Commentary

The hunt for the CIA: factors which demonstrate corticotrophin-inhibitory activity

A. Grossman and S. Tsagarakis

In the halcyon days when life was simple, many thought that pituitary hormones were under the control of single hypothalamic factors which regulated their synthesis and release. Matters became a little more complex when the search for growth hormone (GH)-releasing hormone was punctuated by the discoveries of somatostatin, which inhibited both GH and thyrotrophin (TSH), by the co-release of TSH and prolactin by thyrotrophin-releasing hormone, and then by the substantiation of other prolactin-releasing factors such as vasoactive intestinal peptide. It has since become increasingly clear that pituitary peptides are regulated by a whole series of hypothalamic factors, both stimulatory and inhibitory, and are also subject to intrapituitary paracrine modulation.

There has, however, been slow acceptance of the concept that the release of adrenocorticotrophin (ACTH) too may be finely tuned by an inhibitory factor. There is clearly a predominant role for a stimulatory factor to ACTH release, the earliest candidate for which was vasopressin. With the subsequent identification of corticotrophin-releasing factor-41 (CRF-41), and the demonstration of physiological synergism between vasopressin and CRF-41, it appeared that the major factors controlling ACTH release had been isolated, although other peptides such as angiotensin II, peptide-histidine-isoleucine and gastrin-releasing peptide may play a lesser role, and the function of catecholamines remains contentious (Al-Damluji, 1988). However, these developments have overshadowed persistent reports in the literature that a factor or factors are able to inhibit ACTH release at a pituitary site. Egdahl (1960) originally demonstrated in the dog that if the pituitary was disconnected from the hypothalamus, there remained a high basal level of corticosteroids, and that this was not due to any brain-stem stimulatory factor (Egdahl, 1962). In the rat, total hypothalamic deafferentation leads to a maintained content and output of pituitary ACTH, although this could be due to circulating stimulatory factors, and there is some residual uncertainty regarding the completeness of the lesions (Halasz, Vernikos-Danellis & Gorski, 1967). Furthermore, agents such as substance P were noted to inhibit the pituitary release of ACTH directly (Jones, Gillham, Holmes et al. 1978), and there is a dissociation between the effects of noradrenaline on bioactive and immunoreactive CRF release in vitro (Jones, Gillham, Campbell et al. 1987; Tsagarakis, Holly, Rees et al. 1988). More recently, it has been found that, in the sheep, hypothalamo-pituitary disconnection leads to the expected failure of ACTH to respond to stress stimuli, but at the same time there is a significant increase in the basal level of ACTH and cortisol: since ACTH is derived entirely from the anterior lobe, this suggests that disconnection leads to a release from tonic inhibition (Engler, Pham, Fullerton et al. 1988). If corticotrophin-inhibitory activity (CIA) is indeed present, there are two principal approaches to its identification: a classical approach of hypothalamic extraction and purification, or a more empirical investigation of probable candidates, assuming that the factor is related to one of the known neuroactive peptides. Both approaches have been used, and appear to have been fruitful.

In their study of hypothalamic-releasing factors, Gillies, Puri, Linton & Lowry (1984) showed by gel chromatography two principal peaks of ACTH-releasing activity, which corresponded to CRF-41 and vasopressin, as well as at least one further peak required for full activity. However, they also noted the presence of ACTH-inhibitory activity in their Bio-Gel (but not Sephadex) chromatograms of a molecular weight intermediate between CRF-41 and vasopressin. Redei & Evans (1987) have further identified this factor as a peptide of probable molecular weight 0.6–2.3 kDa, but have not so far published a sequence analysis.

The other approach, that of systematically investigating putative agents for CIA, has also been actively
explored. Somatostatin is widely inhibitory to a variety of hormones and, in the rat, somatostatin-14 was found to inhibit ACTH release at high concentrations directly (Nicholson, Adrian, Gilham et al. 1984). However, no effect on cultured pituitary cells was shown by Brown, Rivier & Vale (1984), who reported that somatostatin-28 (but not somatostatin-14) inhibited the pituitary-adrenal axis at a suprapi- putitary site. In man, infusion of somatostatin-14 has been reported to blunt the rise in ACTH and cortisol induced by hypoglycaemia (Petraglia, Facchinetti, D’Ambrogio et al. 1986b), but in a recent study we were unable to modify the rise in ACTH and cortisol induced by CRF-41 by a high-dose infusion of somatostatin (Stafford, Kopelman, Davidson et al. 1989). This suggests that in man, as in the rat, any modulation of the pituitary-adrenal axis by somatostatin is likely to be suprapi- putitary.

