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ORIGINAL ARTICLE

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Organisation of connections between the zona incerta and the interposed nucleus

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Abstract We have examined the organisation of connections between the zona incerta (ZI), a small diencephalic nucleus deriving from the ventral thalamus, and the interposed nucleus (Int) of the cerebellum. Injections of the tracer cholera toxin subunit B were made into either the ZI or Int of Sprague Dawley rats by using stereotaxic coordinates. We have two major findings. First, there is a heavy projection from Int to ZI; there is also a small projection back to Int from ZI. After injections into Int, labelled terminals and cells tend to concentrate within the medial region of each of the cytoarchitectonically defined sectors of ZI. Second, there is an unusual laterality of connectivity between the ZI and the Int. The projection from the Int to the ZI is mainly contralateral, whilst the ZI projection back to the Int is mainly ipsilateral. In conclusion, our results indicate that the Int of the cerebellum provides a rich source of afferents to the ZI, rendering the latter in a key position to integrate information from the Int together with many other types of subcortical information it receives, particularly from the brainstem.

Keywords Cerebellum · Thalamus · Laterality · Rat

Abbreviations *ABC* Avidin-biotin-peroxidase complex · *CM* central medial nucleus · *cp* cerebral peduncle · *CTb* cholera toxin subunit B · *DAB* 3,3 – diaminobenzidine tetrahydrochloride · *Hb* habenula · *Int* interposed nucleus · *Inta* interposed nucleus anterior division · *Intp* interposed nucleus posterior division · *LGd* dorsal lateral geniculate nucleus · *LGv* ventral lateral geniculate nucleus · *LP* lateral posterior nucleus · *MD* medial dorsal nucleus · *NTBS* nickel tris base saline · *PBS* phosphate buffered saline · *Rt* thalamic reticular nucleus · *VP* ventral posterior nucleus · *ZI* zona incerta · *ZIc* caudal sector of zona incerta · *ZId* dorsal sector of zona incerta · *ZIr* rostral sector of zona incerta · *ZIv* ventral sector of zona incerta

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Introduction

The ZI is formed by a heterogeneous collection of cells that lies, to a large extent, at the base of the dorsal thalamus of all mammals examined thus far (see Jones 1985). Many authors have described well-defined sectors for the ZI, each having a largely distinct cytoarchitecture, immunocytochemical character and pattern of connections (e.g. Ricardo 1981; Roger and Cadusseau 1985; Romanowski et al. 1985; Shammah-Lagnado et al. 1985; Nicolelis et al. 1992). For instance, in terms of connections, many nuclei of the brainstem and the intralaminar thalamic nuclei project principally to the dorsal sector of the ZI (Kim et al. 1992; May et al. 1997; Kolmac et al. 1998; Power et al. 1999), the higher-order thalamic nuclei project to the ventral sector (Power et al. 1999), the hypothalamus projects to the rostral sector (Wagner et al. 1995), and the spinal cord projects to the caudal sector (Ricardo 1981; Roger and Cadusseau 1985; Nicolelis et al. 1992). Further, functionally distinct neocortical areas have been shown to project to distinct ZI regions, with cingulate cortex projecting to the dorsal sector, visual cortex to the lateral edge of the dorsal, caudal and ventral sectors, and sensorimotor cortex to discrete regions of the ventral and dorsal sectors (Mitrofanis and Mikuletic 1999).

The precise function of the ZI is not known, although it has been implicated in aspects of visual, nociceptive and somatosensory processing (Legg 1979; Nicolelis et al. 1992, 1995; Lechner et al. 1993; May et al. 1997), locomotion (see Mogenson et al. 1985), sociosexual behaviour (see Edwards and Isaacs 1991), feeding and drinking (see Gonzalez-Lima et al. 1993), and arousal and attention (Shammah-Lagnado et al. 1985; Berry et al. 1986; Hermanson et al. 1995; but see Jurkowlaniec et al. 1990). More recently, it has been suggested that the

ZI may also form a thalamic centre for the integration of various types of brainstem information, for example somato and/or viscerosensory (Kolmac et al. 1998; Power et al. 1999). This particular function was suggested because of the large and overlapping projections evident from many different brainstem nuclei (Kolmac et al. 1998) and the large ZI output to the dorsal thalamus, in particular to the higher-order and intralaminar nuclei (Power et al. 1999).

