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Diencephalic Asymmetries

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HARRIS, J. A., V. GUGLIELMOTTI AND M. BENTIVOGLIO. *Diencephalic asymmetries*. NEUROSCI BIOBEHAV REV 20(4) 637-643, 1996.—Structural asymmetry in diencephalic regions has been reported in a number of studies since the pioneering observations by Kemali and Braitenberg, Atlas of the frog's brain. Springer Verlag: 1969. Anatomical differences between the left and right habenulae have been identified in many lower vertebrate species. While there are few reports of structural asymmetry in the dorsal thalamus, there is evidence that asymmetrical thalamofugal projections can be induced in the visual system of chicks by lateralized sensory stimulation prior to hatching. Finally, there have been consistent reports of differences between left and right sides of the hypothalamus in their sensitivity to the effects of circulating gonadal hormones in rats. In most cases, these asymmetries are sex-linked and correspond to a lateralization of function. Although the significance of many of these diencephalic asymmetries is still enigmatic, their existence indicates that asymmetry is not a phylogenetically recent feature of the brain, and that left-right differences in the brain may be mediated by a common ontogenetic mechanism and may underlie the development of highly specialized functions. Copyright © 1996 Elsevier Science Ltd.

Biological rhythms Epithalamus Frontal organ Habenula Hypothalamus Lateralization of function Lower vertebrates Neurohormonal regulation Thalamus

INTRODUCTION

FOR MORE than a century, researchers have been collecting data revealing significant anatomical and functional asymmetries in the cerebral cortex of humans (as outlined in several papers in this issue). As a result, it would be easy to assume that asymmetry is a specific property of the human cortex. However, in the last 20 years, researchers have identified instances of brain asymmetry outside the cerebral cortex, including in the brain stem (46). Moreover, cortical and subcortical asymmetries have been reported in other animals (40), and these asymmetries are often sex-linked and correspond to a lateralization of function. Accordingly, it is the intention of this review to illustrate this point by providing examples of anatomical and functional asymmetries identified at the subcortical level in diencephalic structures, comprising the epithalamus, thalamus and hypothalamus.

1. EPITHALAMUS

Right-left differences in the habenular complex, which is a major component of the epithalamic region, stand as a peculiar feature of the non-mammalian diencephalon. Asymmetries have been identified in the habenula of an impressive number of lower vertebrates,

including the shark *Scyllium stellare* (28), the eel *Anguilla anguilla* (5), the newt *Triturus cristatus* (5), the frog *Rana esculenta* (5,23), the lizard *Lacerta sicula* (9,22) and the chicken (16).

In these species, an asymmetric organization has been predominantly detected in the structures homologous to the medial nucleus of the habenular complex in mammals. It is worth mentioning, in this respect, that the mammalian medial and lateral habenular nuclei are very different not only in their cytological organization (6,18), but also in their connectivity (44). The medial habenula, innervated predominantly by septal fibres, projects to the interpeduncular nucleus of the midbrain via the fasciculus retroflexus, and this latter connection is highly conserved in evolution. The lateral habenula of mammals, on the other hand, seems to play a role as motor-limbic interface, since it receives pallidal, limbic and hypothalamic afferents, and projects to the ventral midbrain tegmentum.

A right-left difference has also been observed in the habenulae of a macrosmatic mammal, the mole *Talpa europaea*, in which a row of dark cells is aligned along the lateral border of the left medial habenula (21). Such an asymmetric feature is, however, relatively inconspicuous when compared to the striking asymmetries described in the frog and lizard habenulae (Figs 1,2). In the lizard, the medial habenula in the left

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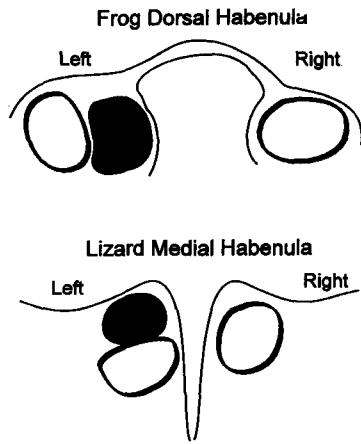


