Asymmetry of the Neuroendocrine System
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There is information on the lateralization of hypothalamic, limbic, and other brain structures involved in the control of the endocrine glands. Sided differences between paired glands, including their peripheral innervation, and relevant clinical observations on asymmetry are also known. Data suggest predominance of the right half of brain structures in controlling gonadal function.

The discovery of asymmetry and cerebral dominance dates back to 1861, when Paul Broca reported that the lesions in his aphasic patients lay on a delimited region of the left hemisphere. On the basis of this fundamental and subsequent observations, a classic theory of asymmetry was formulated comprising the existence of a single dominant (left) hemisphere and the presence of asymmetry exclusively in humans, in the cerebral cortex. The theory of asymmetry discouraged scientists for a long time from research aimed at extending asymmetry to brain regions other than the cerebral cortex and/or to other species. Since the late 1960s, it has become evident that each hemisphere is superior in certain functions and that asymmetry is present throughout the animal kingdom. Furthermore, a wealth of data indicates asymmetry in subcortical areas and in nonneuronal structures. Morphological, biochemical, and pharmacological asymmetries have been revealed underlying biological mechanisms of functional asymmetry. Recent findings even indicate that asymmetry also exists in nonliving structures down to the level of elementary particles.

The discovery of asymmetry in the neuroendocrine system was quite accidental. Studies leading to the first description of asymmetry in neural control of the endocrine glands were originally designed to demonstrate the existence of a direct neural pathway between the brain and the peripheral endocrine glands. To provide experimental observations supporting this view, a special experimental protocol was designed: brain lesion, right or left, was performed in animals subjected to removal of the right or the left endocrine gland, or changes in biochemical parameters were measured in the right and left halves of the hypothalamus following right- or left-sided extirpation of the ovary. Unexpectedly, the results of the experiment, in which the gonadotropic hormone-releasing hormone (GnRH) content of the hypothalamus halves, studied in hemiovariectomized rats, indicated that in intact control animals the GnRH content is significantly higher in the right half of the hypothalamus than in the left half (7). This observation was followed by other findings indicating the existence of different kinds of asymmetries at each level of the neuroendocrine system. In this review, we summarize these data obtained in animals and also include relevant clinical observations. Hypothalamic asymmetry is discussed first, followed by asymmetry of temporolimbic and cerebral cortical structures. The next section describes asymmetry at the level of peripheral innervation of paired endocrine glands. Finally, the data that indicated asymmetry at the level of paired endocrine glands are discussed.

Hypothalamic asymmetry

As mentioned above, the first observation concerning the asymmetry in the neuroendocrine system was the significant difference in the GnRH content between the right and left halves of the hypothalamus of intact female rats. Further studies indicated that in the male rat the right side of the hypothalamus also contains significantly more GnRH than the left (1). In male mice, the number of GnRH neurons has been reported to be more numerous on the right side of the brain (9). In humans, a higher concentration of thyrotropin-releasing hormone was found in the left hypothalamic ventromedial, dorsomedial, and paraventricular nuclei (3).

Besides the biochemical differences between the right and left sides of the hypothalamus, some data indicate functional asymmetry within the hypothalamus. In the male rat, unilateral deafferentation of the hypothalamus prevents the hemicastration-induced follicle-stimulating hormone (FSH) rise only when right hypothalamus intervention is combined with right orchidectomy. In female rats, right- but not left-sided lesion of the anterior hypothalamus or the retrochiasmatic area interferes with the hemiovariectomy-induced compensatory ovarian hypertrophy and the rise in serum FSH concentration that follows hemiovariectomy. Lesion or atropine implantation on the right side of the anterior hypothalamus on the day of estrus severely affects ovulation. Development of female sexual behavior can be differentially disturbed by early implantation of estradiol in the right or the left half of the hypothalamus. Implantation of the steroid hormone in the right side of the hypothalamus leads to masculinization (e.g., preference for other females), whereas a similar intervention on the left side induces defeminization (e.g., loss of estrous cycle) (for details and references see Ref. 6).

These findings clearly indicate that gonadal and, in more generalized terms, reproductive functions are governed by the hypothalamus, which exhibits both biochemical and functional asymmetry. On the basis of the data available, it seems that the right side of the hypothalamus plays a dominant role in the control of reproductive functions.
Concerning the functional asymmetry of neural pathways to and from the hypothalamus involved in the control of the mitotic activity of the thyroid follicular cells, it has been reported that posterior deafferentation on the left side of the hypothalamus induces a decrease in the mitotic index of the follicular cells of both lobes of the gland. In hemithyroidectomized rats, a similar knife cut on the same side prevents the hemithyroidectomy-induced increase in the proliferative activity of the remaining lobe (10).

**Asymmetry in temporolimbic and cerebral cortical structures**

In adult males, left-sided deafferentation in the temporal lobe combined with left orchidectomy results in a decrease in steroidogenesis of the remaining testis with no change in serum luteinizing hormone (LH) concentration. Other combinations are ineffective in this respect. A similar effect was observed in prepubertal animals. However, in this case the right-sided brain surgery plus left hemicastration combination was effective. In contrast in hemiovariectomized adult females, right- but not left-sided deafferentation in the temporal lobe interfered with the development of compensatory ovarian hypertrophy, regardless of the side of hemicastration (5). These observations indicate the functional asymmetry of the amygdala in the control of gonadal functions. Furthermore, the data also suggest that the dominance is sex and age dependent.

