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Invited Review

Immunocytochemical correlates of an extrapituitary adrenocortical regulation in man

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Summary. Investigations reviewed in this article provide cytochemical and functional support for a significant involvement of extrapituitary factors in human adrenocortical functions. Among these factors neural messengers may play a crucial role in the adrenocortical regulation, arising from specifically coded postganglionic neurons with both, extrinsic and intrinsic locations, as well as from chemically characteristic afferent neurons. The close association of varicose transmitter segments with steroid hormone synthesizing cells and their occurrence at arteries and sinusoid capillaries are indicative for both direct and indirect regulatory mechanisms on cortical functions. The immunohistochemical presence of neuropeptides and cytokines in endocrine and/or immune cells of the human adrenal medulla and cortex as well as specific binding sites on steroidogenic cells indicate the modulatory implication of additional short-paracrine-and ultrashort-autocrine-feedback loops on cortical cell proliferation and steroid metabolism. The summarized data suggest that basal endocrine influence of the hypothalamo-pituitary axis on adrenocortical growth and functions in man is controlled by the nervous system that also regulates local fine-tuning of human cortical activity.

Key words: Adrenal cortex, Immunohistochemistry, Modulators, Nerve fibres, Neuropeptides, Transmitters, Ultrastructure

Introduction

For a long time the hormonal hypothalamo-pituitary axis has been thought to be the only important factor controlling the adrenal cortex (Axelrod and Reisine, 1984; Chrousos et al., 1985). There is now a considerable body of evidence suggesting that other factors have a significant role not only in modulating hypothalamo-pituitary signals but also in actively regulating cortical growth and functions. The autonomic nervous system provides several prominent factors. Although a series of anatomical studies, stretching back a century, described an innervation of the human adrenal cortex (Fusari, 1890; Alpert, 1931; Stöhr, 1935; MacFarland and Davenport, 1941; Bachmann, 1954; Mikhail and Amin, 1969; Garcia-Alvarez, 1970), the functional implication of cortical nerves has been neglected for many years. It is now generally accepted that autonomic nerves are not only involved in the regulation of steroidogenesis and release but also in cortical proliferation (Engeland and Dallman, 1975; Fehm et al., 1984; Edwards and Jones, 1987; Holzwarth et al., 1987). From the association of nervous structures with blood vessels it can be inferred that another important function of neural activity in the adrenal cortex is the regulation of blood flow and concomittant hormone supply to the deeper cortical layers (Engeland and Gann, 1989).

Nerve fibres exert their actions by the release of an array of messengers (transmitters and modulators) in function- and target-specific combinations. Discrepancies in in vitro and in vivo effects of a selective messenger can be explained by the fact that the mere addition of actions exerted by single components does not sum up to the highly integrated function of the adrenal cortex (Hinson, 1990). Multiple intraadrenal factors, derived not only from nerves, but also from cortical and medullary endocrine cells as well as from non-endocrine cells and from vascularization, account for these discrepancies. The present review summarizes available structural and histochemical data on factors possibly involved in the extrapituitary regulation of the human adrenal cortex. As our knowledge, particularly on human tissues, is fragmentary, findings from experimental animals will be cited where relevant. Yet, considerable interspecies variations, applying particularly to the bewildering variety of bioactive peptides in the adrenal gland (Unsicker and Heym, 1996) should be borne in mind when trying to interpret such descriptions.

Adrenocortical innervation

The mammalian adrenal cortex shares with the

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medulla an innervation by nerve fibres some of which run in the splanchnic nerves, while others travel to the gland along with blood vessels (for review see Charlton, 1990). In the human adrenal cortex a complex network of varicose nerve fibres is distributed throughout all layers (Unsicker and Heym, 1996). Unmyelinated fibres arise from intraseptal nerve bundles and from a subcapsular nerve plexus to form a delicate meshwork around cell loops and columns (Fusari, 1890; Alpert, 1931; McNicol et al., 1994). Endocrine cells of the zonae glomerulosa, fasciculata and reticularis receive a direct innervation. Nerve terminals also abut upon subcapsular arterioles and cortical sinusoid capillaries (Heym et al., 1995b). Ultrastructurally, varicose segments of nerve fibres are in close apposition to the steroidogenic cells without intervening tissue. The terminal boutons contain small clear, and large granulated vesicles (Dorovini-Zis and Zis, 1991; Heym et al., 1995b). As discrete synaptic complexes were not detected between nerve terminals and neither endocrine nor endothelial cells (Heym et al., 1995b), the innervation of the human adrenal cortex resembles the postganglionic autonomic innervation of other endocrine organs and other species (Fawcett et al., 1969). Morphological and functional evidence indicate that the messengers released from the terminal boutons diffuse into the narrow intercellular space and act on receptor sites of target cells (see Weiss, 1983).

Messengers in adrenocortical nerve fibres and their functional significance

Highly sensitive immunohistochemical techniques for light- and electronmicroscopy have provided some clues to the chemical nature of the human cortical innervation. The demonstration of specific synthesis enzymes, as a rule, is accepted for the proof of small molecule transmitters. However, visualization of choline acetyltransferase (ChAT), the synthesis enzyme of the small molecule transmitter acetylcholine, has not so far been accomplished in human peripheral tissues. Therefore, the present information is confined to the less specific occurrence of the acetylcholine-degrading enzyme, acetylcholine-esterase (AChE) (Silver, 1974; Charlton et al., 1991).

Varicose AChE-positive, presumably *acetylcholine*-containing, nerve fibres supply the human adrenal cortex (Charlton et al., 1991). Branching from AChE-positive nerve trunks that travel along cortical septs on their way to the adrenal medulla, fine varicose fibres terminate on the cortical parenchyma in all layers and abut upon endocrine cells and small blood vessels. Acetylcholine in cattle can act directly on muscarinic receptors of steroid cells to increase glucocorticoid secretion by a non-cyclic AMP pathway (Hadjian et al., 1982). Moreover, acetylcholine is able to cause vasodilation, thereby increasing ACTH-delivery to the gland (Charlton, 1990; Edwards and Jones, 1990). In a third mechanism, acetylcholine may activate intraadrenal nerve cells to release transmitters/modulators that amplify the adrenal response to ACTH (Charlton, 1990). It is likely that acetylcholine also exerts these mechanisms in the human adrenal cortex, but this remains to be unravelled.