In addition to the above-mentioned connections, there have also been reports of a projection to the zona incerta from the cerebellum, in particular from its interposed nucleus (Faull and Carman 1978; Aguirre et al. 1989; Vaudano and Legg 1992; Yatim et al. 1995; Aumann et al. 1994, 1996; Aumann and Horne 1996). The details of this projection are not clear, however. For instance, it is not known if these connections are extensive and hence whether the Int may play a part in ZI function; further, it is not clear how these Int afferents relate to other ZI afferents (e.g. from brainstem or cortex), in other words, it is not known which ZI sector the Int relates to. The aim of this study was to clarify these issues. To this end, we injected the tracer CTb into the ZI and Int, and then examined the resultant patterns. We chose to use rats in this study, as this species has been the focus of many previous examinations of the connections and functions of these nuclei (Paxinos 1995). Our results should furnish insights into whether the cerebellum plays a part in the overall function of the ZI.

The Int is one of the three major deep cerebellar nuclei identified in rats, the others being the medial (or fastigial) and lateral (or dentatus) nucleus. The Int itself can be divided into two parts, Inta and Intp. The anterior division has major projections to the red nucleus, basilar pons, olivary complex and to the ventral posterior nucleus of the thalamus. The projections of the posterior division are similar, although slightly more extensive. Projections have been described to the periaqueductal grey matter, deep layers of the superior colliculus, nucleus of Darkschewitsch, spinal cord, olivary complex and the ventral medial, ventral posterior, ventral lateral and intralaminar nuclei of the thalamus. Both divisions have been shown to receive projections from various sources, including the neocortex, spinal cord, inferior olive, red nucleus, and cerebellar cortex (reviewed Voogd 1995; Aumann et al. 1996). The current functional paradigm for the Int is that it is primarily a centre involved directly in motor control, particularly during ongoing movements (Allen and Tsukahara 1974; Voogd 1995; Ruigrok and Cella 1995). More recently, autonomic and cognitive functions have been attributed to this cerebellar nucleus also (Reis and Golanov 1997; Ackerman et al. 1998).

Materials and methods

Subjects

In this study, results were obtained from ten male Sprague Dawley rats (250–300 g). Animals were housed with a 12 h light dark cycle and had continual access to food and drink. All experiments were approved by the Animal Ethics Committee of the University of Sydney.

Tracer injections

Rats were anesthetised after an intraperitoneal injection of Ketamil (100 mg/kg) and Rompun (30 mg/kg). CTb (low salt solution, List Biological Laboratories, USA) was injected iontophoretically (6 s on / 6 s off, 10–20 minutes; 10–15μA) at positions determined by stereotaxic coordinates (Paxinos and Watson 1986). The neural centres injected were the ZI (n=6) and the Int (n=4). After 5 days, the rats were anesthetised deeply with Nembutal (sodium pentobarbital: 60 mg/ml) and perfused transcardially with phosphate buffered saline (PBS; pH 7.4; 0.1 M) followed by 4% buffered formaldehyde. The brains were removed, postfixed for 12 h in the same fixative, and then immersed in PBS with the addition of 20% sucrose until the block sank. Coronal sections were cut at a thickness of 50μm by using a freezing microtome. Every second section was collected and incubated with goat anti-Choleragenoid (1:4,000; List Biological Laboratories, USA) for 48 h at 4°C. The sections were then incubated with biotinylated anti-goat IgG (1:300; Sigma) for 2 h at room temperature and then with the ABC (1:100 in PBS; Vector Laboratories, Burlingame, Calif., USA) for 4 h at room temperature. Sections were then washed thoroughly with several changes of PBS and then with nickel TRIS base saline (pH7.6; 0.1 M; NTBS) for 1 h (Clemence and Mitrofanis 1992). They were then immersed in a solution containing DAB (Sigma, Mo., USA) and NTBS. Sections were then washed in distilled water, mounted on gelatinised slides and air dried overnight. Finally, the mounted sections were counterstained lightly with 1% neutral red and then dehydrated in ascending alcohols, cleared in Histoclear and coverslipped with DPX.

Analysis

Coronal sections were drawn with reference to the atlas of Paxinos and Watson (1986) and the labelled terminals and cells in the ZI and Int were plotted with use of a camera lucida. Drawings and plots were then scanned onto a computer graphics programme (McDraw Pro) and the schematic diagrams were constructed. In addition, some counts of labelled cells in the ZI and Int after each tracer injection were done. For each injection, all the labelled cells from eight sections were counted and collated. Sections were approximately 200μm apart.

