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メタデータ	言語: eng 出版者: 公開日: 2017-10-05 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属:
URL	http://hdl.handle.net/2297/9905

Anatomical plasticity in brainstem auditory nuclei following unilateral ablation of the inferior
colliculus in neonatal rats

by

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Text pages: 14

Figures: 3; Tables: 2

Running Head: Neonatal IC lesions

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Acknowledgements: This research was supported by a grant to J.B.K. from the Natural Sciences
and Engineering Research Council (NSERC) of Canada.

ABSTRACT

Anatomical plasticity of projections from brainstem auditory structures to the inferior colliculus (IC) was examined in albino rats to determine the effects of unilateral destruction of the IC during early development. The IC in the right hemisphere was destroyed by aspiration on postnatal day 3. Upon reaching adulthood, the rats were examined by retrograde tract tracing methods with fluoro-gold (FG) and [³H]-glycine to determine patterns of brainstem projections to the undamaged left IC. In our FG experiments, the results confirmed the presence of aberrant crossed projections from the right medial superior olive (MSO) to the undamaged left IC. Following injections of [³H]-glycine or FG into the undamaged left IC, however, no other aberrant projections were found in the superior olive, including those from the ipsilateral lateral superior olive (LSO) or the superior paraolivary nucleus (SPN). These results suggest that projections from the MSO to the IC may have the latent ability to create aberrant crossed projections during development. On the other hand, the neurons in LSO and SPN do not form aberrant projections following early unilateral IC lesions.

Key words: inferior colliculus (IC); superior olivary complex (SOC); retrograde transport; [³H]-glycine; Fluorogold (FG)

List of abbreviations:

FG, fluoro-gold; IC, inferior colliculus; SOC, superior olivary complex; LSO, lateral superior olive; MSO, medial superior olive; SPN, superior paraolivary nucleus; DNLL, dorsal nucleus of lateral lemniscus; VNLL, ventral nucleus of the lateral lemniscus;

INTRODUCTION

The superior olivary complex (SOC) is a major mammalian auditory brainstem structure that contains several distinct nuclei, each with its own pattern of afferent and efferent projections (Grothe and Park, 2000). The SOC is generally accepted as playing an important role in sound localization and binaural hearing (Kavanagh and Kelly, 1992; Kelly and Sally, 1993; Sally and Kelly, 1992; Wu and Kelly, 1992). Three principal nuclei comprise the SOC in the rat: the lateral superior olive (LSO), the medial superior olive (MSO), and the superior paraolivary nucleus (SPN). In the rat, as in many other mammals, these three nuclei (LSO, MSO and SPN) constitute part of the main ascending afferent sources of projections to the inferior colliculus (IC) (Adams, 1979; Glendenning and Masterton, 1983; Kelly et al., 1998; Moore et al., 1995; Pollak et al., 2002). The major excitatory inputs to the IC emerge from the ipsilateral MSO and contralateral LSO. Also, a major inhibitory input emerges from glycinergic neurons in the ipsilateral LSO. The MSO-IC projection is predominantly ipsilateral in normal rats (Beyerl, 1978; Coleman and Clerici, 1987). Animals with early ablation of the IC, however, display an aberrant crossed projection from the MSO to the undamaged IC, which is never seen when the IC is ablated in adulthood (Okoyama et al., 1995a).

The projections from LSO to IC can be segregated, immunocytochemically, into 3 components: 1) a crossed, glycine-negative (-) projection; 2) an uncrossed, glycine-positive (+) projection; and 3) an uncrossed, glycine-negative (-) projection (Saint Marie and Baker, 1990; Saint Marie et al., 1989). Recent anatomical and physiological studies have suggested that the principal sources of glycinergic inputs to the IC are the ipsilateral LSO and the ventral nucleus of the lateral lemniscus (VNLL), and that these glycinergic pathways are major sources of synaptic inhibition of IC neurons (Loftus et al., 2004). Although the LSO is easily distinguished from other SOC nuclei by shape, investigating anatomical plasticity of the projection from the LSO to the contralateral IC following unilateral destruction of the IC is

difficult using simple retrograde tract-tracing techniques because the LSO has projections to both ipsilateral and contralateral IC in normal animals. Several lines of evidence suggest that glycinergic projections from LSO to IC are almost entirely ipsilateral; in other words, the crossed projections from LSO to IC do not appear to be glycinergic (Saint Marie and Baker, 1990; Saint Marie et al., 1989). The present study investigated possible changes in the projections from LSO and SPN to IC using Fluorogold (FG) tract-tracing together with neurotransmitter-specific uptake and retrograde axonal transport of [^3H]-glycine. This approach allowed us to determine the effects of early unilateral ablation of the IC on glycinergic projections from the superior olivary complex to the intact IC.