FIG. 1. Schematic drawings of the dorsal habenula of the frog *Rana esculenta* and medial habenula of the lizard *Lacerta sicula*. Note that in both cases, the left habenular nucleus is divided into two distinct compartments (as inferred from refs 5 and 9). Moreover, in each case, there is evidence suggesting that one of the two nuclei in the left habenula (depicted here by shading) may be involved in circuitry underlying the entrainment of seasonal and circadian rhythms to light cycles.

hemisphere is divided into two distinct subnuclei, one located dorsally and the other ventrally; in contrast, the right medial habenula contains only one nucleus (9). Similarly, in the frog, the left dorsal habenula has a more lobate structure than its right counterpart, and is composed of a medial and a lateral subnucleus, whereas the right dorsal habenula consists of only one nucleus (5,23) (Fig. 2).

Importantly, these asymmetries appear to correspond to functional differences between the left and right habenulae. In the frog, the structural asymmetry in the habenula displays a seasonal variation which suggests that it may be involved in the regulation of the animal's sexual activity (27). Furthermore, the medial subnucleus of the left dorsal habenula in the frog has been found to contain endocellular "crystal-like" inclusions that are not present in either the lateral subnucleus of the left dorsal habenula or in the right dorsal habenula (25). These inclusions have been interpreted as photosensitive organelles, based on their morphological resemblance to photoreceptors in the frog retina and pineal complex (20).