Results

The following section will be presented in four parts. We will consider the tracers used, cytoarchitectonic organisations of the ZI and Int, labelling after Int injections and after ZI injections.

Tracers

CTb has been shown by previous studies to not be readily picked up by intact and/or damaged fibres of passage, but by dendrites, cell bodies and axonal terminals only (Angelucci et al. 1996; Kolmac et al. 1998; Power et al. 1999). In this study, we were confident that tracer pick up by intact and/or damaged fibres of passage was rather limited since two of our other injection sites centred on the white matter of the middle cerebellar peduncle. In these cases we saw very few labelled cells in the pons

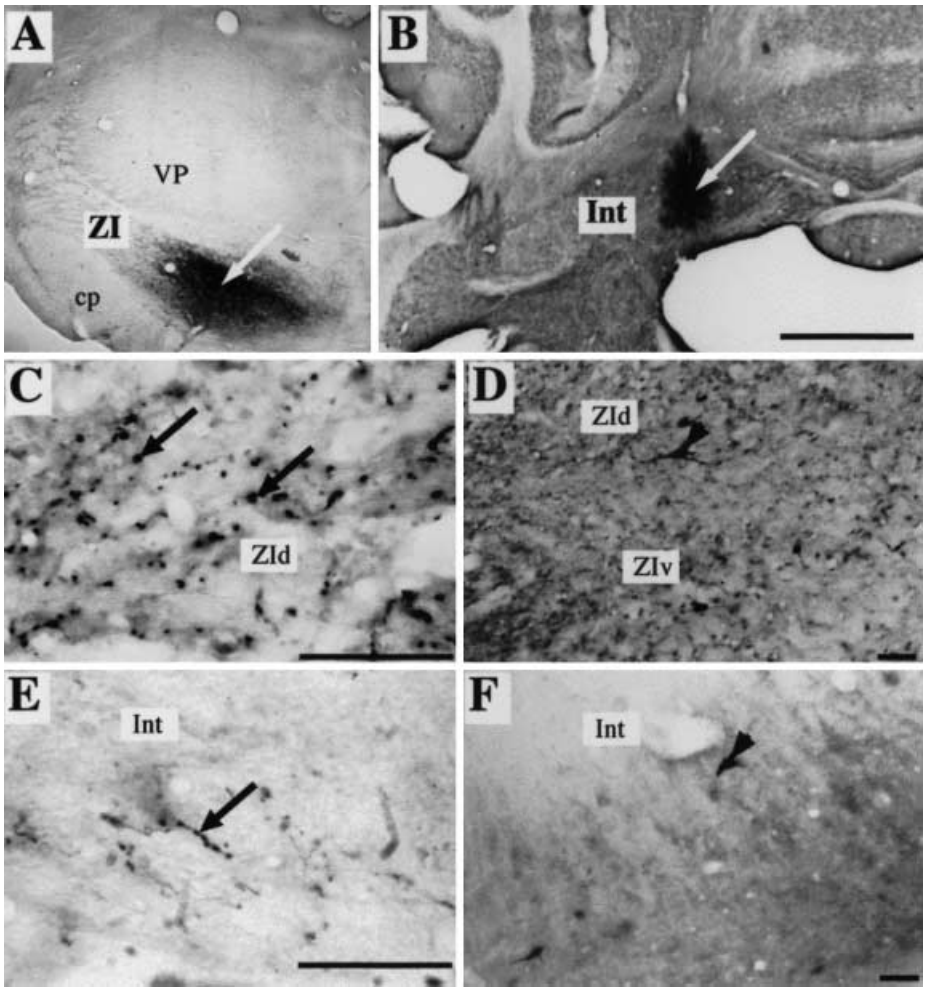

Fig. 1A–F Examples of labelling seen after CTb injections into either the ZI or Int. **A** A CTb injection site in the ZI of the ventral thalamus; **B** a CTb injection site in the Int of cerebellum; **C** shows CTb-labelled terminals in the medial region of ZI after an Int injection; **D** shows CTb-labelled cells in the medial region of ZI after an Int injection; **E** shows CTb-labelled terminals in the anterior division Int; **F** shows CTb-labelled cells in the anterior Int. In **A** and **B** *arrows* indicate focal point of injection site (regions of maximal tracer uptake), in **C** and **E** *arrows* in indicate labelled boutons, in **D** and **F** *arrowheads* indicate labelled cells. All figures are of coronal sections; dorsal to top, lateral to left. *Bars* **A, B** 1 mm; **C, E** 25 µm; **D, F** 25 µm

and few labelled terminals in the cerebellar cortex, regions where one would expect to see extensive labelling if the tracers were picked up by fibres of passage (these cases were not considered for analysis in this study).

