–19,36,44,46,53]. Histological, electrophysiological and pharmacological studies have demonstrated that the majority

Abbreviations: VP, ventral posterior thalamic nucleus; VL, ventral lateral thalamic nucleus; CL, centrolateral thalamic nucleus; PC, paracentral thalamic nucleus; CM, centromedial thalamic nucleus; VM, ventromedial thalamic nucleus; VA, ventral anterior thalamic nucleus; MD, mediodorsal thalamic nucleus; LP, lateral posterior thalamic nucleus; PF, parafascicular thalamic nucleus; Po, posterior thalamic nucleus; Rt, thalamic reticular nucleus; ZI, zona incerta; CC, corpus callosum; CuP, caudate putamen; IC, internal capsule; F, fornix; MT, mamillothalamic tract; OPT, optic tract; 3V, 3rd ventricle; D3V, dorsal 3rd ventricle; ST, stria terminalis; IMD, intermediodorsal thalamic nucleus; DLGN, dorsolateral geniculate nucleus; MRe, mammillary recess of the 3rd ventricle; Layer V, cortical layer V.

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of the nigral projections to the thalamic nuclei are GABAergic [14,17].

The dorsal thalamus is the major relay to the cerebral cortex. The first-order relays (ventrobasal, lateral geniculate, etc.) receive their driving afferents from subcortical structures whereas higher-order thalamic nuclei (CL, CM, PC, PF, VM, MD PUL, LD, etc.) receive their driving afferents from the cortex [48,50,56]. Both the first and the higher-order thalamic relays receive drivers and modulatory afferents. It is the drivers that actually carry the message for relay to the cortex, whereas the modulators produce changes in the way the message is transmitted [28,29,37,55]. The major difference between first and higher-order thalamic relays is in the organization of cortico-thalamic projections. It is this distinction that is important for identifying a particular relay as first or higher-order: for higher-order relay, the driver afferents must come from cortex itself. Both first and higher-order thalamic relays receive cortico-thalamic modulatory inputs from layer VI, whereas relay cells of higher-order thalamic nuclei also receive characteristic large excitatory terminals from collaterals of layer V pyramidal cells [8,9,17,22,27,33,34,45,49]. Studies have shown some thalamic nuclei such as MD are not pure higher-order and, contain a mixture of first and higher-order relays. Further, the Rt is regarded as neither higher nor first-order thalamic nucleus. The Rt is regarded as neither a higher nor a first-order thalamic nucleus.

Recent studies have shown that specific populations of inhibitory inputs from the zona incerta (ZI) and the anterior pretectal nucleus go exclusively to the higher-order relays [3,5,6,10,32]. In the present study we aimed in particular to explore whether the inhibitory axons of the SNR relate to all dorsal thalamic nuclei equally or just to one particular group of nuclei, such as first-order and/or higher-order. In addition we studied the organization of the projection from SNR to the several distinct thalamic nuclei receiving this input.

2. Materials and method

Ten successful injections, made into adult male Sprague–Dawley rats, weighing 250–300 g, were included in the study. All animals were housed in a room with a 12 h light and 12 h dark cycle with food and water access ad libitum. All experiments were carried out in accordance with the Marmara University Ethical Committee for Experimental Animals (61.2002.Mar), the European Communities Council Directive (86/609/EEC) and the German Law on the Protection of Animals.

2.1. Biotinyated dextran amin (BDA)

The anterograde and retrograde tracer BDA, additionally labelled with rhodamine (D-3312, Molecular Probes, Eugene, OR, USA), was used as a 10% solution in 10 mM phosphate buffer at pH 7.3. The rhodamine allows the use fluorescence microscopy and does not change the properties of the BDA; the BDA provides a permanent label. Animals were deeply anesthetized with pentobarbital [Narcoren®] given as 35 mg/kg body weight (bw) i.p. together with a mixture of 1 ml/kg bw of ketamine (25 mg/ml), xylazine (1.3 mg/ml) and azepromazine (0.25 mg/ml). The anesthetized animal was mounted in a stereotaxic apparatus (Stoelting, Woods Dale, IL, USA), the skull was opened at the position for the SNR and a pipette (tip diameter 20–50 μm) was lowered to the SNR on one side. Coordinates were taken from the stereotaxic atlas. The planned coordinates of the SNR were anterior–posterior −5.6 mm; mediolateral −2.4 mm; dorsoventral −7.8 mm from bregma. A single injection of BDA was administered iontophoretically into one side of the SNR of each rat. A positive current of 5 μA was applied for 15 min at an interval cycle of 7 s on/off with a custom build current source (Stoelting CO, Digital Midgard Precision Current Source). The pipette was left at the injection site an additional 3 min to prevent leakage of tracer into the track.

After a survival of 7 days the animals received a lethal dose of pentobarbital [Narcoren®] (100 mg/kg bw i.p.) and were transcardially perfused with 0.9% saline (250–350 ml per animal) followed by a mixture containing 4% paraformaldehyde and 15% saturated picric acid in 0.1 M phosphate buffer (PB) at pH 7.4 (500 ml per animal). Brains were immediately removed from the skull, postfixed in the same fixative overnight and stored in 20% sucrose solution in PB at 4 °C for 2 days. Coronal cryostat sections were cut at 40 μm and collected in PB in tissue-culture plates. The transport of BDA was revealed by incubating the sections in an ABC-elite solution (1:125, Vector Laboratories Burlingame, CA, USA) for 2 h at room temperature and by subsequent treatment with heavy metal-intensified diaminobenzidine [1]. Stained preparations were mounted on gelatin-coated slides, air-dried over night, dehydrated in alcohol, cleared in xylene, and coverslipped with DPX. The sections were examined with a light microscope. Localized swellings on the axon were identified as presynaptic swellings and were termed “terminals”.