Catecholamine-containing nerves have been demonstrated by formaldehyde-induced fluorescence in the mammalian adrenal cortex (Kleitman and Holzwarth, 1985). Scattered nerve fibres in the human adrenal cortex immunohistochemically contain the enzymes of noradrenaline synthesis: tyrosine hydroxylase (TH) (Unsicker and Heym, 1996); and dopamine-ß-hydroxylase (DBH) (Charlton et al., 1992). Immunoreactive fibres arise from small nerve bundles below the capsule to supply subcapsular blood vessels. Some scarce fibres reach the parenchyma of the zonae glomerulosa and fasciculata (Charlton et al., 1992; Charlton, 1995). Nerve fibres in the zona reticularis are coarser and increase in number towards the medullary border (unpublished observation). Processes of adrenomedullary chromaffin cells in the guinea pig adrenal, shown to extend into the zona reticularis and fasciculata (Unsicker et al., 1978), and/or noradrenergic intrinsic neurons, present also in man (Heym et al., 1994), may contribute to the observed distribution pattern. Aldosterone secretion of the zona glomerulosa is inhibited by dopamine in rats (Pratt et al., 1987). From pharmacological experiments in this species it was postulated, that local noradrenergic axon terminals are able to take up dopamine from the circulation and release it upon the appropriate stimulus (Vizi et al., 1993). While in the human adrenal cortex dopamine-binding sites have been demonstrated (Stern et al., 1986); receptors for noradrenaline have not been described. This may point to a differential catecholaminergic innervation of cortical blood vessels and endocrine cells.

Nerve fibres that are immunoreactive for the generating enzyme of the small molecule transmitter *nitric oxide* (NO), NO-synthase (NOS), are sparsely distributed in the human adrenal cortex and capsule to supply blood vessels and steroid cells (Heym et al., 1994). NOS-immunoreactive nerve cells in the human adrenal medulla (Heym et al., 1994) may take part in the cortical innervation. NO is regarded as a powerful vasodilator agent (Vincent and Hope, 1992). Localization of NOS-immunoreactivity in fibres to cortical blood vessels is consistent with the idea of NO acting as a putative regulatory agent for the control of local blood flow (Bredt et al., 1990). The close association of NOS-positive axons with cortical cells (Unsicker and Heym, 1996) probably reflects a particular but hitherto unknown role of NO in the regulation of human corticosteroid hormone secretion.

Immunohistochemical investigations on the human adrenal cortex further revealed the intraneuronal presence of various peptides that are thought to significantly contribute to the modulation of adrenocortical activities (see Malendowicz, 1993).

A rich meshwork of substance P-immunolabelled

nerve fibres is distributed throughout the human adrenal cortex (Figs. 1a, 3a, 4a, 5a) (Linnoila et al., 1980; Bucsics et al., 1981; Helen et al., 1984; Heym et al., 1995b). In addition to substance P-immunoreactive fibre bundles that travel along cortical septs, varicose fibres surround subcapsular blood vessels and follow endocrine cell strands and sinusoids in all cortical layers (Fig. 1b). Ultrastructurally, substance P-immunoreactive varicosities are in intimate contact with cortical cells (Heym et al., 1995b). A significant role of substance P has been emphasized not only in the modulation of adrenocortical innervation (Konishi et al., 1983) and acetylcholine action (Livett et al., 1990), but also in the direct inhibition of aldosterone and potentiation of corticosterone release (Neri et al., 1990b). The role of SP in regulation of adrenocortical growth and functions has been reviewed previously (Hinson, 1990; Jessop et al., 1992, Malendowicz, 1993).

The human adrenal cortex displays a rich supply of *calcitonin gene-related peptide* (CGRP)-immunoreactive nerve fibres throughout all layers (Heym et al., 1995b). Close contacts of CGRP-immunolabelled terminals with endocrine cells probably provide the structural correlate for the inhibitory effect of CGRP on aldosterone release in vivo and in vitro (Murakami et al., 1989) and of its stimulatory action on fasciculata functions (Kuramoto et al., 1987; Hinson and Vinson, 1990). Accordingly, CGRP-binding sites were demonstrated in rat adrenocortical homogenates (Goltzman and Mitchell, 1985). Direct effects of CGRP on aldosterone secretion (Murakami et al., 1989) remain to be verified in man.

In the human adrenal cortex, moderate numbers of varicose nerve fibres with immunoreactivity for vasoactive intestinal peptide (VIP) supply subcapsular blood vessels and surround endocrine cells of the glomerulosa, fasciculata and reticularis zones (Linnoila et al., 1980; Heym et al., 1995b; Unsicker and Heym, 1996). These axons, at least in part, may arise from intraadrenal VIP-positive nerve cell bodies, as deduced from retrograde tracing and demedullation in rat (Dagerlind and Hökfelt, 1991). VIP-positive medullary perikarya are present also in man (Colombo-Benkmann et al., 1996). The ultrastructural demonstration of VIP-immunoreactive terminals apposed to human glomerulosa cells (Unsicker and Heym, 1996), suggests a direct action of VIP in the human external adrenocortex. In fact, in laboratory animals exogeneously administered VIP causes hypertrophy of the zona glomerulosa and markedly raises the blood level of aldosterone (Mazzocchi et al., 1987). Moreover, the increase of 11-hydroxylase activity by splanchnic nerve stimulation in conscious calves can be mimicked by VIP (Bloom et al., 1987; Ehrhart-Bornstein et al., 1991), indicating the significance of nervous VIP in adrenocortical functions. Actions of VIP on human steroidogenic cells, however, remain to be elucidated.

Neuropeptide tyrosin (NPY)-immunoreactive nerve fibres occur scattered in the human adrenal cortex (Fig. 2) (Unsicker and Heym, 1996); they are less abundant than VIP-immunolabelled fibres. Immunoelectron microscopy revealed nonsynaptic contacts of NPY-immunostained axon varicosities with glomerulosa cells in the human adrenal cortex (Unsicker and Heym, 1996). Accordingly, glomerulosa cells exhibit specific binding sites for NPY in cattle (Torda et al., 1988). Demedullation studies in rat suggest a dual origin of NPY nerves from extraadrenal ganglia as well as from intraadrenal ganglion cells (Maubert et al., 1993). Consistent with its cortical localization, a regulatory role of NPY on glomerulosa cells and, less expressed, also on fasciculata cells has been reported (Rebuffat et al., 1988; Malendowicz et al., 1990, 1996), affecting plasma aldosterone levels in laboratory animals independent of an intact hypothalamo-pituitary axis (Mazzocchi and Nussdorfer, 1987). The potent vasoconstrictory effect of NPY is in favour of another, indirect action of NPY on adrenocortical secretion (for review see Malendowicz, 1993).