Each of our injection sites of CTb into either ZI or Int was small, with little spread from the focal point (arrows, Fig. 1A, B), and limited to the targeted nucleus. After such injections, rich patterns of retrograde, as well as anterograde labelling, were seen in either ZI or Int.

Cytoarchitectonic organisations

For ZI, there are four cytoarchitectonic sectors, namely rostral, dorsal, ventral and caudal (Nicolelis et al. 1995; Kolmac and Mitrofanis 1999a). For the most part, these sectors were distinguished by their distinct cytoarchitecture. We also examined sections prepared for another study in order to define the sectors more confidently (Kolmac and Mitrofanis 1999a). For example, parvalbumin immunocytochemistry defines the ventral sector, whilst NADPH-diaphorase histochemistry defines the dorsal sector. For Int, this nucleus is separated into anterior and posterior divisions by cytoarchitecture and by a cell-free border (Voogd 1995). The Int and its divisions were distinguished in this study after Nissl counterstaining.

Int injections

Following CTb injections into the anterior and posterior divisions of the Int (n=4), labelled terminals were seen in the ZI. The labelled terminals were made up of boutons that were connected by very finely labelled fibres (arrows, Fig. 1C). After the same CTb injections, labelled cells were seen in the ZI also. The labelled cells typically had oval-shaped somata with several labelled primary dendrites (arrowhead, Fig. 1D).

Figure 2A shows the distribution of labelled terminals and cells in the ZI resulting from a CTb injection into the Int. This injection site was located in the posterior division of the nucleus (Fig. 2B). The other cases examined in this series, another posterior division injection and two anterior division injections, yielded very similar labelling. After each injection, there was a distinct tendency for labelled terminals to concentrate within the medial region of each of the cytoarchitectonically defined sec-