The nuclear borders of the thalamic nuclei and of the SNR were extremely difficult to identify in the sections stained for the BDA. For this reason, after completing drawings of the distribution of the labelled axons and terminals, major blood vessels and landmarks in the thalamus, and verifying that Nissl staining produces no significant loss of the BDA stain, the slides were soaked in xylene, the coverlips and the mounting medium were completely removed and the sections were hydrated so that they could be counterstained with thionin. The sections were then once more dehydrated, cleared and mounted.

3. Results

The injection sites for the 10 experimental rats are shown in Fig. 1a–j. Fig. 1a–d shows 4 large injections which covered the greater part of the SNR and Fig. 1e–j shows 6 smaller injections. In 3 of the latter injections, the BDA extended ventrally beyond the SNR and contaminated the cerebral peduncle (Fig. 1e, g and h). .

3.1. Large SNR injections

The fine labelled axons and terminals in thalamic nuclei were denser in the large SNR injections (Fig. 1a–d) when compared with the smaller injections. Bilateral labelled axon terminals were observed in the VM and the CM, PF, and PC thalamic nuclei. The labelling was denser in the ipsilateral compared to the contralateral related thalamic nuclei.

The MD, CL and the Rt nuclei showed unilateral BDA labelling. The MD showed consistent labelling in its lateral part. The Rt showed few ipsilateral labelled axons and terminals in its rostral regions. Further, constant labelling was also observed in the zona incerta in all large SNR injections.

3.2. Smaller injections

Of the 6 smaller SNR injections (Fig. 1e–j), the BDA labelled fibers were found to have different distributions varying in accordance with the rostrocaudal extent of the SNR injection site.

3.2.1. Rostral SNR injections

In the 3 smaller predominantly rostral SNR injections (Fig. 1e–g) the BDA labelled fibers coursed dorsally and passed through the medial border of the ZI although some fibers terminated in the ZI (Fig. 2a and b)). The labelled fibers further coursed dorsally, passed lateral to the mammillothalamic tract and showed evenly distributed dense labelled terminals and axons in the VM thalamic nuclei and few labelled axon terminals in the contralateral VM thalamic nuclei (Figs. 2a and 3a The dorsal fibers coursed through the lower parts of ventral posterior and posterior thalamic nuclei without any axon terminations and reached the CL nucleus. Labelled axon terminals were also observed in the CL, PC and CM thalamic nuclei of the IL group (Figs. 2a and 4). Further, constant terminal labelling was observed in the inferior part of the PF thalamic nucleus, similar regional labelling was observed on the contralateral side, but less and scarce (Figs. 2b and 5a). Labelled axon terminals were observed in the ipsilateral lateral part of the MD thalamic nucleus with no labelling in the contralateral MD (Figs. 2a and 4). In the Rt, there were labelled axon terminals only in the ipsilateral rostral regions (Fig. 2a and 6).

3.2.2. Caudal SNR injections

Three BDA injections were mostly in the caudal part of the SNR (Fig. 1h–j). The majority of BDA labelled fibers coursed dorsomedial to the ZI and a few fibers terminated in this nucleus. The BDA labelled axons and terminals were observed locally in the superolateral part of the VM thalamic nucleus, and were not evenly distributed throughout the nucleus (Figs. 2c and 3b). There