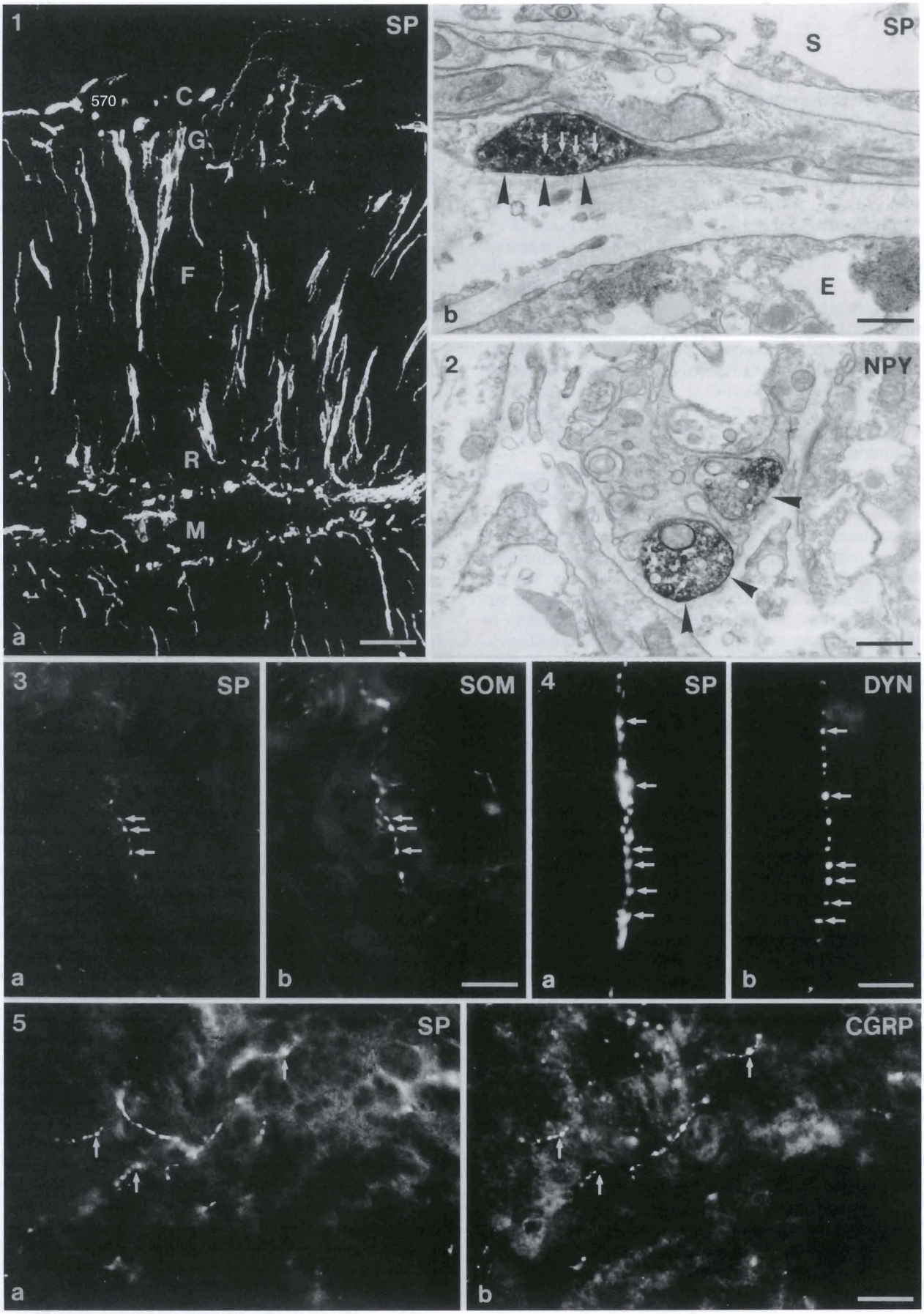
Somatostatin-immunoreactive nerve fibres have recently been detected in association with endocrine cells of the human adrenal cortex (Heym et al., 1995b). Although not yet verified for man, in laboratory animals somatostatin-receptors are particularly frequent in the zona glomerulosa (Maurer and Reubi, 1986). In agreement with its receptor demonstration, somatostatin inhibits growth (Boscaro et al., 1982) and steroidogenic capacity of the zona glomerulosa (Rebuffat et al., 1984) and decreases the aldosterone response to angiotensin II (Aguilera et al., 1981).

Opioid peptides, derived from the prodynorphin-precursor appear to contribute to the human adrenocortical innervation. Dynorphin 1-8, generated by prodynorphin, has been found in a considerable number of varicose fibres (Heym et al., 1995b), and Leu-enkephalin, part of the dynorphin sequence, is also contained in human cortical nerves (Linnoila et al., 1980). Consistent with these findings, dynorphin was demonstrated to inhibit adrenocortical secretion in vivo and in vitro (Mazzocchi et al., 1990; Neri et al., 1990a).

Few nerve fibres, immunostained for the C-terminal octapeptide cholecystokinin 8 were demonstrated in the human adrenal cortex (Heym et al., 1995b). While intraperitoneal injections of cholecystokinin were demonstrated to increase plasma corticosterone levels (Itoh et al., 1982), direct effects of cholecystokinin on steroidogenesis have not been reported.

Galanin-immunolabelled nerve fibres in the human adrenal cortex occur frequently in the subcapsular region but are rather sparse in deeper cortical layers (Bauer et al., 1986). Corticosteroid release is inhibited in rats by hypothalamic administration of galanin (Crawley et al., 1990), and direct galanin secretagogue effects on adrenocortical cells have been shown by Mazzocchi et al. (1992).

Some other neuroactive peptides have been distinguished in adrenocortical nerve fibres of non-primate mammals (neurotensin - cat: Lundberg et al., 1982; CRH - sheep: Rundle et al., 1988; pituitary


1
SP
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C
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E
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2
NPY
3
SP
a
SOM
b
4
SP
a
DYN
b
5
SP
a
CGRP
b

adenylate cyclase-activating peptide - rat: Wakade et al., 1992; - cattle: Edwards and Jones, 1994), that await investigation in man.