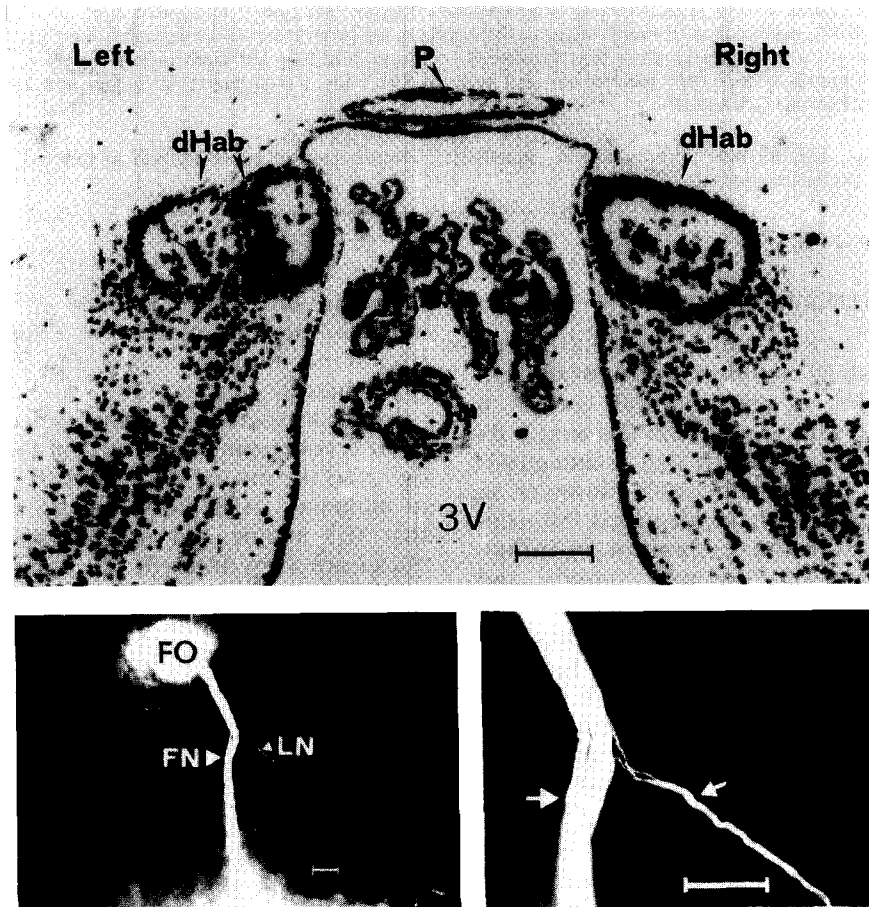


FIG. 2. Microphotographs of the dorsal habenula (top) and frontal organ (bottom) of the frog *Rana esculenta*. In the top microphotograph, it should be noted that the left dorsal habenula is comprised of two distinct nuclei (one medial, the other lateral), whereas the right dorsal habenula consists of only one nucleus. In the bottom microphotographs (reprinted with permission from ref. 15), the frontal organ, frontal nerve and lateral nerve are visualized after applying the fluorescent dye carbocyanine DiI to the cut end of the frontal nerve. On the right, the branching of the fine lateral nerve from the frontal nerve (arrows) can be seen at a higher magnification. Abbreviations: dHab: dorsal habenula; FN: frontal nerve; FO: frontal organ; LN: lateral nerve; P: pineal gland; 3V: third ventricle. Scale bars correspond to 100 μ m.

It is important to recall in this respect that the pineal complex in lower vertebrates plays a substantial role in photoreception, and its organization is more complex than in mammals. In particular, the pineal complex of some poikilothermal vertebrates includes not only an intracranial component, represented by the pineal organ or epiphysis, but also an extracranial component. This is represented in anuran amphibians by the frontal organ, located in the skin between the eyes, which is presumably equivalent to the parietal organ described in reptilian species. Both the frontal organ and the parietal organ are photoreceptive structures, and are thus involved in the transduction of environmental cues. The frontal organ, interconnected with the epiphysis and the brain by means of the frontal nerve, has both bilateral and unilateral central projections (24). In addition, a recently described unilateral nerve branch of the frontal nerve, the lateral nerve (Fig. 2) (15), interconnects the frontal nerve with the network of cutaneous innervation, thus further supporting the assumption that this system is asymmetrical and is involved in the integration of extrinsic and intrinsic information necessary for the control of autonomic functions.

There is also evidence that the dorsal subnucleus of the left medial habenula in the lizard is involved in the entrainment of behavioral or endocrine cycles conditioned to environmental cues and, in particular, to light. First, the projections of the parietal organ are confined to the dorsal subnucleus of the left medial habenula, and are not distributed either to the left ventral subnucleus or to the right medial habenula (9). Moreover, the receptors for melatonin, the hormone secreted by the pineal gland, are asymmetrically distributed in the lizard habenula (47). Although the authors did not mention this specifically, we are led to believe from their microphotographs (see Fig. 2 in ref. 47) that melatonin receptors are concentrated in the dorsal subnucleus of the medial habenula, and are absent from both the ventral subnucleus of the left medial habenula and the right medial habenula.

The findings described above suggest that the asymmetry in the habenulae of the frog and lizard may well reflect a distinct function of one unpaired nucleus (the dorsal subnucleus of the medial habenula in the lizard, the medial subnucleus of the dorsal habenula in the frog) in the entrainment of endogenous biological rhythms to light cycles via its connections with the pineal complex, including the frontal or parietal organs, which are unpaired structures. In this case, it is conceivable that the lack of striking habenular asymmetries in the mammalian brain may be linked to the lack of an extracranial component of the pineal complex. In support of this hypothesis, the habenulae are symmetrically organized in reptiles that lack a parietal organ (9).

Habenular asymmetry has been reported to be sex-dependent. Specifically, in the chicken brain, the right medial habenula is larger than the left in males, but not in females (16). However, treatment with testosterone induces this asymmetry in the medial habenula of female chicks (17), indicating that the sex-linked asymmetry is mediated by testosterone.

It is perhaps relevant that the striking asymmetry in the medial habenula is lost in mammals, in which the

neural mechanisms underlying photoreception and the entrainment of endogenous biological rhythms underwent a substantial phylogenetic evolution. However, residual asymmetries have been identified in the habenulae of some lower eutherian mammals. Specifically, detailed morphometric analysis in developing and mature rats has revealed that the left medial habenula is slightly (5%) but significantly ($p < 0.001$) larger than the right medial habenula in this species (48). Further, as mentioned earlier, in the macrosomatic mole, a row of dark cells has been described lying along the lateral border of the left but not the right medial habenula (21). Finally, in reference to habenular asymmetry in mammals, it should be mentioned that a volumetric asymmetry has been identified in the lateral, but not medial, habenula of white mice during development and adulthood; in contrast to the asymmetries in the medial habenula, this lateral habenular asymmetry favours the right side over the left (51).