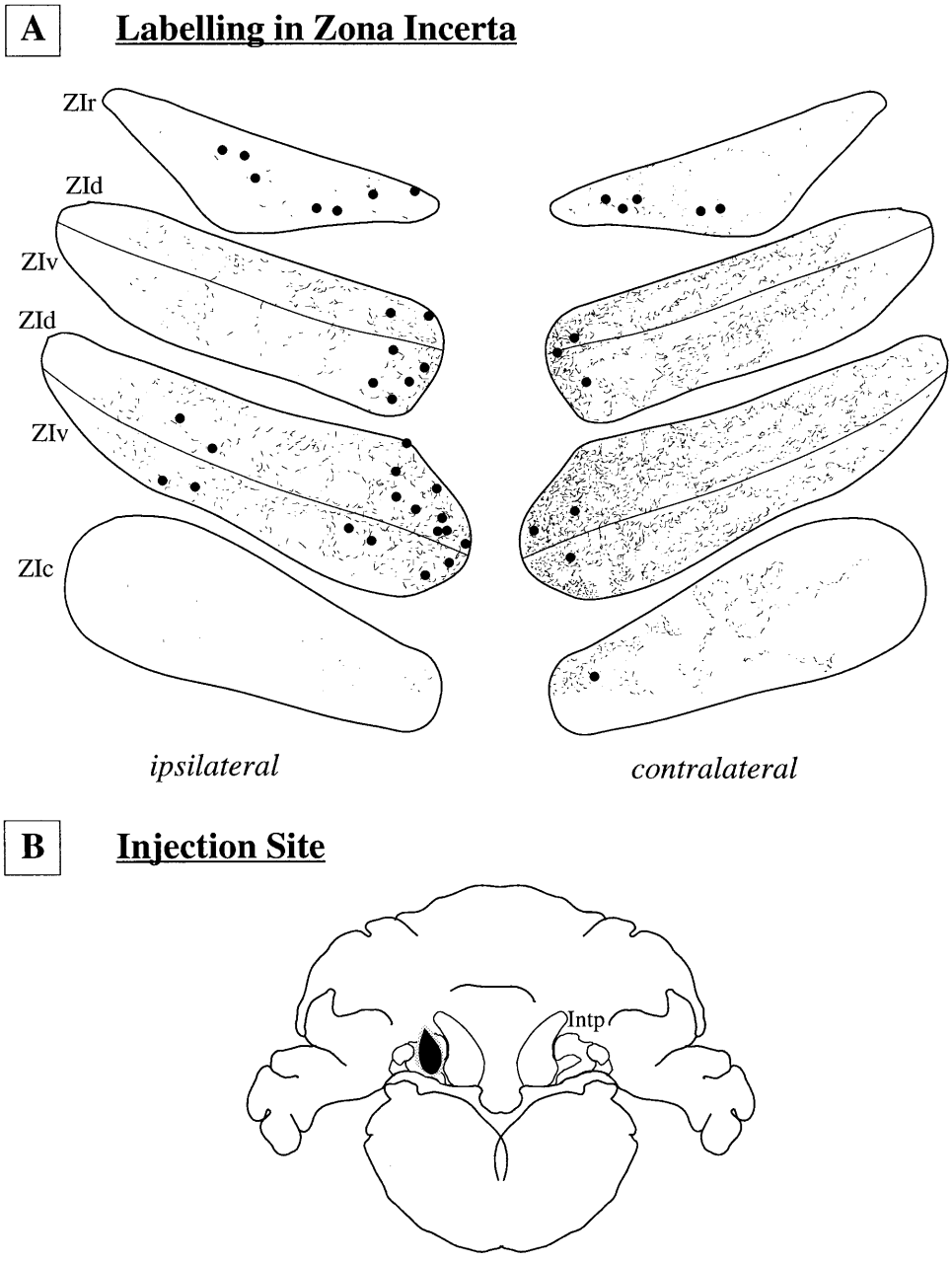

Fig. 2 Schematic diagrams of the distribution of labelled terminals and cells in the ZI (**A**) after an injection of CTb into the Int (**B**). Labelling is shown in the ZI of both ipsilateral (left hand column) and contralateral (right hand column) side. The orientation and course of labelled axons containing a set of boutons or small swellings are shown. Axons of passage are not shown (they were much thicker and lacked boutons). Each *black circle* represents one labelled cell. All figures are of coronal sections; rostral to top, medial to midline. In **B** *black* represents focal point and *shading* represents the halo of the injection site

tors of ZI (Fig. 2A). Each injection yielded labelled terminals within the ZI of both sides of the brain, with the contralateral labelling being predominant. The distribution of this label within the ZI was very similar on both sides (Fig. 2A). From the same injections, labelled cells were found in the ZI also. Such cells were relatively few in number, and were located within the medial region of the nucleus (Fig. 2A). Although labelled ZI cells were found on both sides of the brain, they tended to be more numerous on the ipsilateral side, unlike the predominantly contralateral distribution of labelled terminals. From four cases analysed, there were 128, 127, 140 and 134 labelled cells on the ipsilateral side, while there were 52, 43, 50 and 51 labelled cells on the contralateral side in the corresponding cases.

ZI injections

Following CTb injections into the ZI (n=6), labelled terminals and cells were seen in the Int. The labelled terminals were made up of fine fibres with many small boutons (arrow, Fig. 1E). The labelled cells typically had oval-shaped somata with several labelled primary dendrites (arrowhead, Fig. 1F). There were no major differences in the morphology of labelled terminals and cells located in the anterior and posterior divisions of the Int.

Figure 3A shows the distribution of labelled terminals and cells in the Int resulting from a CTb injection into the ZI. This injection site was located in the medial region of the ZI, spanning both dorsal and ventral sectors (Fig. 3B). The other cases examined in this series had