Putative extraadrenal origins of adrenocortical fibre populations

Application of antibody combinations permits the simultaneous distinction of two or more intraneuronal messengers. In selective human adrenal nerves pathway-specific "chemical codes" have been revealed by this technique that point to their origin and functional implication, when correlated with findings in other species.

Retrograde neuronal tracing in laboratory animals has confirmed previous suggestions on a complex adrenal innervation including efferent and afferent nerves from the thoracic sympathetic chain and dorsal root ganglia as well as from the vagus (for review see Parker et al., 1993). On the basis of their vesicle content, cortical nerves were classified as autonomic efferents (Garcia-Alvarez, 1970). Axon terminals with densely packed mitochondria are indicative for an additional sensory fibre supply of the mammalian adrenal cortex (Unsicker, 1971). Both efferent and afferent nerve fibres contact endocrine cortical cells and innervate vascular elements in the human adrenal cortex (Heym et al., 1995b; Unsicker and Heym, 1996).

Varicose fibres with DBH-immunoreactivity in the human adrenal cortex indicate noradrenaline-containing *postganglionic efferents from the sympathetic system* (Charlton et al., 1992). Moreover, intracortical NPY-immunoreactive varicose nerve fibres with colocalized DBH- or TH-labelling are presumably of sympathetic origin (Lundberg et al., 1988), as in human paravertebral thoracic ganglia approximately 30% of the post-ganglionic perikarya colocalize TH/NPY (Baffi et al., 1992).

A subpopulation of dynorphin-immunoreactive nerve fibres with colocalized NPY may also belong to the sympathetic efferents. These two peptides appear to be colocalized in human thoracic paravertebral ganglion cells (Heym et al., to be published), well corresponding with the described absence of cleavage products of the proenkephalin-A precursor from human sympathetic neurons (Helen et al., 1984).

VIP-immunolabelled human intracortical nerve fibres are TH-negative (Unsicker and Heym, 1996). The assumption that such nerve fibres represent an axon type different from adrenergic fibres, was previously deduced from the observation that VIP-labelled fibres in the rat adrenal remained unaffected by chemical sympathectomy with 6-hydroxydopamine (Kleitman and Holzwarth, 1985). This finding is supported by the incongruency of TH and VIP in two postganglionic neuron populations of human paravertebral ganglia (Järvi et al., 1989), and by the colocalization of AChE and VIP in the latter neurons (Lundberg et al., 1988).

Adrenocortical axons with immunoreactivity for somatostatin in man partly belong to the VIP-ergic fibre population (Unsicker and Heym, 1996). As an identical coding has been reported for human ganglion cells in thoracic sympathetic chain neurons (Schmitt et al., 1988); VIP/somatostatin-positive nerve fibres probably derive from paravertebral ganglia.

Also, NOS-positive fibres in the human adrenal cortex are TH-nonreactive, and in some fibres NOS- is colocalized with VIP-immunolabelling (Unsicker and Heym, 1996). Such efferents may derive from a non-catecholaminergic postganglionic paravertebral neuron population, described in laboratory animals (Fischer et al., 1993). In support of this observation, NOS and VIP colocalization was shown in the guinea pig peripheral innervation (Klimaschewski et al., 1994). NOS remains to be distinguished in human sympathetic nerve cell bodies.

A considerable proportion of CGRP-positive cortical nerve fibres in the human adrenal, that lack substance P-labelling (Heym et al., 1995b) may originate from CGRP-containing sympathetic postganglionic neurons in human thoracic paravertebral ganglia, shown partly to colocalize somatostatin and VIP (Schmitt et al., 1988).

Substance P-immunolabelling is absent in para-vertebral sympathetic neurons of man (Schmitt et al., 1988; Colombo-Benkmann et al., 1996), consequently

Fig. 1. SP immunoreactive nerve fibres in the human adrenal cortex. **a.** Substance P-immunofluorescent fibre bundles gather subcapsularly (C), and traverse the cortex to reach the medulla (M); fine varicose fibres branch off into the zonae glomerulosa (G), fasciculata (F) and reticularis (R). Bar: 160 μm. **b.** Pre-embedding PAP-immunoelectronmicrograph of the zona reticularis in the human adrenal cortex. An SP-positive transmitter segment containing numerous small clear vesicles and some large dense-cored vesicles (arrows), is partly exposed to the interstitial space (arrowheads) and runs alongside a cortical sinus (S) and an endocrine cell (E). Bar: 0.6 μm.

Fig. 2. Pre-embedding PAP-immunoelectronmicrograph of a human adrenocortical sept showing an unmyelinated nerve fibre with two NPY-immunoreactive axonal profiles that in part are devoid of the glial sheath (arrowheads). E: endocrine cell. Bar: 0.6 μm.

Fig. 3. Double labelling-immunofluorecence of the human adrenal cortex. An intracortical nerve contains a varicose fibre with colocalized substance P **(a)**- and somatostatin **(b)**-immunoreactivities (arrows). Bar: 22 μm.

Fig. 4. Double labelling-immunofluorescence of a varicose nerve fibre in the zona fasciculata of the human adrenal cortex with colocalized substance P **(a)**- and dynorphin **(b)**-immunostaining (arrows). Bar: 22 μm

Fig. 5. Double labelling immunofluorescence of the human adrenal cortex - zona reticularis. Some of the substance P-immunoreactive nerve fibres **(a)** exhibit colocalized CGRP-immunolabelling (**b**; arrows). Bar: 22 μm.

substance P-positive adrenocortical nerve fibres probably derive from non-sympathetic sources. Similarly, galanin appears not to be a constituent of postganglionic perikarya in human paravertebral ganglia (Baffi et al., 1992). This peptide, however, has been shown to occur in rat sympathetic neurons after axotomy (Schrieber et al., 1994). It is possible that galanin levels in the investigated perikarya were too low to be detected, or that galanin is only expressed after injury (Klimaschewski et al., 1994).

Postganglionic efferents from other sources (presumably the vagal system) have been supposed to supply the adrenal cortex in animals (see Parker et al., 1993). Acetylcholine is the classical transmitter of vagal nerve fibres also in man (Lundberg et al., 1988). Our knowledge on further chemical codes of neuron populations in human vagal ganglia as yet is fragmentary.

In a substantial proportion of adrenocortical fibres, NPY appears to be colocalized with VIP (Unsicker and Heym, 1996), a modulator combination, absent in human paravertebral sympathetic neurons (Schmitt et al., 1988), but present in intramural ganglia of the human gallblader, thought to belong to the vagal system (Talmage et al., 1996). NPY, therefore, appears to take part in the catecholaminergic as well as in the non-catecholaminergic (presumably vagal) adrenal innervation.