Oxytocin is another peptide of interest: in man it has variously been described to inhibit (Petraglia et al. 1986b; Legros, Chiodera, Geenen & Von Frenckell, 1987) or have no effect on (Lewis & Sherman, 1985; Nussey, Page, Ang et al. 1988) pituitary-adrenal responses to hypoglycaemia. According to one recent report, oxytocin had no effect on the pituitary-adrenal response to CRF-41 but attenuated the response to the combination of CRF-41 and vasopressin, suggesting that it acts as an antagonist at vasopressin receptors (Suh, Liu, Rasmussen et al. 1986). However, another study failed to replicate these findings, noting inhibition to CRF-41 alone but not the CRF-41/vasopressin combination (Page, Ang, White & Jenkins, 1989). Whatever the case in man, the situation is quite different in the rat, in which a mild stimulatory effect of oxytocin on pituitary ACTH release is seen (Antoni, Holmes & Jones, 1983), while immunoneutralization leads to a fall in ACTH (Gibbs, 1985). The significance of the human studies therefore remains uncertain. Substance P was found to inhibit the release of ACTH from pituitary cells in vitro (Nicholson et al. 1984), and is thus possible that this peptide or one of its tachykinin congeners is important in ACTH inhibitory regulation, but the effect is weak and has not been confirmed in a more recent study employing freshly dispersed pituitary cells (Chowdrey, Jessop & Lightman, 1989). GABA is another neurotransmitter that appears to be involved in the neuroregulation of ACTH; while increasing GABA bioavailability has no effect on the pituitary-adrenal axis under basal conditions (Abraham, Dornhorst, Wynn et al. 1985), such pharmacological manipulation appears to inhibit the response of the axis to hypoglycaemia (Petraglia, Bakalakis, Facchinetti et al. 1986a). However, in spite of the presence of GABA receptors within the pituitary, GABA does not appear to inhibit pituitary ACTH release directly (Hashimoto, Yunoki, Takahara & Ofuji, 1979; Anderson & Mitchell, 1986), and most evidence suggests that GABA acts within the hypothalamus to inhibit the release of CRF bioactivity (Jones, Hillhouse & Burden, 1976) and immunoreactive CRF-41 (S. Tsagarakis, G. M. Besser & A. Grossman, unpublished observations).

Another group of neuropeptides which has attracted particular interest is the endogenous opioid peptides: these are profoundly inhibitory to the pituitary-adrenal axis in man, and cause long-term pituitary-adrenal suppression in the rat. However, few studies have been able to substantiate an early report that opioids could directly inhibit pituitary ACTH release in the rat, and it is generally thought that their principal site of action is in the hypothalamus. What is of considerable interest is the recent finding that opioids inhibit the release of CRF-41 into rat hypophysial portal blood (Plotsky, 1986), while morphine suppresses the secretion of CRF-41 from rat hypothalamic explants in vitro (Tsagarakis, Navara, Rees et al. 1989). As similar opiates stimulate CRF bioactivity in vitro (Buckingham, 1982), it is possible that the resultant biological effect is due to inhibition of both CRF-41 and a corticotrophin-inhibitory factor, the latter influence being predominant in short-term studies (Cover & Buckingham, 1989; Tsagarakis et al. 1989). In man, in whom opiates only inhibit ACTH, this disinhibitory control is not seen, and modulation most probably occurs via changes in CRF-41 and vasopressin alone.

Most recently, another candidate peptide has received increasing scrutiny. Atrial natriuretic peptide (ANP) has profound effects on salt balance and vascular tone, and also inhibits aldosterone and renin release (Anderson & Bloom, 1986). While one study reported that ANP(4–28) inhibited pituitary ACTH release (Shibasaki, Naruse, Yamauchi et al. 1986b), this was not confirmed in several later investigations (Heisler, Simard, Assayag et al. 1986; Abou-Sa‘ma, Catt & Aguilara, 1987; Hashimoto, Hattori, Suemaru et al. 1987). However, Antoni & Dayanithi (1989) have recently shown that activation of cyclic GMP (cGMP) suppresses secretagogue-induced ACTH release from corticotrophs, and atropinepsins may increase cGMP. Furthermore, two studies have now demonstrated significant inhibition of stimulated ACTH release from pituitary cells by ANP(1–28) (Dayanithi & Antoni, 1990; King & Baertschi, 1989). Only Dayanithi & Antoni (1990) also found an effect of ANP(5–28), which may relate to their use of freshly dispersed as opposed to cultured cells. ANP(4–28) and ANP(5–28) are the predominant molecular forms of ANP found in the hypothalamus and median eminence (Jacobowitz, Skofitsch, Keiser et al. 1985; Shiono, Nakao, Morii et al. 1986), moderate numbers...
of ANP receptors are found in the anterior pituitary (Quirion, Dalpe, De Lean et al. 1984) and ANP mRNA is present in the hypothalamus (Standaert, Needleman, Day et al. 1988); furthermore, ANP release may be stimulated by potassium depolarization from the rat hypothalamus in vitro (Shibasaki, Naruse, Naruse et al. 1986a). Thus, the stage is set for further exploration of its role as a physiologically important corticotrophin-inhibitory factor, particularly in terms of changes in ACTH in response to blood volume homeostasis.

Finally, there is a recent suggestion that the mammalian homologue of melanin-concentrating hormone contains a weak ACTH-inhibitory factor in its precursor peptide (Presse, Nahon, Sawchenko & Vale, 1989). However, it is still too early to judge whether this is a physiological as opposed to a pharmacological function.

Thus both investigatory stratagems have postulated peptides with CIA, the first a novel 10-20 residue peptide, the second a series of possibilities, including ANP or its central nervous system derivative and other completely original structures. Certainly, the linking of cGMP to inhibition of ACTH release is strong presumptive evidence in favour of an endogenous inhibitory factor. Clearly it is also possible that the peptide described by Redei & Evans (1987) is identical to one of the putative peptides with CIA, and it would be extremely interesting to know whether immunoneutralization with antisera to oxytocin or ANP is able to abolish the biological activity of this peptide. Further studies are awaited with interest, particularly with regard to the effects of ANP in man.

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REFERENCES


Department of Endocrinology, St Bartholomew’s Hospital, London EC1A 7BE.