MATERIALS AND METHODS

Early IC lesions were made in albino Wistar rat pups born to females obtained from Charles River Ltd. (St. Constant, Quebec, Canada). Eight of these animals provided useful data for analysis. Twenty-eight rats with IC lesions were excluded from analysis because their lesions and/or injection sites of tracers were either too small or too large. An additional 7 adult rats were used as normal controls. Animals were housed in clean cages and maintained in good health in the Life Science Center vivarium for the duration of the experiment. During all surgical procedures, neonatal rats were anesthetized using halothane with the help of hypothermia and adult rats were anesthetized using intraperitoneal injection of sodium pentobarbital at 65 mg/kg. In developing rats, the right IC was destroyed by aspiration on postnatal day three (P3). While partial removal of the caudal pole of the occipital cortex was necessary to expose the IC in adult rats, neonatal surgery was performed without such removal, because the occipital cortex does not extend over the IC surface in neonatal rats. At 6 months after the IC lesion, rats were re-anesthetized and tracers were injected through glass micropipettes (inner tip diameter, 25-35 μm) into the undamaged left IC so that possible aberrant projections to the IC could be detected in the SOC. Neurotransmitter-specific uptake

of [^3H]-glycine and retrograde tract-tracing were used to investigate anatomical connections. Fluoro-gold (FG; Fluorochrome, Colorado, USA) was used as a simple retrograde marker and [^3H]-glycine was used to detect possible changes in the pattern of glycinergic projections to the remaining IC. Each animal received multiple injections of tracers to maximize labeling. FG (2% solution dissolved in saline) was delivered iontophoretically by passing a continuous 7.5 μA DC positive current for a total of 15 min and [^3H]-glycine (20 $\mu\text{Ci}/\mu\text{l}$, 0.5 μl) was injected by air pressure. Normal adult animals ($n=7$) received injections of [^3H]-glycine ($n=2$) and FG ($n=5$) into the left IC as controls. These experimental procedures are summarized in Table 1.

Following a survival period of 3-4 days, animals were re-anesthetized with an overdose of intraperitoneal sodium pentobarbital (120 mg/kg) and perfused transcardially with phosphate-buffered saline followed by 4% paraformaldehyde. Brains were cut serially at 40 μm in the frontal plane on a freezing microtome (Reichert-Jung, Nussloch, Germany), divided into three parallel series and sections were mounted on gelatin-coated slides. To identify distributions of [^3H]-glycine labeling, sections on slides were defatted and coated with NTB-3 emulsion (Kodak, USA), exposed for 1-2 months, then developed with D-19 developer (Kodak). Slides were then examined for FG labeling using a fluorescence microscope and for labeling of [^3H]-glycine under bright-field illumination (Zeiss, Germany and Nikon Eclipse E1000 microscope; Nikon, Auckland, New Zealand). Autoradiographically labeled neurons were identified by a focal concentration of silver grains in the emulsion layer. For quantitative evaluation, the number of FG or [^3H]-glycine positive neurons was counted in the LSO and SPN on both sides of the brainstem. The difference in the percentage of ipsilateral and contralateral neurons was compared statistically using Student's t test, $p = 0.05$.

-----Insert Table 1 About Here-----

RESULTS

-----Insert Figure 1 About Here-----

In all 8 cases with IC ablation, aspiration removed the greater part of the right IC (central, external and pericentral nuclei and commissure of the IC) without any damage to the contralateral IC. In some cases there was partial damage to adjacent areas such as the central gray and caudal part of the superior colliculus (SC). The ablated area (Fig.1 A) and typical injection sites of FG (B) and [³H]-glycine (C) for tracers are shown in Figure 1. FG injections affected a major part of the IC including the pericentral and external nuclei and the rostral extent of the central nucleus but did not spread to either the dorsal nucleus of lateral lemniscus (DNLL) or any other tegmental area (Fig.1 B). Injections of [³H]-glycine were always placed in the central nucleus of the IC and affected a major part of the IC. Tritiated tracer diffused ventrally along the path of fibers projecting from the lateral lemniscus and into a portion of the ipsilateral DNLL (Fig.1 C). In no case did either tracer spread to the other side of IC, as the right IC was totally destroyed by aspiration.