As substance P apparently is localized in human postganglionic vagus neurons at other locations (Talmage et al., 1996), the co-occurrence of substance P/VIP (Heym et al., 1995b) substance P/NPY or substance P/somatostatin (Fig. 3) in human intracortical nerve fibres that lacked CGRP-labelling (Heym et al., 1995b), may indicate the existence of a postganglionic vagal innervation with extrinsic (Parker et al., 1993) and/or intrinsic origin (Colombo-Benkmann et al., 1996). It should be emphasized, however, that even when a postganglionic vagal innervation of the human adrenal cortex appears likely (Parker et al., 1993), considerations on the transmitter equipment of an adrenal vagal innervation as yet are speculative.

Retrograde neuronal tracing indicated an additional innervation of the mammalian adrenal cortex by *afferent systems* (Parker et al., 1993). Congruent coding of a subpopulation of human cortical nerve fibres and human dorsal root neurons at T6-T10-levels (Heym et al., 1995b) substantiates the supposition of an afferent adrenocortical pathway also in man. In a small proportion of adrenocortical nerve fibres immunoreactive substance P is colocalized with immunostaining for dynorphin (Fig. 4) and, more frequently, for CGRP (Fig. 5) (Heym et al., 1995b). In addition, cholecystokinin- and also NOS-immunolabelling have been distinguished in some of the substance P-immunoreactive cortical nerve fibres (Heym et al., 1995b). Morphological and pharmacological findings presented evidence for the significance of the combination CGRP/substance P in afferent (sensory) functions in man (Quartu et al., 1992). In human thoracic sensory ganglia all substance P-positive neurons were also found CGRP-immunostained (Heym et al., 1995b). Therefore, and for the reasons above, this transmitter combination is considered clearly indicative for sensory fibres. Moreover, cell bodies with immunolabelling for substance P/dynorphin, substance P/cholecystokinin, and substance P/NOS are present in human dorsal root ganglia (Heym et al., 1995b), underscoring the sensory character of identically coded adrenocortical fibres. Notably, the combination substance P/NOS in nerve fibres was exclusive to the adrenal cortex (Heym et al., 1995b), suggesting a specific effect of the respective mediator combination on steroid cells.

Galanin in animals was described to participate in sensory functions (Ju et al., 1987); galanin-immunoreactive sensory neurons in dorsal root ganglia, however, were not detected projecting to the adrenal gland. In support of this finding in guinea pig (Heym et al., 1995a), galanin-positive adrenocortical nerve fibres were not identical with substance P-immunolabelled fibres (Unsicker and Heym, 1996). Colocalization experiments will help to elucidate the origin of cortical galanin-immunostained nerve fibres.

Putative origins of an extrinsic - efferent and afferent - adrenocortical innervation are summarized in Fig. 6b.

Intraadrenal neurons contribute to the cortical innervation

The human adrenal cortex, in addition to extrinsic nerve fibres, receives an intrinsic postganglionic innervation by intraadrenal neurons (Swinyard, 1937; Mikhail and Amin, 1969; Heym et al., 1994; McNicol et al., 1994). As in other species (Tomlinson and Coupland, 1990), human intraadrenal neurons have axodendritic synaptic input by preganglionic terminals with small clear and a few large dense-cored vesicles (Heym et al., 1995b). Hence, these neurons are considered to be the postganglionic targets of an efferent autonomic adrenal innervation and to constitute the neuronal link of an intrinsic circuitry between adrenal medulla and cortex (Parker et al., 1993). When compared with other species, intraadrenal neurons in man are particularly numerous (Mikhail and Amin, 1969; Colombo-Benkmann et al., 1996), occuring at subcapsular, cortical and medullary sites (Mikhail and Amin, 1969; Heym et al., 1994, 1995b; Colombo-Benkmann et al., 1996).

In correlation with the presence of mRNA for ChAT or DBH, two intraadrenal neuron populations in rat were shown to be cholinergic and noradrenergic, respectively, each of them equipped with specific mediator combinations (Dagerlind and Hökfelt, 1991). This differentiation is also supposed to apply for man, because selective comediators immunohistochemically occur either in TH-positive or TH-negative nerve cell bodies (Colombo-Benkmann et al., 1996).

Intraadrenal neurons have been hypothesized to be derived from the sympathoadrenal cell lineage (Le

Douarin, 1982) with *catecholamines* as main transmitter. This assumption is also substantiated in man by the immunohistochemical presence of TH in adrenal nerve cells (Colombo-Benkmann et al., 1996). Contrary to cholinergic *NPY*-immunolabelled neurons in rat (Schalling et al., 1988) such neurons in the human adrenal medulla appear to be TH-positive (unpublished observation), suggesting that in man they are members of the noradrenergic - sympathetic - neuron subset.

A second, TH-negative, adrenal nerve cell population has been detected in the human adrenal gland (Colombo-Benkmann et al., 1996). *NOS*- (Heym et al., 1994), *VIP*- (Bryant et al., 1976; Heym et al., 1995b), or *somatostatin*- (Heym et al., 1995b) immunolabelled nerve cell bodies were demonstrated to belong to this TH-nonreactive neuron population. Likewise, *cholecystokinin*-immunostained neurons in the human adrenal (Heym et al., 1995b), and also *substance P*-positive nerve cell bodies (Heym et al., 1995b), that make up approximately 20% of the human intramedullary neuron population, were shown to be non-aminergic (Colombo-Benkmann et al., 1996). TH-negative cell bodies may be the intraadrenal equivalent of the non-catecholaminergic (presumably cholinergic) cell population in human sympathetic ganglia (Lundberg et al., 1988). Accordingly, AChE- activity was discerned in presumably *acetylcholine*-containing human adrenal nerve cell bodies at cortical and medullary locations (Charlton et al., 1991). On the other hand, acetylcholine is the characteristic transmitter of vagal postganglionic neurons, and evidence from chick-quail chimera (Le Douarin, 1982) and from retrograde neuronal labelling in laboratory animals (Coupland et al., 1989) points to the relationship of some adrenal neurons with the brain stem neural crest at the site of the vagus anlage. In analogy to the extrinsic non-catecholaminergic adrenocortical innervation, the roots of cholinergic adrenal neurons may be deduced from their differential chemical coding with respect to substance P-co-localization. Substance P-immunoreactive intra-medullary nerve cell bodies of possibly vagal developmental origin, in part colocalized NOS, dynorphin or cholecystokinin (Heym et al., 1995b). As substance P and VIP-immunoreactivity never co-occur in human adrenal neurons (Colombo-Benkmann et al., 1996), nerve cell bodies with immunoreactivity for the latter peptide consequently may be counted in the cholinergic sympathetic neuron population. It is supposed that the human CGRP-positive adrenocortical innervation is of exclusive extrinsic

