NEW DATA ON THE NEURAL CONTROL OF GONADAL FUNCTIONS. SUPRASPINAL INNERVATION OF THE GONADS

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ABSTRACT

Gonadal functions are governed by the hypothalamo-hypophyseal system. Recent studies have demonstrated the existence of a multisynaptic neural pathway between the brain and the gonads. This review summarizes the morphological and physiological data that suggest the role of the brain-gonadal circuitry in the control of gonadal functions and discusses relevant clinical observations.

Key Words: supraspinal innervation, gonads, viral tracing technique, neural control

INTRODUCTION

The brain controls gonadal functions primarily through the hypothalamic regulation of pituitary gonadotropic hormone secretion. In the past decade convincing experimental data accumulated suggesting the involvement of fine-tuning control mechanisms regulating gonadal functions. These include the local action of biologically active substances synthesized in the gonads and a direct, pituitary-independent neural control via the recently described multisynaptic pathway between the brain and the gonads.

The review summarizes neuromorphological data on the innervation of the gonads including also its supraspinal components and the functional significance of central nervous system structures connected transneuronally with the ovary and the testis.

INNERVATION OF THE GONADS

It is well known that in both sexes the gonads and other organs of the reproductive system are innervated by sympathetic and parasympathetic efferent (motor) fibers belonging to the autonomic nervous system. In addition, these nerves possess afferent (visceral sensory) fibers that carry information towards the central nervous system (CNS). The preganglionic sympathetic neurons are located in the intermediolateral cell column of the spinal cord at lower thoracic and upper lumbar spinal cord segments. The parasympathetic preganglionic fibers originate from the dorsal motor nucleus of the vagus and from the sacral parasympathetic nucleus (in the rat: L₄-S₁ spinal cord segments). Postganglionic fibers innervating the reproductive organs originate from paravertebral, prevertebral or pelvic ganglia. The nerve fibers to and from the organs, besides the classical neurotransmitters of the autonomic nervous system noradrenalin, adrenalin and acetylcholine, contain several other neurotransmitters and neuropeptides including...
serotonin, vasoactive intestinal polypeptide, substance P, calcitonin gene-related peptide, galanin, etc. 1-3

Nerves innervating the ovary are the superior ovarian nerve that runs along the ovarian suspensory ligament and the ovarian plexus accompanying the ovarian artery.

The testis is innervated by the superior spermatic nerve and the inferior spermatic nerve. The superior spermatic nerve, the major contributor of testicular innervation originates from the coeliac and aortic plexuses and runs alongside the testicular vessels. The parasympathetic component of the nerve belongs to the vagus nerve. The inferior spermatic nerve, which accompanies the ductus deferens, then travels within the epididymis, reaches the testis at its lower pole.1

It is generally accepted that autonomic nerves of the gonads play a physiological role in vasomotor control of blood vessels, secretion of exocrine glands and in the contraction of smooth muscles composing the muscular coat of tubular organs' wall. Increasing number of evidences indicate that in the gonads neurotransmitters released from nerve terminals can act on receptors located on specific hormone secreting cells.

It seemed to be very likely that neural inputs to the reproductive organs transmitted via the autonomic nerves are integrated signals that include neuronal impulses from different parts of the CNS. However, cerebral structures, which contribute to the modulation of neuronal input to the gonads were unknown till recently. The tracing of a long, multisynaptic pathway became possible only in recent years when the transneuronal viral tracing technique was introduced.4-6 Following inoculation of neurotropic virus, in most cases Bartha’s strain7 of Aujeszky’s disease8 (common name: pseudorabies) into an end organ or into the CNS is taken up by nerve terminals located in the infected area. Then the virus is transported along the axon to the perikaryon where replication of the virus takes place. The virus passes transneuronally through synapses and infects neurons that are presynaptic to infected cells. With advancing time, virus passes through chains of synaptically linked neurons. Therefore, the organization of circuits can be defined by immunocytochemical localization of the virus. Since the virus travels primarily retrogradely, infected neurons in the CNS represent structures which give rise efferent fibers involved in the innervation of the inoculated organ or brain area.

