CENTRAL NERVOUS CONTROL OF GONADOTROPHIC AND THYROTROPHIC SECRETION

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The effects exerted by the central nervous system on endocrine activity may be compared with the influence the nervous system imposes on the body musculature. In general, the nerve supply of a muscle acts to maintain a tonic background of postural activity and also to mediate the excitation involved in reflex or voluntary movements. Similarly with many endocrine glands the nervous system maintains what may be regarded as a normal level of tonic background activity and is also instrumental in bringing about sudden changes in endocrine function according to sensory stimuli arising in the external environment. Thus the normal female rat or rabbit may show a set pattern of ovarian and thyroid function under constant environmental conditions, and this pattern may be acutely changed by the stimuli associated with, for example, sterile coitus or exposure to low environmental temperatures.

The overall effects of the nervous system on gonadotrophin and thyrotrophin secretion are most clearly revealed by comparing ovarian and thyroidal activity in hypophysectomized, pituitary “denervated” and normal animals. As is well known the hypophysectomized animal shows no evidence of endocrine activity on the part of the gonads but does retain some slight thyroidal function in that the uptake and release of $^{131}$I by the thyroid are not abolished, though markedly reduced. This residual activity may represent autonomous function by thyroid cells or be dependent upon thyrotrophic substance derived perhaps from the pars tuberalis (left in situ after the classical hypophysectomy). After “denervating” the pituitary gland (by cutting the pituitary stalk and placing a plate between the gland and the hypothalamus, or by transplanting the pituitary to a distant site in the body) the ovaries show atrophy of the follicles and interstitial tissue (see Harris 1955; Greer 1957; Ganong 1959)
although recent studies (Desclin 1950, 1956; Everett 1954, 1956) have shown that pituitary transplants in the rat still release prolactin or luteotrophic hormone (LTH) and therefore maintain luteal function. The reported maintenance of the testes in male rats by pituitary transplants (Courrier 1956; Fry & Long 1956; Goldberg & Knobil 1957) may possibly be explained by the continued release of LTH. Secretion of thyrotrophic hormone (TSH) continues, but at a reduced rate, if the pituitary gland is “denervated” (Scow & Greer 1955; von Euler & Holmgren 1956; Brown-Grant, Harris & Reichlin 1957). The effect of various procedures [exposure to cold, Uotila (1939), von Euler & Holmgren (1956); exposure to various “stresses”, von Euler & Holmgren (1956), Brown-Grant, Harris & Reichlin (1957)] in eliciting the usual changes in thyroid function is absent after pituitary stalk section or transplantation. In summary, separation of the pituitary gland from the influence of the central nervous system results in loss of secretion of FSH and probably LH, a maintained secretion of LTH, and a continued but reduced secretion of TSH.

In contrast to the above results, obtained when the pituitary gland is transplanted to a site remote from the sella turcica, are those observed when the gland is removed from the sella but replaced in contiguity with the hypothalamus (Greep 1936; Harris & Jacobsohn 1952; Nikitovitch-Winer & Everett 1958, 1959). In this case the secretion of gonadotrophic and thyrotrophic hormones appears to be normal. The results of such experiments also indicate that the type of activity shown by pituitary tissue depends on the nervous system rather than the gland itself, for pituitary tissue obtained from newborn animals or from male animals will maintain adult female reproductive functions if transplanted under the hypothalamus of an hypophysectomized female (Harris & Jacobsohn 1952; Martinez & Bittner 1956). Pituitary transplants under the hypothalamus which show apparently normal pituitary function have been found to be revascularized to a major extent by the primary plexus of the hypophysial portal vessels (Harris & Jacobsohn 1952; Nikitovitch-Winer & Everett 1958). These portal vessels normally convey blood from the median eminence of the tuber cinereum to the anterior pituitary gland, and it seems clear from the above studies and from experiments on pituitary stalk section (Harris 1950; Benoit & Assenmacher 1953; Donovan & Harris 1956 a; and others) that normal function of the gland is dependent on this specific blood supply. Many possibilities exist as to how the hypophysial portal vessels might exert such an influence over anterior pituitary activity but the most likely seems to be that nerve fibres from the hypothalamus liberate some humoral substance(s) into the primary plexus of vessels in the median eminence and that this substance is carried by the portal vessels to excite or inhibit the cells of the pars distalis. Experimental data has been adduced that such humoral substances regulating gonadotrophic secretion may be (i) cholinergic in type (Taubenhaus & Soskin 1941), (ii) adrenergic in type (Markee, Sawyer &
many rats gland. respectively. Harris Hollinshead thyroid the optic oestrogens that female.