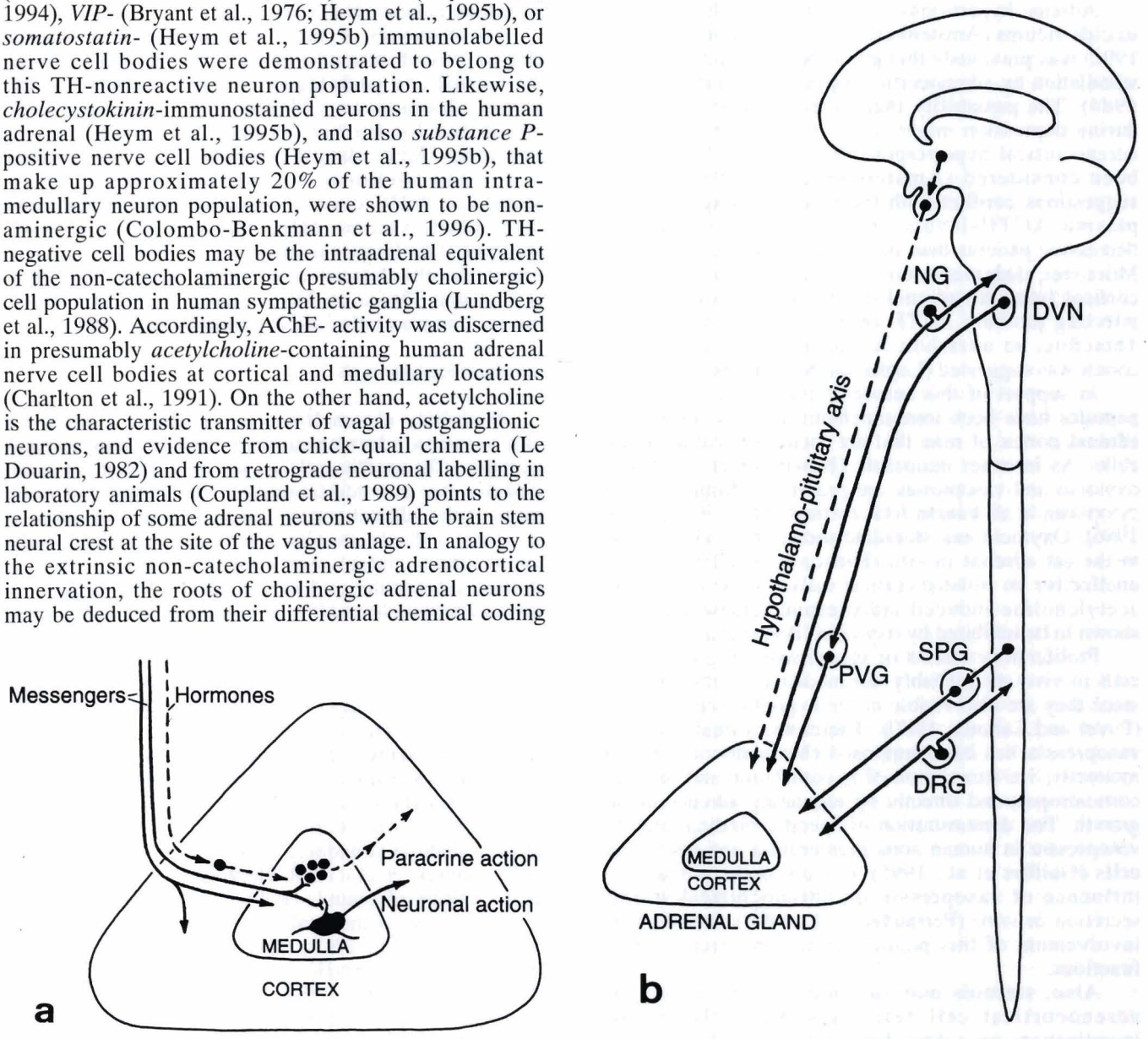

Fig. 6. Endocrine and nervous control of the adrenal cortex. **a.** Extrinsic and intrinsic adrenocortical regulation. **b.** Extrinsic nervous pathways to the adrenal cortex. DRG: Dorsal root ganglia; DVN: Dorsal nucleus of the vagus; NG: Nodose ganglion; PVG: Peripheral vagal ganglia; SPG: sympathetic paravertebral ganglia.

sympathetic origin, since intraadrenal neurons in man immunohistochemically lack CGRP (Heym et al., 1995b).

Transmitter combinations found in extrinsic and intrinsic nerve cell bodies have been summarized in Fig. 7.

Other sources of factors that influence the adrenal cortex

Adrenocortical cells

Adrenal hypertrophy, in patients with depression or suicide victims (Amsterdam et al., 1986; Nemeroff et al., 1992) was previously thought to be the result of chronic stimulation by adrenocorticotropin (ACTH) (Gold et al., 1984). The possibility that hypersecretion of cortisol during depression might result in part from peripheral adrenocortical hyperresponsiveness to ACTH has also been considered (Amsterdam et al., 1983). These suggestions conflict with the recent finding that basal plasma ACTH-levels are significantly lower in depressive patients than in controls (Rubin et al., 1995). Moreover, dexamethasone can suppress the release of cortisol from the adrenal cortex without significantly affecting pituitary ACTH or beta-endorphin liberation. Therefore, an ultrashort feedback loop in the adrenal cortex was suggested (Lupka and Szczundlik, 1985).

In support of this autocrine regulatory loop, some peptides have been immunochemically revealed in the adrenal cortex of man that are localized within steroid cells. As in other mammals (Hawthorn et al., 1987), oxytocin and vasopressin are present in droplets of the cytoplasm in all human fetal cortical zones (Ravid et al., 1986). Oxytocin can stimulate secretion of aldosterone in the rat adrenal in situ (Hinson et al., 1987) but is uneffective on isolated cortical cells. On the other hand, acetylcholine-induced aldosterone release has been shown to be inhibited by oxytocin (Porter et al., 1988).