After injection of the pseudorabies virus into the ovary the first neurons in the CNS exhibiting viral antigen were found in the intermediolateral cell column of the spinal cord (origin of preganglionic sympathetic fibers) and in medulla oblongata (nucleus of the solitary tract, dorsal motor nucleus of the vagus).9

The density of infected neurons in the vagal nuclei was remarkably rich. (Fig. 1B)

In animals subjected to unilateral vagotomy prior to virus inoculation ipsilateral to vagotomy, the labeling in the spinal cord did not differ from that observed in rats with intact vagi. After unilateral transection of the vagus nerve no infected cells could be detected in the vagal nuclei and in the area postrema. In addition, in several brain stem nuclei, such as the A1, A5 and the caudal raphe nuclei and in the hypothalamic paraventricular nucleus, the proportion of infected cells was less than in controls.10 On the basis of these observations it can be assumed that the structures exhibiting infected neurons belong to the cranial parasympathetic system. The finding that the number of labeled cells is reduced in certain cerebral structures suggests that these nuclei on the one hand are interconnected with preganglionic sympathetic neurons of the spinal cord, and on the other hand that these cell groups receive ovarian-related fibers also via vagal nuclei.

In the brain stem, virus-infected neurons could be detected, among others, in the A1, A5, (Fig. 1A) A7 noradrenergic cell groups, in the caudal raphe nuclei (raphe obscurus, raphe pallidus, raphe magnus), in the locus coeruleus, Barrington’s nucleus and in the mesencephalic periaqueductal gray.

The main diencephalic structure in which we found labeled nerve cells was the parvocellular division of the hypothalamic paraventricular nucleus. (Fig. 1C) In addition, moderate number of labeled neurons could be detected in the lateral hypothalamus, medial preoptic area, dorsal hypothalamus, periventricular area, and arcuate nucleus.
In the telencephalon a moderate number of infected neurons was evident in the bed nucleus of the stria terminalis and in the central amygdala. Following virus injection into the testis the distribution of virus-labeled neurons in the brain was similar to that observed after virus inoculation into the ovary. However, the number of neurons in the brain infected from the testis was less than from the ovary. This phenomenon is probably due to the poor innervation of the testicular tissue. Consistent with this view are the data of Card et al., who observed that the infection of transneuronally labeled neurons largely depends on the density of nerve terminals in the area of virus injection. As mentioned, only minor differences in the labeling pattern between the male and female gonad could be noticed. The number of labeled neurons in the vagal nuclei was significantly less. This difference can be explained by the fact that the parasympathetic fibers innervating the testis arise both from the cranial and sacral parasympathetic system. A brain region that exhibited a considerable difference in the labeling pattern between the male and female gonad could be noticed. The number of labeled neurons in the vagal nuclei was significantly less. This difference can be explained by the fact that the parasympathetic fibers innervating the testis arise both from the cranial and sacral parasympathetic system. A brain region that exhibited a considerable difference is the insular cortex. At the late stage of infection a great number of virus-labeled neurons (mainly pyramidal cells) could be detected in a well-defined region of the insular cortex. (Fig. 3A) Such localization of transsynaptically infected perikarya from the ovary could not be detected.