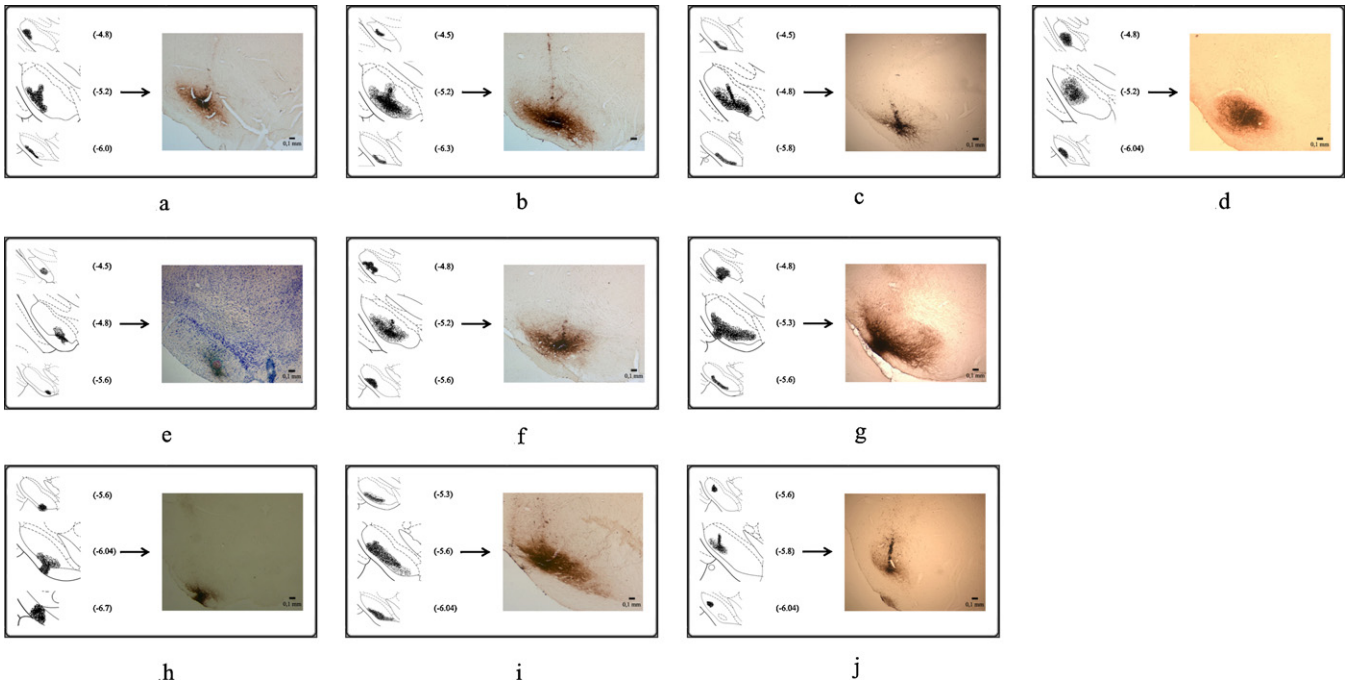


Fig. 1. (a–j) Photographs of the maximal BDA injection sites of the 10 animals (a–d: large, e–g: rostral and h–j: caudal injections) with schematic illustrations of the rostro-caudal extensions of the injections.

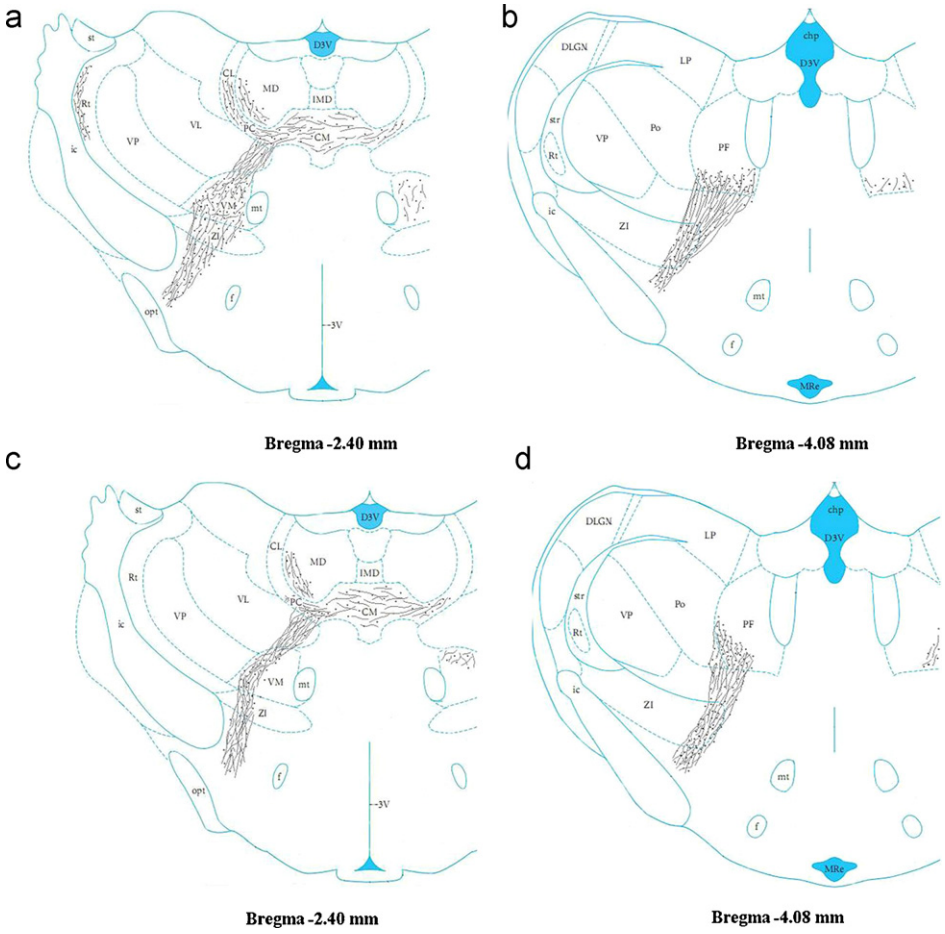


Fig. 2. (a–d) Coronal sections through the thalamus showing the distribution of labelled axons, terminals and fibers of the rostral (a, b) or caudal (c, d) SNR injections. The drawings are from rostro-caudal sequence and are obtained from the results of BDA rostral (Fig. 1e–g) or caudal (Fig. 1h–j) SNR injections.

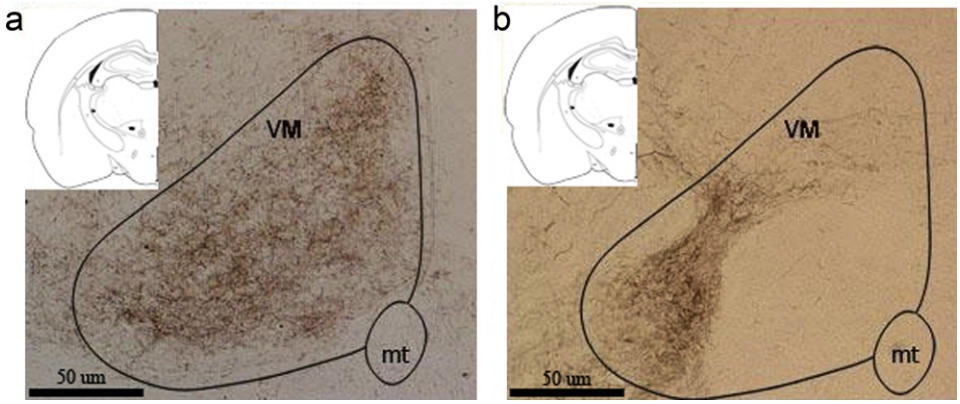


Fig. 3. (a, b) The BDA injections to the rostral (Fig. 1e–g) SNR showed dense evenly distributed labelled axon terminals and fibers throughout the VM thalamic nucleus. (b) Caudal (Fig. 1h–j) SNR injections showed labelled axon terminals and fibers specifically localized in the superolateral parts of the VM thalamic nucleus. A drawing of the whole thalamus, was added on the left corner of the figure for orientation.