-----Insert Figure 2 About Here-----

LSO and SPN are easily identified as relatively simple structures in both normal and IC lesioned animals. Following injection of [³H]-glycine into the undamaged left IC, autoradiographically labeled neurons were found in the LSO, SPN and the ventral nucleus of lateral lemniscus (VNLL) on the same side (left) of the brain (Fig.2). These neurons were not likely labeled by diffusion of the tritiated tracer, as neurons in neighboring nuclei did not express the tritiated label. The means and standard errors based on cell counts of [³H]-glycine labeled neurons were 155.5 ± 35.5 (control) and 170 ± 24.9 (IC lesion) in the ipsilateral LSO and 118 ± 20.5 (control) and 137 ± 14.2 (IC lesion) in the ipsilateral SPN (Table 2). No labeled neurons were observed in the contralateral right LSO or SPN (Fig.3 A, C) in either normal or experimental animals (Table 2). The distribution of [³H]-glycine-labeled neurons in the brainstem auditory nuclei was similar to that seen in normal animals. Thus, in our [³H]-glycine experiments, we found no evidence of aberrant projections from the SOC (including LSO and SPN) to the undamaged left IC.

-----Insert Figure 3 About Here-----

-----Insert Table 2 About Here-----

Brainstem auditory neurons retrogradely labeled with FG were clearly recognized by the appearance of fluorescence in the perinuclear cytoplasm and proximal dendrites. When FG injections were made into the undamaged left IC in cases with unilateral ablation of the right IC during early development, many neurons in the brainstem auditory nuclei were retrogradely labeled with FG. The pattern of distribution of FG-labeled neurons was almost the same as the normal pattern, except in the right (IC-lesioned side) MSO. Neurons labeled with FG were found in the DNLL and LSO on both sides. Figure 3 shows these nuclei on the right side, contralateral to the injection. In addition to the numerous labeled neurons in the right LSO, some FG-labeled neurons were found in the contralateral right MSO (Fig. 3D, Table 2). As the ascending MSO-IC projection is predominantly ipsilateral in normal rats, the labeling of contralateral MSO neurons in rats with early lesions implies the presence of aberrant crossed projections. The ratios of FG labeled neurons in the ipsilateral to contralateral MSO were 97.8:2.1 in the control and 88.6:11.4 in the experimental animals. This result confirms a previous report by Okoyama et al. (1995b). Abnormally labeled neurons in the right MSO were small in number, but the aberrant crossed projections from the MSO to the undamaged IC were observed in all cases with neonatal (P3) IC ablation. In our FG experiments, the presence of such abnormal labeling was seen only in the MSO ipsilateral to the ablation and remained unchanged regardless of the survival period after ablation. The labeling in both LSO and SPN (bilateral and ipsilateral to the injection respectively) was identical to that found in normal cases. The means and standard errors based on cell counts of FG labeled neurons in the LSO were 602 ± 26.2 (ipsilateral) and 547 ± 36.7 (contralateral) in the control animals and 629 ± 27.1 (ipsilateral) and 538 ± 19.2 (contralateral) in the neonatal IC lesioned animals. The ratios of FG labeled neurons in the ipsilateral to contralateral LSO were 52.4:47.6 in the control and 53.9:46.1 in the experimental animals. The ipsi-contra ratios of FG neurons in the LSO and

SPN were not significantly different for normal and IC lesion cases. No aberrant projections were detected in either LSO or SPN using retrograde FG tract-tracing methods.