**FUNCTIONAL CONSIDERATIONS**

**Experimental data**

The demonstration of transneuronal connections between the brain and the ovary has provided the neuromorphological basis on the existence of a neural pathway that had already been suggested by early physiological studies. The majority of data include studies in which unilateral lesion of the hypothalamus influenced ovarian functions by a pituitary-independent mechanism. Interestingly enough, some of these data revealed functional asymmetry of the hypothalamus (for review see refs. 13, 14). Right-sided lesion of the anterior hypothalamic has been reported to prevent the hemiovariectomy-induced FSH rise. Lesion of the anterior hypothalamic on the right side suppressed the development of compensatory ovarian hypertrophy that follows unilateral ovariectomy. Similarly, right-sided lesion of the preoptic area resulted in a decrease in the number of ova shed, and ovulation was completely blocked by implantation of atropine into the right anterior hypothalamus. In hypophysectomized immature rats lesion of the anterior hypothalamic area on the left side significantly enhanced the vasoactive intestinal polypeptide concentration of the ovary ipsilateral to brain intervention. In addition, early studies indicated that unilateral ovariectomy induces unilateral changes in the GnRH content of the mediobasal hypothalamus. The results of the latter experiment have revealed biochemical asymmetry of the hypothalamus. In intact rats the GnRH content was significantly higher in the right-hand half than in the left-hand one.

Among extrahypothalamic structures transneuronally connected with the ovary, the amygdala and the locus coeruleus have been reported to be involved in the direct neuronal control of the ovary. Right- but not left-sided deafferentation of the mediobasal portion of the temporal lobe (the isolated area included the centro-medial amygdala) suppressed the rate of compensatory ovarian hypertrophy without altering gonadotrop hormone secretion. In addition, lesion of the amygdala on the right side prevented ovulation or induced a significant decrease in the number of ova shed.

Taking into account that brain structures could be labeled from the testis and connections exist between the labeled cerebral structures and the autonomic preganglionic neurons of the spinal cord innervating the organ, it can be assumed that the areas detected might be involved in the neural control of testicular functions. Early physiological studies have provided indirect evidence on a pituitary-independent neural mechanism. Unilateral deafferentation of the hypothalamus prevented the hemicastration-induced FSH rise if the brain intervention and hemiorchidectomy were performed on the right side. Beside suggesting the role of a direct neural mechanism, these data also reveal functional asymmetry of the hypothalamus. Removal of one of the testes has been reported to induce unilateral changes in the RNA-synthesizing activity of the hypothalamic arcuate nucleus and in the gonadotrop hormone-releasing hormone (GnRH) content of the hypothalamus. Furthermore, intracerebroventricular administration of corticotropin-releasing factor (CRF), interleukin-1b or b-adrenergic receptor agonists have been reported to blunt human chorionic gonadotropin-induced testosterone response without changing LH secretion. These data suggest that testicular steroidogenesis is under the control of adrenergic pathways.

Following identification of structures transneuronally connected with the testis, areas which exhibited intensive and consistent virus labeling from the testis and not known to control testicular functions, such as the hypothalamic paraventricular nucleus, amygdala and the insular cortex were examined.

Electrolytic lesion of the paraventricular nucleus did not influence Leydig cell responsiveness to hCG.
but prevented the inhibitory effect of CRF or the b-adrenergic agonist on the response. The role of the amygdala as one of the extrahypothalamic nuclei modulating GnRH secretion is known for decades. Two recent studies indicate that the cell group is involved also in the pituitary-dependent neural control of testosterone secretion. Unilateral lesion of the amygdala with kainic acid resulted in a significant decrease in basal testosterone secretion in vitro of both testes and in serum testosterone secretion. LH secretion was suppressed following left- but not right-sided lesion. (Fig. 2)

These results indicating functional asymmetry of the amygdala concerning the mechanism by which the left (via the hypothalmo-hypophysial-testicular axis) and the right amygdala (via direct neural route) controls testosterone secretion. These data are consistent with the results of previous experiments in which deafferentation of an area in the temporal lobe containing the amygdala was performed in hemicastrated rats. Deafferentation on the left side in left orchidectomized rats resulted in a significant decrease in the steroidogenesis of the remaining (right) testis with no change in serum LH level. Any other combination of the two interventions was ineffective to alter the parameters studied.

Unilateral lesion of the insular cortical area where testicular-related neurons could be detected resulted in a significant decrease in basal testosterone secretion in vitro and in serum testosterone concentration when the intervention was on the right side. (Fig. 3B) Lesion on either the left or the right side induced a significant increase in serum LH level. Nevertheless, the hormone level was significantly higher after right- than after left-sided injury. The results indicate that also the insular cortex modulates the final neuroendocrine/neural input to the testis. In addition, data also suggest functional predominance of the right insular cortex over testicular functions.