Proliferatory effects of vasopressin on glomerulosa cells in vivo are probably not mediated by the pituitary, since they are also visible in the hypophysectomized rat (Payet and Lehoux, 1980). Therefore, a dual action of vasopressin has been supposed (Malendowicz, 1993): indirectly, via stimulation of hypothalamic and pituitary corticotropes; and directly by regulating adrenocortical growth. The demonstration of specific binding sites for vasopressin in human zona glomerulosa and fasciculata cells (Guillon et al., 1995) as well as the stimulatory influence of vasopressin on adrenocortical steroid secretion *in vitro* (Perraudis et al., 1993) underline the involvement of this peptide in human adrenocortical functions.

Also, steroids may provide the fine tuning for adrenocortical cell responses. Recently, earlier investigations on a dose-dependent effect of the locally produced steroid *ouabain* (Hamlyn et al., 1991) on aldosterone production (Szalay, 1971) were shown to be based on the concentration of extracellular calcium (Szalay, 1993).

Growth factors (cytokines) are soluble peptides produced by different tissues including adrenal cells. Cytokines are thought to be involved in the fine regulation of adrenal functions under normal and stressful conditions (Abraham, 1991). Human zona reticularis cells, for example, produce two members of the *interleukin* (IL) family, *IL-1* (González-Hernández et al., 1995) and *IL-6* (González-Hernández et al., 1994a,b), as well as the *tumor necrosis factor (TNF)*-α (González-Hernández et al., 1996). These cytokines act on adrenocortical functions in an autocrine, paracrine, or endocrine manner (Roh et al., 1987).

The discovery of *major histocompatibility complex (MHC) class II* molecules in the zona reticularis of both the normal and pathologically altered human adrenal cortex (Jackson and McNicol, 1988) opened the possibility for further insights into adrenocortical physiology; MHC class II expression changes according to age and hormonal status (Khoury et al., 1987). Moreover, MHC class II-negative cells in the zona fasciculata become MHC class II-positive when changing their hormonal equipment by transformation to reticularis cells (Khoury et al., 1987). Modulatory effects of IL-1 and TNF-α on MHC class II expression underline the complex intra- and intercellular cross talk.

Adrenomedullary cells

Medullary chromaffin cells constitute a paracrine link between adrenomedullary activity and cortical secretion. Chromaffin cells are not only assembled in the medulla, but can additionally be detected in all three zones of the adrenal cortex in man as well (Bornstein et al., 1994). Ultrastructurally, cortical and chromaffin cells are in direct contact with each other. Both catecholamines, *adrenaline* and *noradrenaline*, are present in human adrenal chromaffin cells (Benchimol and Cantin, 1977), and these catecholamines directly stimulate adrenal steroidogenesis (Bornstein et al., 1990). Chromaffin cells for their part are influenced by glucocorticoids through the induction of phenylethanolamine-N-methyltransferase (PNMT) synthesis, the enzyme catalizing the conversion of noradrenaline to adrenaline (Wurtman and Axelrod, 1966). Numerous *leu-* (Linnoila et al., 1980) and *met-enkephalin*-containing chromaffin cells, present in the human adrenal medulla (Lundberg et al., 1979; Varndell et al., 1982; Andreis et al., 1988; Hervonen et al., 1989), are likely sources of opioids (Racz et al., 1980) interacting with dopamine in the control of aldosterone production (Bevilacqua et al., 1982). Moreover, *VIP* (De Lellis et al., 1984; Ehrhart-Bornstein et al., 1991), *NPY* (Lundberg et al., 1986; Rebuffat et al., 1988; Malendowicz et al., 1996), *CGRP* (Pelto-Huikko and Salminen, 1987), *somatostatin* (Bucsics et al., 1981; Heym et al., 1994), *substance P* (Bucsics et al., 1981), *NOS* (Heym et al., 1994), or a*trial natriuretic peptide (ANP*; Suda et al., 1984) are constituents of human

adrenal chromaffin cells. ANP was shown to inhibit aldosterone, cortisol, and dehydroepiandrosterone secretion in human adrenal cell cultures, and to enhance the accumulation of intracellular cGMP (Higuchi et al., 1986), suggesting the involvement of ANP in the early pathway of human steroidogenesis. Accordingly, intravenous injections of ANP in man cause significant decreases in plasma aldosterone concentrations (Ishii et al., 1985). Two different types of binding sites for ANP have been distinguished in the zona glomerulosa and in deeper cortical regions of tupaia, a low primate (Fuchs et al., 1986). The presence of a third type of binding site in the adrenal medulla raises the possibility of an additional action of ANP on cortical functions via the regulation of catecholamines (Fuchs et al., 1986). The presence of *oxytocin* and *vasopressin* in the human adrenal medulla (Ang and Jenkins, 1984) emphasizes the relevance of these peptides in adrenocortical functions. Steroidogenic cells in man are also a possible site of action for pro-opiomelanocortin (POMC)-derived peptides (Pedersen et al., 1980), as *α-melanocyte-stimulating hormone* and ß-endorphin have been detected in the human adrenal medulla (Evans et al., 1983). Even *ACTH* is present immunohistochemically in a few human medullary chromaffin cells (Lloyd et al., 1984). In support of this observation, mRNA from human adrenal medulla hybridizes the cDNA probe for the ACTH precursor (Jingami et al., 1984).

Some cytokines with adrenocortical relevance have been distinguished in the mammalian adrenal medulla, the immunohistochemical presence of which has not yet been proven in man. For example, *IL-1*, synthesized in rat chromaffin cells, is liberated upon cholinergic stimulation (Bartfai et al., 1990). Moreover, several TGF-ß isoforms appear to be expressed by rat adreno-medullary cells (Unsicker and Krieglstein, 1996) and are releasable from bovine chromaffin granules upon cholinergic stimulation (Krieglstein and Unsicker, 1996). Another member of the TGF-ß superfamily, *glial cell line-derived neurotrophic factor (GDNF)*, is also synthesized in rat chromaffin cells (Krieglstein et al., 1996), some cortical effects of which have been suggested. Effects of cytokines on cortical functions require further investigation although their large number would suggest complex autocrine and paracrine regulatory mechanisms, directly or indirectly affecting the adrenal cortex (Unsicker and Krieglstein, 1996).