DISCUSSION

The present study investigated anatomical plasticity of projections, including the glycinergic pathways, from lower brainstem structures to the auditory midbrain following unilateral destruction of the IC during early development (P3). The autoradiographic study and quantitative data from cell counts of FG neurons did not show any evidence of aberrant crossed projections from the LSO or the SPN to the contralateral undamaged IC. In previously published studies, it has been shown that the neurons in each LSO project about equally to the ipsilateral and contralateral IC in the cat (Brunso-Bechtold et al., 1981; Glendenning and Masterton, 1983) or ferret (Henkel and Brunso-Bechtold, 1993; Moore, 1988; Moore et al., 1995). Our data in the normal rat also showed equal proportions of neurons in the ipsilateral and contralateral LSO and this ipsi-contra ratio did not change following IC ablation on P3. The ipsi-contra ratio of FG labeled neurons in the SPN was not significantly different for normal cases and IC lesion cases. These results are consistent with the finding of our autoradiographic study and provide evidence that the neurons in LSO and SPN do not form aberrant projections to the IC. In contrast, our FG retrograde labeling confirmed the results of previous studies showing aberrant crossed projections from the MSO to the undamaged IC following IC ablation during development, a projection never seen in normal rats (Okoyama et al., 1995a; Okoyama et al., 1995b). Since the normal projection from MSO to IC is predominantly ipsilateral in adult rats, as in many other mammals, aberrant axons of spared MSO neurons must have reached the contralateral IC during the course of development.

These results show a fundamental difference in plasticity between the LSO-IC and SPN-IC projections on the one hand and the MSO-IC projection on the other. We used [³H]-glycine as a neurotransmitter-specific retrograde label to investigate possible changes in

glycinergic projections to the remaining IC after unilateral IC ablation during early development. The normal glycinergic projections from the LSO and SPN to the IC are predominantly ipsilateral in rodents (Saint Marie and Baker, 1990) and cats (Saint Marie et al., 1989). Glycinergic neurons are common in the rodent CN, SOC and VNLL (Aoki et al., 1988; Wenthold et al., 1987). Glycine and GABA are generally accepted as important inhibitory neurotransmitters in the central auditory system. Part of these glycinergic and GABAergic neurons project to the central nucleus of the IC and play a significant role in neural inhibition in the IC (Faingold et al., 1989; Loftus et al., 2004). Thus, the ascending projections from glycinergic neurons in LSO, SPN and VNLL constitute a major inhibitory input to the ipsilateral IC.

Our results demonstrate that the pattern of glycinergic projections to the IC in rats with unilateral IC ablation during development resembles that of normal projections in rats and other rodents including chinchilla and guinea pig (Saint Marie and Baker, 1990). The glycinergic projections to the undamaged IC, including projections from the LSO and the SPN, are unchanged, whereas part of the projection from the MSO forms an aberrant crossed pathway to the undamaged IC. Although the time course of postnatal development of glycinergic afferent projections to the IC in rat pups has not been studied in detail, connections to the IC from the CN, SOC and the lateral lemniscus are partially present at birth. The auditory system, compared with other sensory systems, develops relatively late in rats and other mammals (Friauf, 1993; Friauf, 1994; Friauf and Kandler, 1990; Parks and Rubel, 1978). Projections from the MSO to the IC are established gradually over a prolonged period after birth (Friauf, 1993; Okoyama et al., 1995b). Thus, MSO neurons might have the potential to produce exuberant projections and form new connections following axotomy probably due to growth of axons that were undamaged by the lesion. In contrast, glycinergic LSO-IC or SPN-IC projections might be relatively well established at P3 with no late-developing neurons that could promote aberrant crossed projections after IC ablation during development.

The difference in plasticity between LSO-IC and MSO-IC connections might be related to evolutionary differences in these two projections. The projection from the MSO to the IC is largely or entirely ipsilateral in many mammals, including cat, rat, gerbil, bat and ferret (Adams, 1979; Coleman and Clerici, 1987; Glendenning and Masterton, 1983; Moore, 1988; Nordeen et al., 1983; Okoyama et al., 1995b; Zook and Casseday, 1982). On the other hand, in some primitive species such as the mole (*Mogera*), opossum (*Didelphis*) and northern native cat (*Dasyurus*), the MSO has been shown to project bilaterally to the IC (Aitkin et al., 1986; Kudo et al., 1990a; Kudo et al., 1990b; Kudo et al., 1988; Willard and Martin, 1983; Willard and Martin, 1984). Double-labeling studies in the mole (Kudo et al., 1990a) and opossum (Willard and Martin, 1984) have demonstrated that many MSO neurons are double-labeled with different tracers injected separately into left and right IC, indicating that these double-labeled neurons project bilaterally via axon collaterals. As input connections from the MSO to the IC are still immature at P3 in the rat (Friauf and Kandler, 1990), exuberant bilateral projections occurring after IC ablation in the immature developing rat might reflect the expression of a more primitive mammalian condition. Our results suggest that projections from the MSO to the IC may have the latent ability to create aberrant crossed projections during development. Conversely, the pattern of LSO-IC or SPN-IC projections in primitive species might be the same in all mammals including the most primitive species. The possibility of such evolutionary differences between MSO-IC and LSO-IC projections might reflect differences in gene expression that could account for the differences in plasticity after developmental IC ablation in rats.