(i) FSH release. This is markedly reduced, as shown by gonadal atrophy, after the placement of lesions in the median eminence in both female (Dey 1943, and others) and male animals (Bogdanove & Halmi 1953; Ganong, Fredrickson & Hume 1955; Daily & Ganong 1958). With lesions in the anterior hypothalamus an increased discharge of FSH has been observed in anoestrous female ferrets (Donovan & van der Werff ten Bosch 1959a) and in immature female rats (Donovan & van der Werff ten Bosch 1959 b; Gellert & Ganong – see Ganong 1959), resulting in an oestrous state in winter and precocious puberty, respectively. It is likely that anterior hypothalamic lesions destroy a region that normally inhibits FSH secretion by the anterior lobe of the pituitary gland. There is data (Flerkó 1954, 1957; Flerkó & Szentagothai 1957) that oestrogens exert their inhibitory effect on FSH secretion through this region of the hypothalamus.

(ii) LH release. Lesions in the anterior hypothalamus [just behind the optic chiasma, Dey (1943); below the paraventricular nuclei, Hillarp (1949); in the ventromedial hypothalamic nuclei, Greer (1953)] have been found to block ovulation in the rat and result in a state of constant oestrus.

(iii) Prolactin or LTH release. Few studies have been made on the effect of hypothalamic lesions on the discharge of prolactin. McCann, Mack & Gale (1959) found that lesions in the supraoptichypophysial tract of lactating rats produced a block of milk secretion.

(iv) TSH release. Lesions in the anterior hypothalamus, in the region of the supraoptichypophysial tract have been found by Greer (1951, 1952) and many subsequent workers (see review by Harris 1959) to result in reduced thyroid function. Thyroid atrophy, abolition of the goitrogenic response to propylthiouracil, reduction of compensatory hypertrophy after partial thyroidectomy, reduced thyroid activity and a diminished concentration of TSH in the blood have been described after such lesions.

Hypothalamic stimulation has been found to result in increased discharge of LH, as evidenced by subsequent ovulation in the isolated female rabbit, by
Harris (1937, 1948), Haterius & Derbyshire (1937) and Markee, Sawyer & Hollinshead (1946). Stimulation in the region of the median eminence evokes the ovulatory response but similar stimulation applied directly in the anterior pituitary gland does not. Stimulation of the region of the supraoptichypophysial tract was found by Harris & Woods (1958) to result in increased thyroid activity. This response was maintained by prolonged stimulation (48 h) in spite of a raised blood level of thyroid hormone, indicating that the central nervous system may take priority over the thyroid hormone feed-back in influencing TSH release. Few studies have been made of the effect of electrical stimulation on FSH or prolactin secretion. Donovan & van der Werff ten Bosch (1959 a) were unable to detect any increased discharge of FSH by stimulation of the hypothalamus in ferrets during the winter anoestrus.

Studies of lesions and stimulation indicate that the hypothalamus exerts an important influence over the anterior pituitary gland, at least in respect to its secretion of FSH, LH, TSH and ACTH. Few studies of this type have been made with regard to prolactin, but data from work on pituitary transplants may indicate this to be less under hypothalamic control than the other hormones. However even if a steady release of prolactin is an intrinsic property of anterior pituitary tissue it seems likely that the nervous system can exert a reflex modifying influence over this secretion in response to sensory stimuli, such as those associated with suckling or (in the rat) sterile coitus.

Other regions of the central nervous system. In all probability the hypothalamus forms a focal point in the nervous system where a variety of reflex nerve paths from other regions converge to exert an influence over anterior pituitary function through the final common pathway of the hypophysial portal vessels of the pituitary stalk. Investigation of the influence of other regions of the nervous system over pituitary function has only just begun, but evidence is accumulating that the limbic system plays an important role. Bilateral lesions in the amygdaloid nuclei are said to result in atrophy of the anterior pituitary, thyroid and adrenal glands (Koikegami et al. 1955), whereas electrical stimulation of these nuclei evokes ovulation (Koikegami, Yamada & Usui 1954; Shealy & Peele 1957; Bunn & Everett 1957) and a marked elevation of plasma adrenal steroids (Mason 1958). Attention has also been drawn to the possible relations between (a) the habenular region and thyroid function (Szentagothai 1958), (b) the frontal cortical and hippocampal areas and ACTH secretion (Porter 1954) and (c) the mesencephalic reticular structures and secretion of LH, ACTH and TSH (Critchlow 1958; Anderson et al. 1957).
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