2. THALAMUS

The dorsal thalamus represents the major source of monosynaptic subcortical inputs ascending to the cerebral cortex. Therefore, given that asymmetries have been identified in the cerebral cortex (40), it may be somewhat puzzling that structural asymmetries have not, to our knowledge, been reported in the thalamus itself. However, it is important to acknowledge that this apparent absence of thalamic asymmetry may reflect a limitation of research to date. For example, the relative lack of striking structural differentiation within the thalamus of non-mammalian vertebrates would undermine the chances of any asymmetry being identified. In addition, thalamic asymmetries may be identified which correspond to lateralization of function. In this regard, studies in macaques have provided some indication that functional asymmetry in vocalization may correspond to anatomical asymmetries in the medial geniculate bodies (10).

Reports of asymmetry in thalamic cytological organization include the description of an asymmetrical distribution of mast cells in the rat thalamus (14). Further, there are reports that asymmetry can be induced in the thalamus by lateralized sensory stimulation during embryonic development. For example, in chicks, the hyperstriatum (visual Wulst) receives more extensive projections from the left thalamus than from the right thalamus (4,39). This asymmetry corresponds to a lateralization of function in the chick's visual performance. For example, in fine visual discrimination tasks, chicks perform better when using the right eye (which projects to the left thalamus) than the left eye (which projects to the right thalamus) (1,2). Conversely, the left eye is held to be more successful in processing spatial information (34). Importantly, both the anatomical asymmetry and functional lateralization result from a lateralized exposure to light during a critical period in the development of the chick embryo (Fig. 3). Specifically, towards the end of its embryonic development, the chick is positioned inside the egg in such a way that its left eye is occluded while

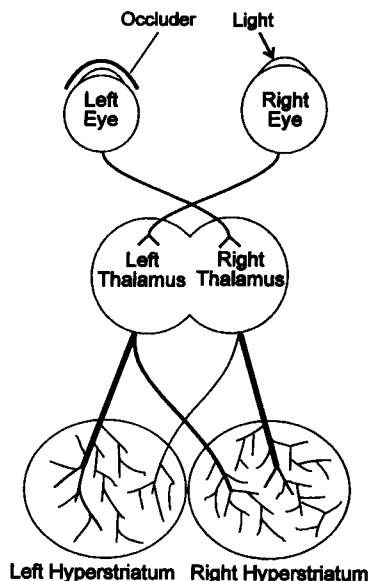


FIG. 3. Diagrammatic representation of the asymmetry in the thalamo-hyperstriatal projection of the chick. Each side of the thalamus projects primarily to the ipsilateral hyperstriatum, and to a lesser extent, to the contralateral hyperstriatum. The projections from the left thalamus to the right hyperstriatum are more extensive than the projections from the right thalamus to the left hyperstriatum (36-39). This asymmetry is induced by lateralized exposure to light prior to hatching, because the orientation of the head of the embryo is such that the right eye is exposed (to light) and the left eye is occluded.

its right eye is exposed (35). Exposing the egg to as little as 2 h of light during this critical stage results in the functional differences between the two eyes (35) and in the more extensive hyperstriatal projections from the left thalamus than from the right thalamus (39). The lateralization of both function and anatomical asymmetry can be prevented by incubating the eggs in darkness (35,37) and can be reversed by occluding the right eye of the chick embryo while exposing the left eye to light (35,39). Finally, the extent of functional lateralization and anatomical asymmetry in the visual system of chicks is sex-dependent and modulated by gonadal hormones. Although it has been reported that female chicks also show an asymmetry in their projections from the thalamus to the hyperstriatum (33), the extent of the bias favouring projections from the left thalamus is much greater in male chicks (36). Lateralized visual performance is also more apparent in male chicks than in females (2). These differences may be attributable to levels of circulating gonadal hormones, because administration of estradiol prevents the asymmetry otherwise present in male chicks (38). Unexpectedly, treatment with testosterone has also been reported to abolish the asymmetry in thalamo-hyperstriatal projections in both males and females (43).

