PITUITARY FUNCTION AND PSYCHOSIS: CAUSE OR EFFECT?

The changes in pituitary gland function in mental illness are under intensive study. This is because the regulation of pituitary function by the brain involves monoamine neurotransmitters, and changes in hormonal secretion may thus reflect general fluctuations in monoamine activity in the brain. Characteristic patterns of change of diagnostic and therapeutic significance may also emerge. Thus, adrenocorticotrophic hormone secretion and adrenal corticosteroid activity are enhanced in depression, largely through the occurrence of additional secretory spikes of ACTH and the lack during the late evening or early morning of the normal fall in cortisol secretion. Dexamethasone is less able to inhibit ACTH secretion in depression, while a fall in plasma glucose may less readily induce growth hormone secretion (Ettigi and Brown, 1977; Gruen, 1978). Nevertheless, there is no assurance that a monoamine neurotransmitter system concerned with pituitary function is affected in the same way as one influencing psychic outlook.

Alternatively, pituitary hormones, or the peptide neurohumors governing their release, may modify mental function by a direct action on the brain, and the evidence for this is becoming persuasive. The direct actions of the releasing factors upon the brain have been reviewed elsewhere (Donovan, 1978), so that we need only note that the gonadotrophin-releasing hormone may also influence sexual behaviour, that the activities of thyrotrophic hormone-releasing factor in depression have merited extensive clinical trial and that the list of effects of growth hormone release-inhibiting factor (somatostatin) on brain function is growing. With regard to the pituitary hormones themselves, prolactin secretion has long been associated with nursing behaviour in laboratory animals, while quite recently impotence in men has been relieved by depression of prolactin secretion (Franks *et al*, 1978). Information of this kind, though fragmentary, takes on added interest in view of the high correlation between prolactin-releasing potency and the antischizophrenic activity of a series of neuroleptics (Langer *et al*, 1977).

There are also changes in learned behaviour and in the EEG in animals and man following treatment with adrenocorticotrophic hormone or α or β-melanocyte-stimulating hormone. The responses are not mediated by changes in adrenal function, for fragments of the ACTH molecule virtually devoid of trophic action on the adrenal gland are also effective. Likewise, the neurohypophysial hormone vasopressin has marked effects upon avoidance behaviour in rats, effects mimicked by variants of the molecule lacking anti-diuretic potency and antagonized by treatment with an antiserum to vasopressin (Donovan, 1978; Nemeroff and Prange, 1978).

In considering the physiological validity of such observations the question arises whether sufficient amounts of pituitary hormone or releasing factor normally reach the brain to modify neural activity. Here new information is of especial value. For a long time the hypophysial portal blood vessel system has been regarded as a one-way channel of communication between the hypothalamus and hypophysis, although some evidence to the contrary was available. Hungarian observations, for example, indicated that blood left the median eminence to re-enter the hypothalamus, and that surgical removal of the posterior lobe of the cat hypophysis without interference with the pars distalis led to severe necrosis of the anterior lobe (Szentágothai *et al*, 1962), perhaps through disturbance of the venous drainage through the pars nervosa. Others have been puzzled by the paucity of vessels draining the anterior lobe, and in a thoroughgoing study of the monkey pituitary gland Bergland and Page (1978) concluded that while the entire afferent supply to the anterior lobe was derived from the portal vessels, the capacity of the veins draining the adenohypophysis appeared small when compared to that of the long portal vessels supplying the organ. It seemed likely that the short portal vessels could carry blood from the adenohypophysis to the posterior lobe and pituitary stalk, and back to the hypothalamus. Flesh has been added to these anatomical bones by the finding that higher concentrations of prolactin and growth hormone were present in the intracranial carotid artery of sheep above the pituitary gland, than in the cervical common carotid artery (Bergland *et al*, 1977). Further, high concentrations of luteinizing hormone (LH), thyrotrophic hormone (TSH), adrenocorticotrophic hormone (ACTH), α-melanocyte stimulating hormone and vasopressin were present in the blood collected from single portal vessels of the hypophyses of rats, even though the tip of the collecting cannula pointed toward the hypothalamus and away from the gland (Oliver *et al*, 1977). The concentrations of LH, TSH, ACTH and prolactin fell after anterior lobectomy. Such findings help to account for the presence of a variety of pituitary hormones in the cerebrospinal fluid (Assies *et al*, 1978; Hyyppä *et al*, 1978), although passage through the choroid plexus is also possible (Walsh *et al*, 1978).