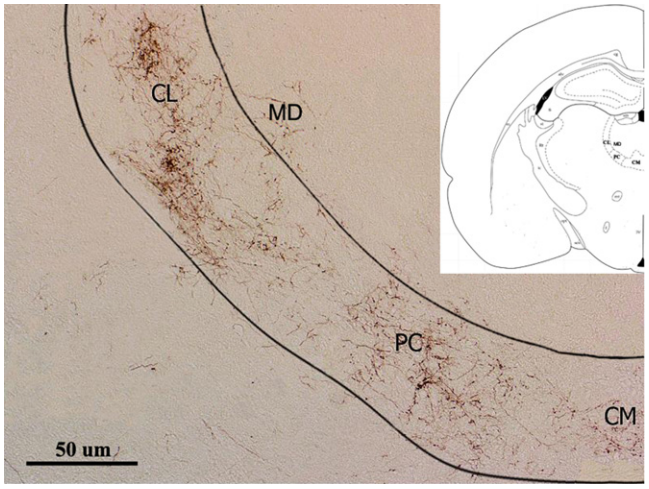


Fig. 4. The BDA injections into rostral (Fig. 1e–g) SNR showed labelled axon terminals and fibers in the CL, PC and CM thalamic nuclei. A drawing of the whole thalamus, was added on the right corner of the figure for orientation.

was labelling in the PC and CM but not in the CL thalamic nuclei of the IL group (Fig. 2c). In the CM labelling extended into the contralateral hemisphere (Fig. 2c). Further, bilateral labelled axon terminals were observed only at the lateral part of the PF thalamic nucleus, numerous on the ipsilateral, scarce on the contralateral side (Figs. 2d and 5b). Again labelled terminals were observed in the lateral part of the MD thalamic nucleus similar to those from

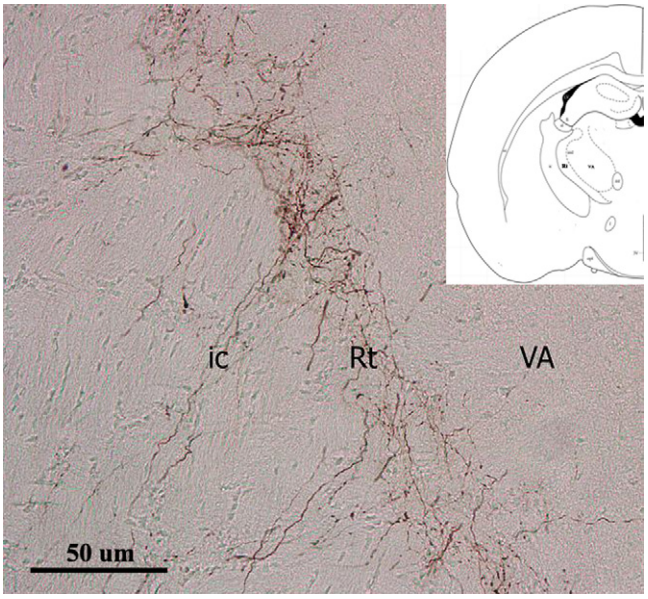


Fig. 6. The rostral (Fig. 1e–g) SNR injections showed axon terminals and fibers along the border of the internal capsule of the rostral Rt. A drawing of the whole thalamus, was added on the right corner of the figure for orientation.

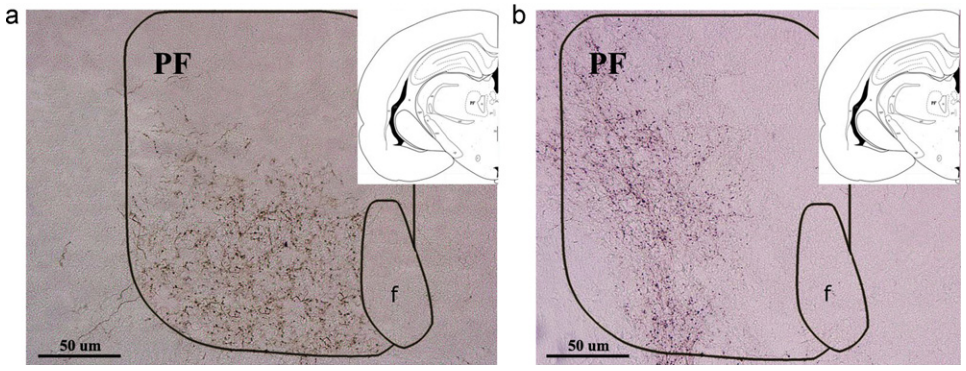


Fig. 5. (a, b): (a) The BDA injections to the rostral (Fig. 1e–g) SNR showed specifically labelled axon terminals and fibers localized in the inferior part of the PF thalamic nucleus. (b) Caudal (Fig. 1h–j) SNR injections showed specifically labelled axon terminals and fibers in the lateral part of the PF thalamic nucleus. A drawing of the whole thalamus, was added on the right corner of the figure for orientation.