Clinical observations

Relatively few clinical data are available on the involvement of neural structures innervating of gonads in the pathogenesis of reproductive endocrine dysfunctions. However, these observations are in accordance with the experimental data mentioned above. Reproductive endocrine dysfunctions are more common among men and women with temporal lobe epilepsy than in the general population or in subjects with general or focal motor seizure disorders. In women there is a strong predominance of right-sided seizures of temporal lobe origin with hypogonadotropic hypogonadism. In contrast, polycystic ovarian syndrome in female subjects with left-sided epileptiform discharges of temporal lobe occurred more frequently than in the case of right-sided partial epilepsy. Furthermore, women with left temporal foci associated with polycystic ovarian syndrome exhibited more than two times higher average LH pulse frequency than patients with hypogonadal hypogonadism and right-sided temporal focus. Recent studies indicate decreased serum estradiol and dihydroepiandrosterone sulfate concentration, greater variability of LH pulse frequency, prolactin pulse amplitude, and FSH level among women with temporal lobe epilepsy than among controls. These findings suggest that the amygdala, a frequent site of adult epilepsy due to its rich connection with the hypothalamus is involved in the promotion of the development of reproductive endocrine dysfunctions. Furthermore, seizure frequency or lifetime number of seizures has been reported to be associated with age at menopause. The timing of cessation of reproductive cycling in women with epilepsy is earlier than in the general population.

Besides the amygdala, the involvement of the...
sympathetic nervous system has also been suggested to be involved in the etiology of polycystic ovary syndrome. Increased density of catecholaminergic nerves in the ovary of patients with polycystic ovarian syndrome has been observed. In addition, both in adult and adolescent polycystic ovary patients peripheral catecholaminergic alterations suggesting a change in noradrenaline deamination and/or uptake have been reported. The potential contribution of the peripheral sympathetic system to the disease is further suggested by the effectiveness of ovarian wedge resection to restore ovulation.

It is well documented that reproductive endocrine disorders and reproductive dysfunctions are unusually frequent among men with epilepsy, particularly among individuals who have partial seizures of temporal lobe origin. In men with temporal lobe epilepsy associated with reproductive endocrine disorders the hormonal parameters of the hypothalamo-hypophyseal-testicular axis are not uniform. The majority of individuals exhibit testosterone and LH concentrations characteristic of hypogonadotropic hypogonadism. Other subjects have hyperprolactinaemia or hypergonadotropic hypogonadism. Furthermore, semen analysis has revealed high frequency of decreased sperm count, abnormalities in sperm morphology and motility in men with epilepsy.

The endocrine reproductive dysfunctions observed in women and men with temporal lobe epilepsy strongly suggest the role of the amygdala in the altered regulation of the neuroendocrine system but the contribution of psychosocial stress and the treatment with antiepileptic drugs should also be considered.

In conclusion, the data summarized above indicate that the control of gonadal functions is more complex than it was previously thought. The demonstration of neural connections between the brain and the gonads using the transsynaptic viral tracing technique has provided the neuromorphological evidence for the existence of the neural pathway. (Fig. 4)

The involvement of some components of the pathway, such as the hypothalamus, amygdala, insular cortex have been reported to be involved in the control of gonadal functions by a pituitary-independent, neural mechanism. Further experiments are needed to clarify whether structures exhibiting consistent and intensive labeling following virus injection into the ovary or the testis play a role or not in gonadal regulatory processes. It can be expected that further clinical observation will be available that, on the one hand, confirm the experimental data and on the other hand contribute to our better understanding of the etiology of some endocrine reproductive dysfunctions.

Figure 4. Simplified schematic drawing illustrating the neuroendocrine (A) and the direct neural (B) control of the gonads.
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