A final significant point concerns the endorphins, β-lipotrophic hormone (β-LPH) and the relief of pain. Some 24 years ago Luft and Olivecrona (1955)

https://doi.org/10.1017/S0007125000058888 Published online by Cambridge University Press

reported an unexpectedly great reduction in, or abolition of, pain in nineteen of twenty-four women totally hypophysectomized for breast cancer. Pain relief occurred promptly after operation and was not due to treatment with adrenal steroid, tumour subsidence or remission. Much more recently it has been shown that pain sensitivity in the rat is increased after adrenalectomy and reduced after hypophysectomy, and that the sensitivity is related to plasma ACTH concentration (Heybach and Vernikos-Danellis, 1978). Now, β-endorphin, βLPH and ACTH seem to be produced in the same pituitary cell, the release of β-LPH parallels that of ACTH, and, not surprisingly, the brain opiate receptors bind both ACTH and β-endorphin. It is thus curious to find that β-endorphin injected into the periaqueductal grey matter of rats produces analgesia, while ACTH causes hyperalgia or hyperaesthesia (Jacquet, 1978). The opiate antagonist naloxone blocks or reverses the analgesia, but not the ACTH action. High doses of naloxone were also beneficial in patients with stupor or catatonia, where the recurrence of speech and motor movements was accompanied by a fall in pain threshold (Schenk *et al*, 1978). Do such observations reflect a direct action of pituitary factors upon the brain? Here it may be noted that, alongside their other actions, the enkephalins and β-endorphin induce prolactin secretion, so that the correlation between the anti-schizophrenic action of neuroleptics and prolactin release may be of even greater consequence.

Although it would be wrong to argue that abnormalities in the secretion of pituitary hormones lie at the heart of many psychiatric disturbances, it is hard to avoid the conclusion that a fresh and thorough look at the direct actions of pituitary hormones upon the brain is well-merited.

References

Assies, J., Schellekens, A. P. M. & Touber, J. L. (1978) Protein hormones in cerebrospinal fluid: evidence for retrograde transport of prolactin from the pituitary to the brain in man. *Clinical Endocrinology*, **8**, 487–91.

Bergland, R. M., Davis, S. L. & Page, R. B. (1977) Pituitary secretes to brain. Experiments in sheep. *Lancet*, *ii*, 276–8.

—— & Page, R. B. (1978) Can the pituitary secrete directly to the brain? (Affirmative anatomical evidence). *Endocrinology*, **102**, 1325–38.

Donovan, B. T. (1978) The behavioural actions of the hypothalamic peptides: a review. *Psychological Medicine*, **8**, 305–16.

Ettigi, P. G. & Brown, G. M. (1977) Psychoneuroendocrinology of affective disorder: an overview. *American Journal of Psychiatry*, **134**, 493–501.

Franks, S., Jacobs, H. S., Martin, N. & Nabarro, J. D. N. (1978) Hyperprolactinaemia and impotence. *Clinical Endocrinology*, **8**, 277–87.

Gruen, P. H. (1978) Endocrine changes in psychiatric diseases. *Medical Clinics of North America*, **62**, 285–96.

Heybach, J. P. & Vernikos-Danellis, J. (1978) The effect of pituitary-adrenal function in the modulation of pain sensitivity in the rat. *Journal of Physiology*, **283**, 331–40.

Hyyppä, M. T., Liira, J. & Långvik, V.-A. (1978) Neuroendocrine aspects of neurology. *Annals of Clinical Research*, **10**, 133–8.

Jacóuet, Y. F. (1978) Opiate effects after adrenocorticotropin or β-endorphin injection into the periaqueductal gray matter of rats. *Science*, **201**, 1032–4.

Langer, G., Sachar, E. J., Halpern, F. S., Gruen, P. H. & Solomon, M. (1977) The prolactin response to neuroleptic drugs. A test of dopaminergic blockade: neuroendocrine studies in normal men. *Journal of Clinical Endocrinology*, **45**, 996–1002.

Luft, R. & Olivecrona, H. (1955) Hypophysectomy in man. Experiences in metastatic cancer of the breast. *Cancer*, **8**, 261–70.

Nemeroff, C. B. & Prange, A. J. (1978) Peptides and psychoneuroendocrinology. *Archives of General Psychiatry*, **35**, 999–1010.

Oliver, C., Mical, R. S. & Porter, J. C. (1977) Hypothalamic-pituitary vasculature: evidence for retrograde blood flow in the pituitary stalk. *Endocrinology*, **101**, 598–604.

Schenk, G. K., Enders, P., Engelmeier, M.-P., Ewert, T., Herdemerten, S., Köhler, K.-H., Lodemann, E., Matz, D. & Pach, J. (1978) Application of the morphine antagonist naloxone in psychic disorders. *Arzneimittel Forschung/Drug Research*, **28** (II), 1274–7.

Szentágothai, J., Flerkó, B., Mess, B. & Halász, B. (1962) *Hypothalamic control of the anterior pituitary*. Akademiai Kiado, Budapest.

Walsh, R. J., Posner, B. I., Kopriwa, B. M. & Brawer, J. R. (1978) Prolactin binding sites in the rat brain. *Science*, **201**, 1041–3.

B. T. Donovan

https://doi.org/10.1017/S0007125000058888 Published online by Cambridge University Press