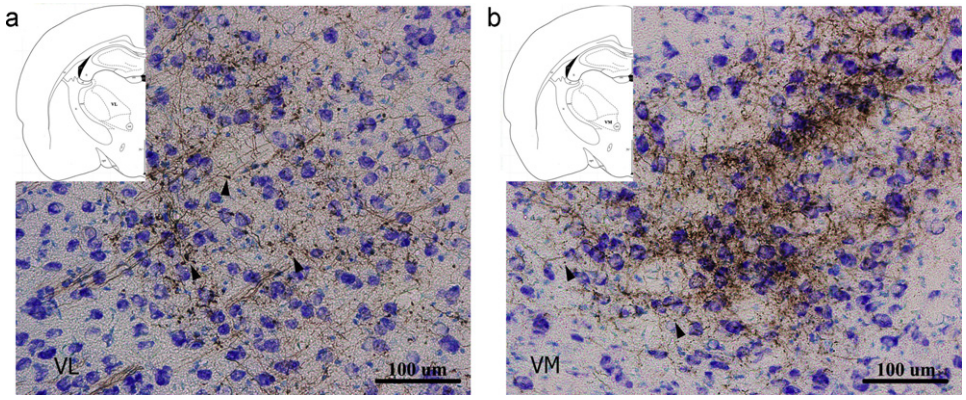


Fig. 7. (a, b) BDA containing sections counterstained with Nissl to identify the thalamic nuclei. (a) In the VL thalamic nuclei there is labelling of large axon terminals. (b) Shows labelling of small terminals in the VM thalamic nuclei. A drawing of the whole thalamus, was added on the left corner of the figure for orientation.

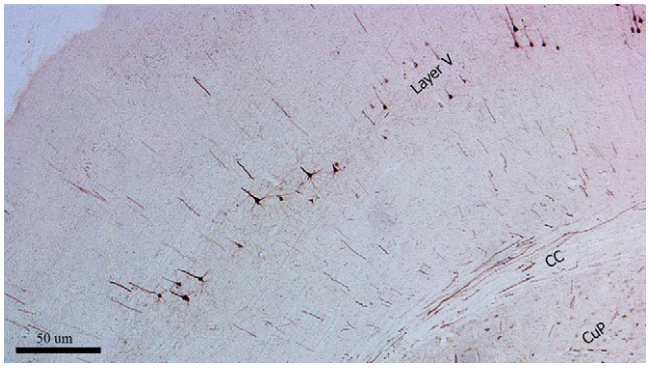


Fig. 8. The injections that included the cerebral peduncle showed labelled layer 5 cells of the motor cortex.

the rostral SNR injections (Fig. 2c). No labelling was observed in any regions of the Rt.

3.3. Cerebral peduncle injections

In 2 of the rostral (Fig. 1e and g) and in 1 of the caudal (Fig. 1h) SNR injections the BDA spread into the cerebral peduncle. The thalamic distribution did not differ from the other rostral and caudal injections except that additional labelling was observed in the VA/VL thalamic nuclei. The axon terminals in the VA/VL thalamic nuclei were strikingly larger than those in the VM and IL nuclei (Fig. 7a and b). Experiments that showed labelling in the VA/VL also contained labelling of layer V cortical cells (Fig. 8).

4. Discussion

4.1. Major finding of the study

The present study provides evidence that some of the motor higher-order relays (VM, IL and MD) but not first-order thalamic relays receive SNR inputs. The results also showed that the thalamic projections from the SNR are topographically organized in relation to the injection sites in the SNR (Fig. 2a–d). The rostral SNR injections showed bilateral labelling, being dense and evenly distributed in the ipsilateral VM and sparse in the contralateral VM thalamic nucleus. In contrast to this the caudal SNR injections showed unilateral labelled axon terminals strictly limited to the superolateral border of VM. The IL thalamic nuclei also showed a topographical arrangement of the labelling, with the rostral SNR injections showing labelling of CL, PC and CM whereas, caudal SNR injections showed no labelling in the CL thalamic nucleus. A labelled crossed component in CM was observed for all injection sites of the SNR. Further, the rostral SNR injections showed bilateral labelled axon terminals in the inferior part of the PF nucleus and caudal SNR injections showed labelled axon terminals in the lateral regions of the PF nucleus. Additionally, the rostral SNR injections had connections with the rostral Rt. All injections showed labelling in the ZI.

4.2. Comparison with previous studies

Earlier tracing studies have shown connections of the SNR with VM, VL, VA, CL, MD, PC, PF, VPL, the anteroventral (AV) and anteromedial (AM) thalamic nuclei in the rat, cat and monkey [4,12,13,17–19,36,44,46,47,53].

In the present study the VA/VL connections were also observed in 3 animals where cerebral peduncle contamination was present. Such corticothalamic axons are known to arise from motor cortex [15], which was the major region showing retrogradely labelled layer V cells in our preparations. This suggested that corticofugal axons were labelled in the peduncle and that the BDA was retrogradely transported to cells in layer V of the cortex with some of these layer V cells having VA/VL thalamic branches. This interpretation is supported by the observation that the VA/VL labelling consisted of large axon terminals compared to the other thalamic nuclei and suggests that these were corticothalamic axons coming from the labelled layer V cells.

The VPL connections of the SNC were described by Cebrián and Prensa [13]. In the present study we observed that the axons from the SNR coursed from the lower end of VP to reach the IL nuclei. However axon termination in VPL were not observed. We also observed MD connections for all of our injections sites. The SN pars compacta (SNC) has been reported as sending axons to the MD thalamic nucleus [13]. We could not avoid the contamination of SNC neurons with BDA. Therefore, further studies are needed to determine the chemical identity of the connections to define whether these connections are from SNR or SNC.