3. HYPOTHALAMUS

Lateralized fluctuations in dopamine, noradrenaline and serotonin levels in the hypothalamus have been reported in the lizard (19). These fluctuations were

shown to correspond to the alternation in ovulation between the ovaries, such that levels of all three monoamines were higher in the hypothalamus contralateral to the ovulating ovary (19). In contrast, a stable asymmetry in distribution of the gonadotropic hormone Luteinizing Hormone Releasing Hormone (LHRH) has been identified in the hypothalamus of female rats, such that the right hypothalamus contains significantly more LHRH than the left hypothalamus (12,13). Further, the levels of LHRH in the hypothalamus are influenced by asymmetrical feedback from the ovaries. Specifically, removal of one ovary produces a significant increase in the level of LHRH in the ipsilateral hypothalamus (13), indicating that LHRH levels in each side of the hypothalamus are under negative neural feedback from the ipsilateral ovary. There is also evidence for a similar neural feedback between the testes and ipsilateral hypothalamus mediating LHRH levels in the hypothalamus of male rats (3,31). In female rats, removal of both ovaries causes a decrease of LHRH content in the right hypothalamus without significantly affecting left hypothalamic LHRH levels (13), suggesting that LHRH in each side of the hypothalamus is under positive feedback from the ovaries. The finding that bilateral ovariectomy reverses the existing asymmetry in hypothalamic LHRH levels suggests that the asymmetrical distribution of LHRH is maintained by positive feedback from circulating gonadal hormones, and that the right hypothalamus is more sensitive to this hormonal feedback than the left hypothalamus (Fig. 4). Further evidence that the right hypothalamus is more sensitive than the left to the effects of circulating gonadal hormones is reviewed below.

It has recently been reported that there are differences in the levels of choline acetyltransferase (ChAT; the enzyme that synthesizes acetylcholine) between the

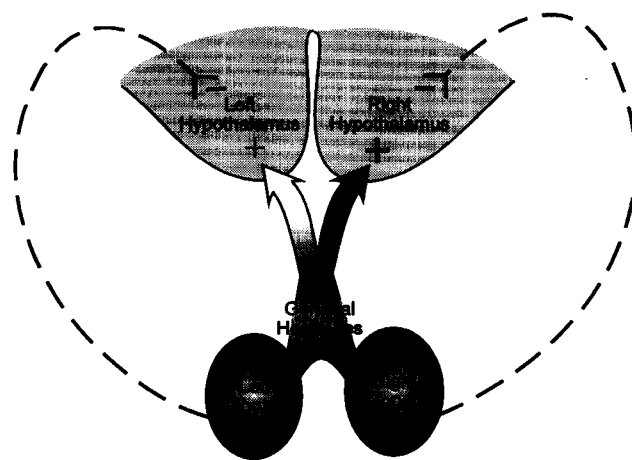


FIG. 4. Diagram depicting the mechanisms of feedback from the gonads to the hypothalamus. As outlined in the text, there is evidence that each gonad is unilaterally connected to the ipsilateral hypothalamus via an inhibitory neural pathway (broken line). Further, the effects of gonadal hormones on hypothalamic function are asymmetrical, such that the right hypothalamus appears to be more sensitive than the left hypothalamus to the effects of testosterone and estradiol.

left and right sides of the hypothalamus of female rats, and this difference varies across the oestrous cycle (41). Specifically, considerable fluctuations in ChAT levels were identified in the right hypothalamus, with levels of ChAT at estrous being almost twice that on the second day of diestrous. Conversely, levels of ChAT in the left hypothalamus did not vary significantly across the estrous cycle. Consequently, compared to those in the left hypothalamus, the levels of ChAT in the right hypothalamus were higher at estrous, equal on the first day of diestrous, and lower on the second day of diestrous. This asymmetry in cholinergic activity is consistent with the findings of an earlier study investigating the effects of atropine microinfusion into the left or right hypothalamus (8). In this latter study, ovulation was blocked by infusion of atropine into the right but not left hypothalamus at estrous. However, atropine was equally effective in blocking ovulation when infused into either side of hypothalamus on the first day of diestrous, and by the second day of estrous, atropine was much more effective when infused into the left than the right hypothalamus.