The inferior colliculus receives massive auditory projections from each of the various brainstem structures that play a role in binaural processing and sound localization. In adult cats and ferrets, unilateral destruction of the inferior colliculus severely disrupts sound localization with the effects most apparent in the spatial field contralateral to the side of the lesion (Jenkins and Masterton, 1982; Kelly and Kavanagh, 1994). Comparable data are not available for adult rats, but one might expect severe deficits after unilateral IC lesions

considering the deficits in sound localization produced by unilateral damage of binaural structures with direct projections to the IC, viz., the superior olivary complex and the dorsal nucleus of the lateral lemniscus (Ito et al., 1996; Kelly et al., 1996; van Adel and Kelly, 1998). It is not yet known, however, whether early unilateral IC lesions would produce any long-lasting sound localization deficits equivalent to those produced after adult lesions or whether the early lesions would be accompanied by functional recovery or compensation associated with the reorganization of central projections. In the present study, re-routing after early unilateral IC lesions occurred for the MSO-IC projection, but not for the LSO-IC projection. It is generally accepted that the MSO is especially important for low frequency sound localization, and that the LSO contributes primarily to high frequency sound localization. The animals with early unilateral IC lesions, therefore, might be expected to show selective effects related to low frequency sound localization. Further investigations of the behavioral effects of destroying the IC in adults and infants are needed to determine the functional consequences of the re-routing of afferent projections from the lower brainstem to auditory midbrain structures after early lesions.

CONCLUSION

1) Following injection of [³H]-glycine into the undamaged IC, autoradiographically labeled neurons were found in the ipsilateral VNLL, LSO and SPN. No [³H]-glycine-labeled neurons were observed in the contralateral LSO or SPN (on the side of the IC ablation) despite heavy retrograde labeling with FG in bilateral LSO and ipsilateral SPN. Distribution of [³H]-glycine-labeled neurons resembled that seen in normal animals. No aberrant projections from brainstem auditory nuclei to the undamaged left IC were observed, including ipsilateral glycinergic projections from the right LSO and SPN.

2) Following injection of FG into the undamaged IC, an aberrant crossed projection from the MSO to the undamaged IC was consistently observed in all cases with early (P3) lesions of the IC. Our results confirm the results of previous studies and further demonstrate that the

presence of such an aberrant projection is seen only in the MSO-IC connection. Our data indicate that aberrant connections exist in the MSO-IC, but not in the LSO-IC or SPN-IC projection after unilateral IC ablation during early development in rats.

FIGURE LEGENDS

Table 1: Experimental procedure for ablation and retrograde tracing studies

Table 2: Means and standard errors based on cell counts of labeled neurons in LSO and SPN for rats with early unilateral IC lesions and adult controls. Data are shown separately for structures located ipsilateral and contralateral to the injection of either [³H]-glycine or FG into the undamaged or left IC.

Figure 1: The placement and extent of the IC lesion (Nissl stain, shown in A) and typical injection sites of FG (B) and [³H]-glycine (C) for tracers. Schematic line drawings of frontal sections of the brainstem to show injection sites of tracers (D). The FG injections affected a major part of the IC, including the central nucleus, the pericentral and external nuclei and the rostral extension of the central nucleus. There was no spread of the FG injection to either DNLL or any other tegmental area. The [³H]-glycine injections were generally larger than the FG injections.

Figure 2: Photomicrographs of frontal sections through the left VNLL (A-C), SOC (D) and LSO (E) showing FG-labeled neurons (A) and neurons autoradiographically labeled with [³H]-glycine (B-E) following injections of FG and [³H]-glycine into the contralateral (left) IC after ablation of the right IC on P3.

Figure 3: Photomicrographs of frontal sections through the right DNLL (A, B) and SOC (C, D)

showing FG-labeled neurons (B, D) and neurons autoradiographically labeled with [³H]-glycine in corresponding sections (A, C) following injections of FG and [³H]-glycine in the contralateral (left) IC after ablation of the right IC on P3. Some aberrantly projecting neurons labeled with FG are seen in the right MSO. Calibration bars, 120 μm.

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