In the present study we demonstrate that the more rostral parts of the SNR had projections to the CL whereas the more caudal injections did not (Fig. 2a and c). In the caudal injections it was difficult to evaluate whether the labelled axon terminals belong to CL or MD. However the MD thalamic nucleus is composed of medial, central (intermediate) and lateral parts. The central part of the nucleus stains much more densely than the medial and lateral parts in Nissl sections. The counterstained sections showed labelled axon terminals were immediately external to the dense labelled central band of the MD. Therefore, we assigned these labellings as lateral MD not CL. Rostral injections showed labelled axon terminals, distributed into a large area, including CL and lateral MD (Fig. 4).

The present study confirms earlier studies showing the principal target of SNR to be the VM thalamic nucleus [8,17,18,35]. Di Chiara et al. have shown that the SNR–VM connections are GABAergic [17]. There is also physiological evidence that the VM thalamic neurons are inhibited by stimulation of the SNR [35,54]. The cortical targets of the VM thalamic nucleus are layer I of frontal and medial cortical areas [21,26,31]. The type of influence that the SNR, via the VM thalamic nucleus, may exert over these fields is currently unknown. More importantly, our data show that the rostral SNR is more densely connected to the VM compared to the caudal SNR.

Pare et al. has reported SNR–Rt connections using WGA-HRP and electrophysiological studies in the cat [39]. The present study confirms this connection from the rostral SNR but not from the caudal SNR to the rostral Rt for the rat. However, we could not trace through the serial sections that whether these are collaterals of the SNR–thalamic connections or direct connections of the SNR. Recently strong projections from the SNC to the Rt have been described [2,13]. Again, the chemical identity of these connections needs to be defined to determine whether these connections are from SNR or SNC.

The results of the present study confirm earlier studies and also report topographical bilateral or/and unilateral efferent connections of the SNR. A further striking result of the present study is SNR specifically connects to the motor higher-order (VM, IL and MD), but not first-order thalamic nuclei. The data suggest that motor higher-order thalamic nuclei may have GABAergic modulatory inputs not only from the anterior pretectal nucleus and ZI but also from the SNR. The higher-order thalamic nuclei as well as calbindin-positive relay cells are known to innervate multiple cortical areas [16,30]; the activity of relay cells, patterned by the extrareticular GABAergic input, will be inhibited on its way to widespread cortical regions. Our earlier study on the quantification of drivers of Wistar rats showed that MD resembles the first-order more than higher-order relays [11]. This may be because the lateral parts of MD receives a significant number of first-order inputs from the amygdala and other subcortical sources therefore, can be a regarded as a mixture of first and higher-order thalamic nuclei [43].

Additionally, the SNR neurons, via the disinhibition of the Rt neurons may produce synchronization of thalamic relay cells. The Rt is an aggregation of GABAergic neurons which has reciprocal connections with almost all thalamic nuclei [23,43]. This nucleus has a key role in pacing some rhythmic activities [42,51,52]. Unlike the Rt, the SNR does not receive thalamic inputs. Thus, the SNR will impose its effects on the thalamus unconstrained by ongoing thalamic activity. As a consequence, instead of a reciprocal excitatory–inhibitory loop, which underlies thalamocortical oscillations in the Rt, the SNR exerts its effect on the thalamus more like an external control.

4.3. Limitations of the study

One of the limitations of this study was contamination of BDA to surrounding structures such as cerebral peduncle or SNC. Results of the cerebral peduncle injections were described as a separate group, but even for the smaller injections involvement of SNC neurons could not be excluded. As mentioned above labelled axon terminals of MD or Rt can be from SNC. Further studies are required to identify these connections chemically to determine whether they come from SNR or SNC. Secondly, although the parameters for iontophoretic method for BDA injection were standardized for all animals, the amount of injected BDA may not have been constant. The density of labelling for not only the injection sites but also the axon terminals of projections may differ due to the injected amount of BDA.

4.4. Pathophysiological implications of the study

Experimental studies reveal that the SNR is critically involved in cognition and in the coordination of motor functions [40] and that it also plays a role in the control of epileptic seizures [20,24,25], acting via its $GABA_A$ receptors. Recent studies have shown that the SNR is divided into two distinct regions which act via GABA receptors to produce either anticonvulsant effects from the rostral parts or proconvulsant effects from the caudal parts [38,57]. These two regions mediate distinct effects on seizures and use divergent output networks in response to localized infusions of GABAergic and glutamatergic agents or electrical stimulation [38,58]. The results of the present study show that the opposite responses to epileptic seizures of the rostral and caudal parts of the SNR may be due to the regional differences in the connections of the SNR with the thalamus.

The present results, showing connections of GABAergic rostral SNR neurons reaching the GABAergic rostral Rt neurons may allow for a nigral control of absence epilepsy and emphasize that different rosto-caudal parts of the SNR are in a position to influence large areas of the neocortex by modulating higher-order thalamic nuclei.