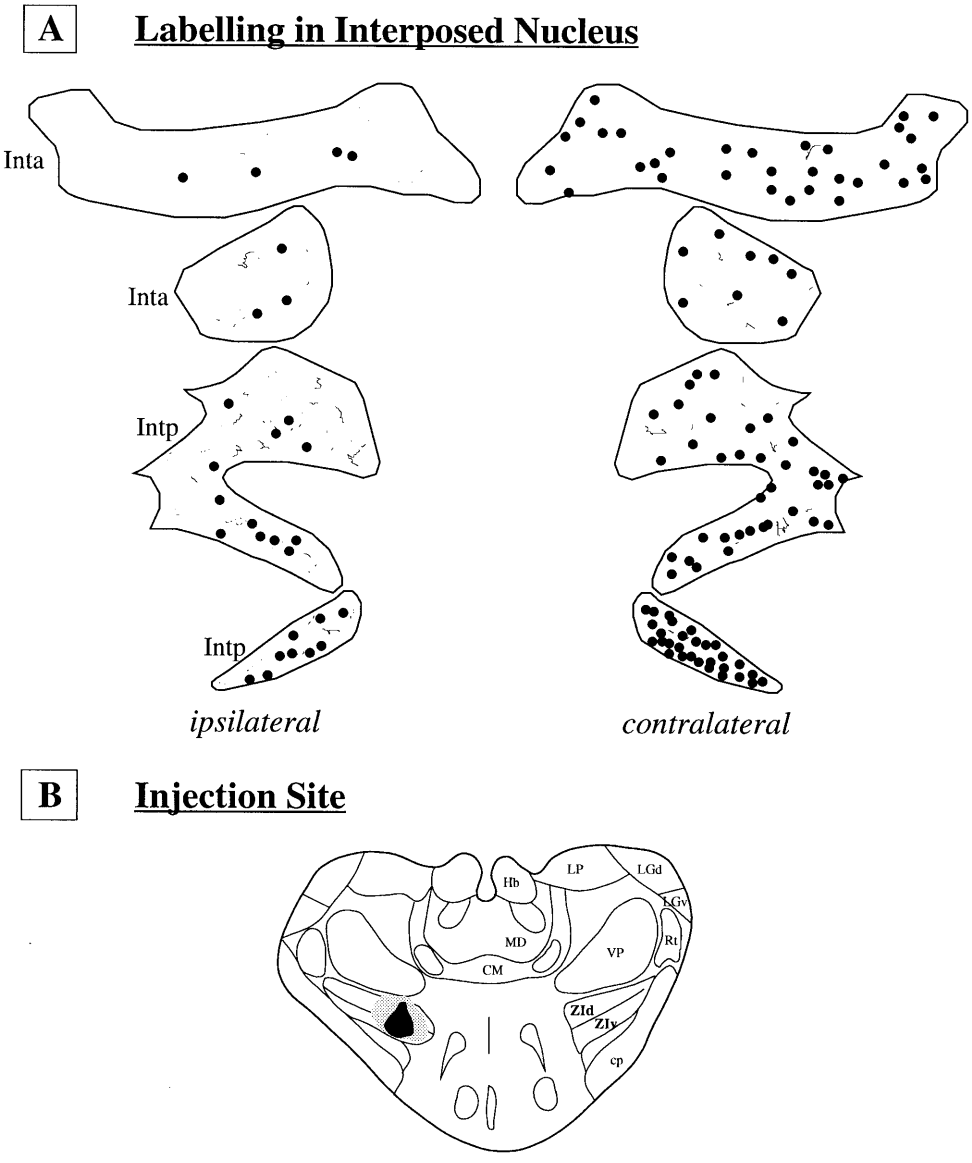

Fig. 3 Schematic diagrams of the distribution of labelled terminals and cells in the Int (**A**) after an injection of CTb into the ZI (**B**). Labelling is shown in the Int of both ipsilateral (left hand column) and contralateral (right hand column) side. The orientation and course of labelled axons containing a set of boutons or small swellings are shown. Axons of passage are not shown (they were much thicker and lacked boutons). Each *black circle* represents one labelled cell. All figures are of coronal sections, rostral to top, medial to midline. In **B** *black* represents focal point and *shading* represents the halo of the injection site

similar-sized injection sites within the ZI and resulted in similar labelling. After each CTb injection, labelled terminals were found throughout the Int, within both anterior and posterior divisions. In general, labelled terminals were rather scarce. There were often more labelled terminals found in the posterior than the anterior Int and more were found ipsilaterally (Fig. 3A). By contrast, the same injections revealed a large number of labelled cells in the Int. As with the labelled terminals, more labelled cells were found in the posterior division of the nucleus. Unlike the terminals, there were more labelled cells on the contralateral side than on the ipsilateral side (Fig. 3A). From three cases analysed, there were 112, 110, and 119 labelled cells on the ipsilateral side, while there were 360, 363 and 370 labelled cells on the contralateral side in the corresponding cases.