There is evidence from studies in rats that hypothalamic control of sexual behaviour is asymmetrical. While the effects of unilateral knife cuts to the hypothalamus indicate that there is little or no consistent difference in the contributions made by the left and right sides in the control of sexual behaviour (49), there is reliable evidence that gonadal hormones have asymmetrical effects on the hypothalamic control of sexual behaviour. Specifically, in female rats, estradiol has been shown to be more effective at eliciting lordosis (the sexually-receptive position) when infused into the right hypothalamus than when infused into the left hypothalamus (41). Conversely, implantation of estradiol pellets into the left hypothalamus, but not into the right hypothalamus, of 2-day-old female rat pups reduces lordosis induced by systemic administration of oestradiol and progesterone in the adult rats (32,49). Thus, it would seem that the right hypothalamus of adult females is more sensitive to the lordosis-inducing effects of estradiol, and that the sensitivity of the left hypothalamus to estradiol can be more easily reduced by neonatal treatment with that hormone. There is also evidence that the right hypothalamus plays a greater role than the left in the control of male sexual behaviour (mounting). While unilateral knife cuts to the right medial preoptic area do not affect mounting, knife cuts to the left medial preoptic area actually increase mounting in male rats (49). Moreover, neonatal application of estradiol or testosterone propionate to the right, but not left, hypothalamus potentiates mounting induced in female rats by systemic injection of testosterone (32,45). Unfortunately, there is no report comparing the effects of microinfusion of testosterone into the left and right hypothalamus on mounting in females. However, it is reasonable to postulate that the right hypothalamus is more sensitive to the pro-copulatory effects of testosterone than the left hypothalamus. In any case, it is clear that the sensitivity of the right hypothalamus to testosterone is influenced by neonatal exposure to male and female gonadal hormones.

Finally, it has recently been reported that there is a left-right asymmetry in the electrical activity of the

suprachiasmatic nucleus of the hypothalamus (50) which is known to play a major role as a circadian pacemaker. Extracellular single unit recordings made from *in vitro* slices of rat hypothalamus revealed that cells in the left and right suprachiasmatic nuclei differ in their pattern of activity across a 24-h period, and that when animals are kept in constant darkness prior to recording, cells in the left nucleus show a greater drift in their free-running activity than do cells in the right nucleus (50).

4. CONCLUDING REMARKS

The findings reviewed here permit several points to be made about the mechanisms and nature of brain asymmetry. First, brain asymmetries are not necessarily genetically determined, but can result from lateralized sensory stimulation during development and/or from differential sensitivity of each side of the brain to hormonal influences during development. Further, the numerous demonstrations of asymmetry in the diencephalon of mammalian and non-mammalian vertebrates indicate that asymmetry is not a special feature of the human cerebral cortex but is a relatively common phenomenon in the vertebrate brain in general (40). Moreover, evidence that many diencephalic asymmetries are sexually dimorphic and are mediated by gonadal hormones is consistent with suggestions that asymmetries in the human brain may also differ between males and females and be subject to hormonal influences (11,29,30).

Given the evidence that asymmetry is a relatively common phenomenon in the vertebrate brain, then a general mechanism responsible for asymmetry may be sought. One possibility, proposed by Corballis and Morgan (7), is that asymmetry results from differences in the rate of ontogenetic development between the right and left sides of the brain. Therefore, exposure to gonadal hormones during critical periods in development may differentially affect the growth of each side of the brain (32). This suggestion is supported by the fact that brain asymmetries are frequently sexually dimorphic.

Finally, the evidence presented here suggests that structural asymmetry in the brain may be linked to evolution of highly specialized systems. For example, the habenular asymmetry in the lizard and frog appears to be linked to the entrainment of biological and behavioural rhythms to light cycles by extra-retinal photoreceptive organs. Equally, the sex-linked asymmetry in thalamo-hyperstriatal projections in chick is associated with a highly developed visual system in this species. The observation that brain asymmetry may be linked to the development of specialized systems is consistent with the evidence for a structural asymmetry in areas of the human cerebral cortex that are involved in language.

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