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References

[1] J.C. Adams, Heavy metal intensification of DAB-based HRP reaction product, J. Histochem. Cytochem. 29 (1981) 775.
[2] V. Anaya-Martinez, A. Martinez-Marcos, D. Martinez-Fong, J. Aceves, D. Erlij, Substantia nigra compacta neurons that innervate the reticular thalamic nucleus in the rat and also projects to striatum or globus pallidus: implications for abnormal motor behaviour, Neuroscience 143 (2006) 477–486.
[3] P. Barthó, T.F. Freund, L. Acsády, Selective GABAergic innervation of thalamic nuclei from zona incerta, Eur. J. Neurosci. 16 (2002) 999–1014.
[4] R.M. Beckstead, Long colateral branches of substantia nigra pars reticulata axons to the thalamus, superior colliculus and reticular formation in the monkey and cat. Multiple retrograde neuronal labeling with fluorescent dyes, Neuroscience 3 (1983) 767–779.
[5] A.L. Bodor, K. Giber, Z. Rovo, I. Ulbert, L. Acsady, Structural correlates of efficient GABAergic transmission in the basal ganglia-thalamus pathways, J. Neurosci. 28 (2008) 3090–3102.
[6] H. Bokor, S.G.A. Frére, M.D. Eyre, A. Slézia, I. Ulbert, A. Lüthi, L. Acsády, Selective GABAergic control of higher-order thalamic relays, Neuron 45 (2005) 929–940.
[7] J.P. Bolam, J.J. Hanley, P.A. Booth, M.D. Bevan, Synaptic organisation of the basal ganglia, J. Anat. 196 (2000) 527–542.
[8] J. Bourassa, M. Deshenes, Corticothalamic projections from the primary visual cortex in the rat: a single fiber study using biocytin as an anterograde tracer, Neuroscience 66 (1995) 253–263.
[9] J.J. Castellanos, F.R. Suárez, Topographical organization of the afferent connections of the principal ventromedial thalamic nucleus in the cat, J. Comp. Neurol. 236 (1985) 297–314.
[10] S. Çavdar, F. Onat, Y.Ö. Çakmak, E. Saka, H.R. Yananli, R. Aker, Connections of the zona incerta to the reticular nucleus of the thalamus in the rat, J. Anat. 209 (2006) 251–258.
[11] S. Çavdar, H. Hacıoğlu, S. Şirvancı, E. Keskinöz, F. Onat, Synaptic organization of the rat thalamus: a quantitative study, Neurol. Sci., PMID 21544663, in press.
[12] C. Cebrián, A. Parent, L. Prens, Patterns of axonal branching of neurons of the substantia nigra pars reticulata and pars lateralis in the rat, J. Comp. Neurol. 492 (2005) 349–369.
[13] C. Cebrián, L. Prensa, Basal ganglia and thalamic input from neurons located within the ventral tier cell cluster region of the substantia nigra pars compacta in the rat, J. Comp. Neurol. 518 (2010) 1283–1300.