Discussion

Previous studies have reported on aspects of the ZI connections with the Int (Faull and Carman 1978; Vaudano and Legg 1992; Yatim et al. 1995; Aumann and Horne 1996; Aumann et al. 1994, 1996). However, these accounts have, for the most part, been part of more general reports of ZI and/or thalamic connections and as a consequence, the details of these connections have not been documented. For instance, although some of these studies have noted that ZI has connections with Int (Vaudano and Legg 1992; Aumann et al. 1996), the particular ZI sector that relates to the Int was not noted. The results of this study largely confirm and extend these earlier reports. We extend previous studies by providing detailed maps of the distribution of the labelled terminals and cells in the Int after tracer injections into the ZI and in the ZI after injections into the Int.

The overall Int projection to the thalamus is not limited to the ZI; indeed, it incorporates many thalamic nuclei. Aumann and colleagues (1994, 1996) have shown that the ventral medial, ventral lateral, ventral posterior, posterior thalamic and intralaminar nuclei, as well as the ZI receive inputs from the Int. In fact, these authors indicate that the projection to the ZI forms only a small part of the overall projections between Int and the thalamus. Aumann and Horne (1996) suggest that the Int projection to ZI forms a modulatory input, rather than a primary drive, as formed by the Int projection to the ventral lateral nucleus. Notwithstanding, in terms of ZI afferents, the Int projections are among the heaviest (in qualitative terms) that the ZI receives. After tracer injections into the Int, our results show areas of very rich terminal labelling in the ZI. Such terminations appear just as extensive, if not more so, than the recently described projections from many nuclei of the brainstem (Kolmac et al. 1998). Our results also show evidence for a small projection from the ZI back to the Int, since some labelled cells were seen in the ZI after Int injections, as were labelled terminals in the Int after ZI injections. These features of connectivity place the Int in a strong position to influence the function of the ZI, and could prove pivotal when one considers the overall function of the ZI.

The particular neurotransmitter system associated with the ZI inputs to the Int remains to be determined. The ZI shows much diversity in terms of neurochemical character, indicating that its input to the Int may comprise more than one neurotransmitter system. Indeed, the ZI output to the Int arises from cells within different sectors of the ZI and these are characterised by different neurochemicals. For example, the ventral sector has many GABAergic cells, while the dorsal sector has many glutamate and nitric oxide synthase cells (Kolmac and Mitrofanis 1999a).

A feature of ZI connectivity with various subcortical centres is that laterality is maintained. That is, if the ZI receives a major projection from a given neural centre on one side of the brain, for example the ipsilateral side, then the reciprocal ZI projection will be to that same side (e.g. Kolmac et al. 1998; Kolmac and Mitrofanis 1999b; Power et al. 1999; Mitrofanis and Mikuletic 1999; Reardon and Mitrofanis 2000). This feature of organisation is not limited to the ZI and can, for the most part, be extended to most other centres of the brain. The ZI connections with the Int are, however, organised very differently. Although the interposed projection to the ZI is predominantly contralateral, ZI projections back to the Int are primarily ipsilateral. In essence, this result suggests that the ZI and Int of opposite sides of the brain have the heaviest connections. The significance of this unusual feature of connectivity is not immediately apparent and remains puzzling, particularly since there are many sites of cross connectivity between the ZI (Power and Mitrofanis 1999) and Int (Dietrichs and Walberg 1979; Voogd 1995) of both sides. Interestingly, May et al. (1992) have reported a similar pattern of laterality between the cerebellum and the near response region of the midbrain. They show that although this region of the midbrain receives a very heavy contralateral projection from the deep cerebellar nuclei, its projection back to the deep nuclei is predominantly ipsilateral. This pattern of laterality may, therefore, be a common feature of cerebellar organisation. The cerebellum may send afferents, for example those driven by proprioceptors, from the contralateral side of the body to the thalamus or midbrain, and is controlled mainly from the higher centres from the ipsilateral side.

Thus, in conclusion, the ZI appears to be in a strong position to collate and sample afferents, not only from various somato and viscerosensory centres of the brainstem (Kolmac et al. 1998), but also from the Int of the cerebellum as well. It remains to be determined what particular function, whether motor, cognitive or autonomic, the Int afferents to the ZI are involved in.

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