There are also clinical data suggesting the asymmetry of the temporal lobe in the control of reproductive functions. Among women with partial seizures of temporal lobe origin, reproductive disorders are unusually common. Furthermore, polycystic ovarian syndrome is predominantly associated with left-sided epileptiform discharges, whereas hypothalamic amenorrhea is related predominantly to right-sided discharges (8). A possible relationship between handedness and female reproductive functions is suggested by the earlier appearance of both menarche and menopause in left-handed women (12).

Recent data indicate that there is a functional asymmetry in the medial prefrontal cortex concerning neuroendocrine and autonomic stress responses of the rat. Both pretest and acute restraint stress-induced plasma corticosterone levels are lower in animals with right or bilateral lesion of the medial prefrontal cortex but not with left-sided surgery. In addition, stress ulcer development is greatly reduced after right or bilateral cortical lesion (13). Furthermore, greater binding capacity of mineralocorticoid receptors has been demonstrated in the right than in the left hippocampus (11). Autopsy data indicate that in suicides the left, but not the right, adrenal gland is heavier than in control, sudden death cases (14).

**Asymmetry at the level of the peripheral innervation of paired endocrine glands**

Few data are available on the asymmetry of nerves to and from the paired endocrine glands. At this level of regulation, the asymmetry mainly concerns the functional laterality of the vagus nerve of the gonads. In adult male rats, right-sided vagotomy results in a significant rise in serum LH concentra-

**Asymmetry at the level of paired endocrine glands**

It is well known that the venous drainage of the left and right gonads and of the left and right adrenal glands is different. The right veins of these organs open into the inferior vena cava, whereas the left veins empty into the left renal vein. In humans, the right testis is heavier than the left, and the left one has a lower position in the scrotum. There are no sided differences between the weight and localization of the ovaries in most species. In birds, however, only the left ovary is functional, the right is rudimentary. Both in humans and rats the left adrenal gland weighs more than the right. The right lobe of the thyroid gland is usually larger and more vascularized than the left lobe.

There are reports indicating functional asymmetry of the testes. The right testis exhibits a greater response either to LH treatment or to hemicastration than the left gonad (4). Besides its lower functional capacity, the left testis is more vulnerable than the right one, and in humans, there is a greater frequency of cryptorchidism and varicocele on the left side. Clinical data indicate that in humans adrenal carcinomas causing Cushing's syndrome occur more frequently on the right side, whereas adrenal tumors inducing primary aldosteronism are more frequent on the left side. Thyroid diseases, such as solitary nodules or disorders causing diffuse increase in size of the gland, affect mostly the right lobe of the thyroid gland (for references, see Ref. 6).

**Conclusion**

The data reviewed here clearly indicate that asymmetry does exist in the neuroendocrine system and that it is present at each organizational level. Most of the findings available are related to the gonads and their regulatory structures. It seems that in the control of endocrine reproductive functions right-sided neuronal structures play a predominant role (this trend is most evident in the hypothalamus). Experimental data suggest that this dominance is sex and age related. During ontogeny, asymmetry shifts from one side to the other, and the characteristic pattern gets fixed only after puberty. On the basis of recent reports, it appears to be well established that the right
hemisphere also plays a dominant role in the control of the hypothalamic-pituitary-adrenal axis. These results are consistent with the view that the right hemisphere has a special role in the control of autonomic functions essential for survival. Concerning the control of thyroid functions, the few data available suggest a left-sided dominance. Systematic experimental work is required to study asymmetry of neural structures controlling the secretion of anterior pituitary hormones with no peripheral endocrine glands (prolactin, growth hormone).

Several important questions arise, such as how the asymmetry of the neuroendocrine system is operating, what is the mechanism of the lateralized effects, and what is the biological significance of asymmetry? None of these questions can be answered satisfactorily at this time. In spite of this, we think these issues should be very briefly discussed.

Depending on whether the asymmetry resides in the central nervous system or in the peripheral endocrine glands (or in both), in essence two basic mechanisms and their combination can be assumed (Fig. 1). The influence generated in the asymmetrical cerebral structures can affect the peripheral endocrine glands through the pituitary and via direct neural pathways between the central nervous system and the target endocrine gland. The effect of the peripheral endocrine glands can be realized by hormonal feedback and/or by pure neural pathways. On the basis of available data, it may be assumed that the full control of the target endocrine glands requires asymmetry of certain regulatory nervous structures, but the pattern of cerebral asymmetry can be modified by the peripheral endocrine glands. If one takes into account that asymmetry is a trait of nature, it may be assumed that the neuroendocrine asymmetry is just one example of this trait.

The biological mechanisms leading to cerebral lateralization and left-right asymmetry in handedness include developmental, hormonal, and genetic aspects (2). Nothing is known, however, about the developmental mechanisms in neuroendocrine asymmetries.

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FIGURE 1. A very simplified scheme of the neural and humoral connections between the different levels of the two sides of the neuroendocrine system. L, left side; R, right side; 1, neurons producing hypophysiotropic neurohormones; 2, hypophysiotropic neurohormones; 3, pituitary tropic hormones; 4, target endocrine gland hormones. Broken lines indicate humoral connections.
References