[14] J.M. Deniau, G. Chevalier, The laminar organization of the rat substantia nigra pars reticulata: distribution of projection neurons, Neuroscience 46 (1992) 361–377.
[15] L.M. Deniau, P.N. Mailly, S. Maurice, Charpier, The pars reticulate of the substantia nigra: a window to basal ganglia output, Prog. Brain Res. 160 (2007) 151–171.
[16] M. Deschênes, J. Bourassa, D. Pinault, Corticothalamic projections from layer V cells in rat are collaterals of long-range corticofugal axons, Brain Res. 664 (1–2) (1994) 215–219.
[17] G. Di Chiara, M.L. Porceddu, M. Morelli, M.L. Mulas, G.L. Gessa, Evidence for a GABAergic projection from the substantia nigra to the ventromedial thalamus and to the superior colliculus of the rat, Brain Res. 176 (1979) 273–284.
[18] R.L.M. Faull, W.R. Mehler, The cells of origin of nigrotectal, nigrothalamic and nigrostriatal projections in the rat, Neuroscience 3 (1978) 999–1002.
[19] C. François, D. Tande, J. Yelnik, E.C. Hirsch, Distribution and morphology of nigral axons projecting to the thalamus in primates, J. Comp. Neurol. 447 (2002) 249–260.
[20] K. Gale, Mechanisms of seizure control mediated by gamma aminobutyric acid: role of substantia nigra, Fed. Proc. 44 (1985) 2414–2424.
[21] L.L. Glenn, J. Hada, J.P. Roy, M. Deschênes, M. Steriade, Anterograde tracer and field potential analysis of the neocortical layer I projection from nucleus ventralis medialis of the thalamus in cat, Neuroscience 7 (8) (1982) 1861–1877.
[22] R.W. Guillery, Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review, J. Anat. 187 (1995) 583–592.
[23] R.W. Guillery, S.L. Feig, D.A. Lozsádi, Paying attention to the thalamic reticular nucleus, Trends Neurosci. 21 (1998) 28–32.
[24] T. Hayashi, A physiological study of epileptic seizures following cortical stimulation in animals and its application to human clinics, Jpn. J. Pharmacol. 3 (1952) 46–64.
[25] T. Hayashi, The efferent pathway of epileptic seizures following cortical stimulation differs from that for limbs, Jpn. J. Pharmacol. 4 (1953) 306–321.
[26] M. Herkenham, The afferent and efferent connections of the ventromedial thalamic nucleus in the rat, J. Comp. Neurol. 183 (1979) 487–517.
[27] P.V. Hoogland, F.G. Wouterlood, E. Welker, H. Van der Loos, Ultrastructure of giant and small thalamic terminals of cortical origin: a study of the projections from the barrel cortex in mice using Phaseolus vulgaris leuco-agglutinin (PHA-L), Exp. Brain Res. 87 (1991) 159–172.
[28] I.A. Ilinsky, K. Kultas-Ilinsky, An autoradiographic study of topographical relationships between pallidal and cerebellar projections to the cat thalamus, Exp. Brain Res. 54 (1984) 95–106.
[29] I.A. Ilinsky, H. Yi, K. Kultas-Ilinsky, Mode of termination of pallidal afferents to the thalamus: a light and electron microscopic study with anterograde tracers and immunocytochemistry in *Macaca mulatta*, J. Comp. Neurol. 386 (1997) 601–612.
[30] E.G. Jones, A new view of specific and nonspecific thalamocortical connections, Adv. Neurol. 77 (1998) 49–71.
[31] J.E. Krettek, J.L. Price, The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat, J. Comp. Neurol. 15 (1977) 157–191.
[32] Y.W. Lam, S.M. Sherman, Different topography of the reticulothalamic inputs to first- and higher-order somatosensory thalamic relays revealed using photostimulation, J. Neurophysiol. 98 (2007) 2903–2909.
[33] C.C. Lee, S.M. Sherman, Synaptic properties of thalamic and intracortical inputs to layer 4 of the first and higher-order cortical areas in the auditory and somatosensory systems, J. Neurophysiol. 100 (2008) 317–326.
[34] J. Li, S. Wang, M.E. Bickford, Comparison of the ultrastructure of cortical and retinal terminals in the rat dorsal lateral geniculate and lateral posterior nuclei, J. Comp. Neurol. 460 (2003) 394–409.
[35] N.K. Mcleod, T.A. James, I.C. Kilpatrick, M.S. Starr, Evidence for a GABAergic nigrothalamic pathway in the rat: II. Electrophysiological studies, Exp. Brain Res. 40 (1980) 55–61.
[36] Y. Miyamoto, K. Jinnai, The inhibitory input from the substantia nigra to the mediodorsal nucleus neurons projecting to the prefrontal cortex in the rat, Brain Res. 649 (1994) 313–318.
[37] J.H. Morrison, S.L. Foote, Noradrenergic and serotoninergic innervation of cortical, thalamic, and tectal visual structures in Old and New World monkeys, J. Comp. Neurol. 243 (1) (1986) 117–138.
[38] S.L. Moshe, L.L. Brown, H. Kubova, J. Veliskova, R.S. Zukin, E.F. Sperber, Maturation and segregation of brain networks that modify seizures, Brain Res. 665 (1994) 141–146.
[39] D. Pare, L.N. Hazrati, A. Parent, M. Steriade, Substantia nigra pars reticulata projects to the reticular thalamic nucleus of the cat: a morphological and electrophysiological study, Brain Res. 535 (1) (1990) 139–146.
[40] A. Parent, L.N. Hazrati, Functional anatomy of the basal ganglia. I. The corticobasal ganglia-thalamocortical loop, Brain Res. Rev. 20 (1995) 128–154.
[41] P. Pasik, T. Pasik, G.R. Holstein, J. Hàmori, GABAergic elements in the neuronal circuit of the monkey neostriatum: a light and electron microscopic immunocytochemical study, J. Comp. Neurol. 270 (1988) 157–170.
[42] D. Pinault, The thalamic reticular nucleus: structure, function and concept, Brain Res Rev. 46 (2004) 1–31.
[43] J.L. Price, Subcortical projections from the amygdaloid complex, Adv. Exp. Med. Biol. 203 (1986) 19–33.
[44] J.P. Ray, J.L. Price, The organization of the thalamocortical connections of the mediodorsal thalamic nucleus in the rat related to the ventral forebrain prefrontal cortex topography, J. Comp. Neurol. 323 (1992) 167–197.
[45] K.S. Rockland, Convergence and branching patterns of round, type 2 corticopulvinar axons, J. Comp. Neurol. 390 (1998) 515–536.
[46] F.T. Russchen, D.G. Amaral, J.L. Price, The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, macaca fascicularis, J. Comp. Neurol. 256 (1987) 175–210.
[47] S.T. Sakai, I. Grofova, K. Bruce, Nigrothalamic projections and nigrothalamocortical pathway to the medial agranular, cortex in the rat: single- and double-labeling light and electronmicroscopic studies, J. Comp. Neurol. 391 (1998) 506–525.
[48] S.M. Sherman, R.W. Guillery, Functional organization of thalamocortical relays, J. Neurophysiol. 76 (1996) 1367–1395.
[49] S.M. Sherman, R.W. Guillery, On the action that one nerve cell can have on another: distinguishing "drivers" from "modulators", Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 7121–7126.
[50] S.M. Sherman, R.W. Guillery, Exploring the Thalamus and its Role in Cortical Function, MIT Press, Cambridge, MA, 2006, pp. 289–303.
[51] M. Steriade, M. Deschênes, The thalamus as a neuronal oscillator, Brain Res. 320 (1984) 1–63.
[52] M. Steriade, L. Domich, G. Oakson, Reticularis thalami neurons revisited: activity changes during shifts in states of vigilance, J. Neurosci. 6 (1986) 68–81.
[53] T. Tsumori, S. Yokota, K. Ono, Y. Yasui, Synaptic organization of GABAergic projections from the substantia nigra pars reticulata and the reticular thalamic nucleus to the parafascicular thalamic nucleus in the rat, Brain Res. 13 (2002) 231–241.
[54] A. Ueki, M. Uno, M. Anderson, M. Yoshida, Monosynaptic inhibition of thalamic neurons produced by stimulation of the substantia nigra, Experientia 15 (1977) 1480–1482.
[55] D.J. Uhlrich, K.A. Manning, T.P. Pienkowski, The histaminergic innervation of the lateral geniculate complex in the cat, Vis. Neurosci. 10 (1993) 225–235.
[56] S.C. Van Horn, S.M. Sherman, Fewer driver synapses in higher order than in first order thalamic relays, Neuroscience 146 (2007) 463–470.
[57] J. Veliskova, S.L. Moshe, Sexual dimorphism and developmental regulation of substantia nigra function, Ann. Neurol. 50 (2001) 596–601.
[58] J. Veliskova, L. Velisek, M.L. Nunes, S.L. Moshe, Developmental regulation of regional functionality of substantia nigra GABAA receptors involved in seizures, Eur. J. Pharmacol. 309 (1996) 167–173.