It has been hypothesized that the adrenal medulla does not participate in adrenal enlargement of depressed patients, because medullary cells are not thought to be increased in size or multiplicity, except when neoplastic (Landsberg and Young, 1985). However, the multiple cortico-medullary interactions make the involvement of all adrenal compartments in disease likely. When considering that the adrenal medulla under basic conditions makes up only about 10% of the whole adrenal volume, even a 100% increase of the medullary volume would comprise only a small proportion of the total volume increase that may easily have escaped previous computed tomographic inspections (Amsterdam et al., 1986). Alternatively, the findings may be explained by qualitative instead of quantitative changes in chromaffin cells under pathological conditions: Hydrocortisone injections in neonatal rats indicated chemical plasticity of chromaffin cells (Eränkö et al., 1966), in that the proportion of catecholaminergic cell populations was significantly shifted towards the adrenaline-storing subset. Similar results were obtained in paraganglionic cell clusters of sympathetic ganglia in neonatal rats after maternal immobilization stress (Heym et al., 1985). Future investigations on chromaffin cell plasticity are required to obtain more information on this important query.

Immune cells

Another extrapituitary influence on cortical functions by immunocytes, has to be considered (Hayashi et al., 1989; González-Hernández et al., 1994a,b); such cells are abundantly present in all zones of the adrenal gland. While stimulatory effects of immune cells on the hypothalamo-pituitary axis have been extensively studied (Wick et al., 1993), interactions between steroidogenic and immune cells, a common constituent of the normal human adrenal, have been largely neglected until recently (Ehrhart-Bornstein et al., 1996). An increase in glucocorticoid levels is observed after administration of EL-4 lymphoma cells but this does not occur in T cell-deficient tumor recipients (Besedovsky and delRey, 1992). Human peripheral leukocytes, like mouse spleen macrophages (Lolait, 1984) synthesize *ACTH* (Smith and Blalock, 1981) which is suppressed by dexamethasone (Smith et al., 1986). These findings suggest that the POMC gene is expressed and controlled both in leukocytes and macrophages. Moreover, macrophages produce a range of cytokines, which stimulate or inhibit adrenocortical functions. *IL-1*, known to influence human steroidogenesis (Tominaga et al., 1991), is thought to provoke corticosterone release via the liberation of catecholamines from adrenal medullary cells (Gwosdow et al., 1992), by way of the intraadrenal CRH/ACTH-system (Andreis et al., 1991), or by an involvement of prostaglandins (Winter et al., 1990). In man, cortisol release is induced by a direct effect of *IL-6* (Späth-Schwalbe et al., 1994) and in cultured human adrenocortical cells IL-6 has a particular effect on the release of androgens (Ehrhart-Bornstein et al., 1996). In contrast, *tumor necrosis factor (TNF)-α* inhibits basal and ACTH-stimulated cortisol synthesis in human fetal adrenals (Jäättelä et al., 1991). Inhibition of basal and ACTH-induced expression of insulin-like growth factor (IGF) by TNF-α in such cultures (Ilvesmäki et al., 1993) indicates the involvement of TNF-α in the adrenal development. Also another cytokine in human macrophages, TGF-ß (Assoian et al., 1987) has been shown to inhibit human adrenocortical steroidogenesis in vitro (Lebrethon et al., 1994) and to hinder growth of

human fetal adrenocortical cells (Stankovic et al., 1994).

Receptors to peptides and neurotransmitters have been identified on macrophages (Hartung et al., 1986, Spengler et al., 1990). High numbers of ß-receptors on human macrophages (Maisel et al., 1989) are indicative for the regulatory influence of the sympathetic system. Vice versa, an exchange of information between the immune system and adrenal endocrine tissues may take place through the action of immune-derived products on adjacent autonomic nerve fibres (Besedovsky and delRey, 1992), as the presence of T cells can modulate the peripheral sympathetic innervation (Besedovsky et al., 1987). Cortisol down-regulates immune functions of monocytes, including cytokine liberation (Jones and Kennedy, 1993). A reduced number of glucocorticoid receptors on peripheral lymphocytes in depressed patients might explain why adrenal cortex activation does not result in features matching with Cushingís symdrome in these subjects (Whalley et al., 1986).

These examples clearly show that interactions between endocrine, autonomic and immune mechanisms can operate between locally produced and released hormones, neurotransmitters and cytokines at organ and tissue levels (Besedovsky and delRey, 1992).

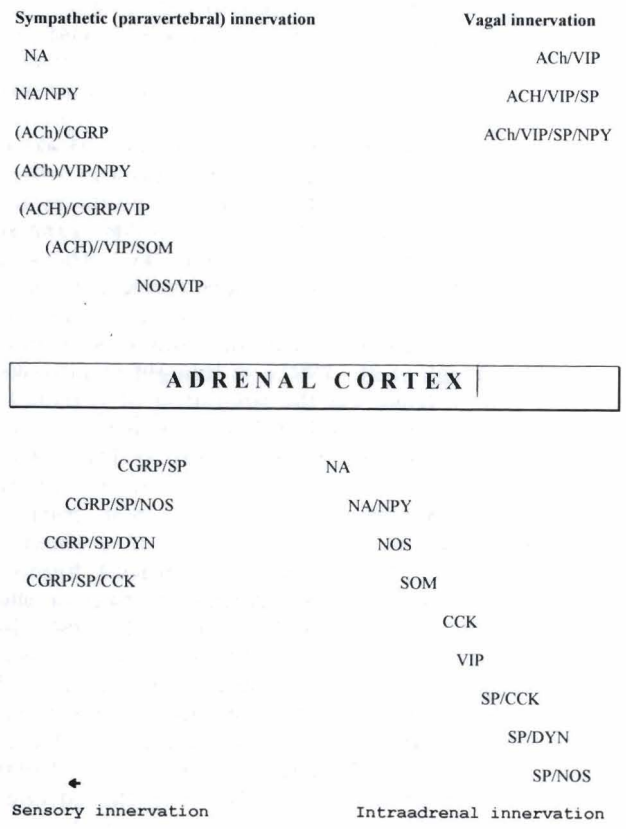

Fig. 7. Putative chemical codes of the extrinsic and intrinsic adrenocortical innervation in man.

Other sources

There is some evidence for adrenocortical effects by mostly blood-borne messengers, with extrapituitary origins. *Histamine*, probably derived from perivascular mast cells, in rat and dog directly stimulates aldosterone and cortisol secretion and induces hypertrophy of the glomerulosa zone (Mikolajczyk, 1965; Hirose et al., 1978). Moreover, it has been shown that *heparin*, also present in mast cells, decreases human cortical aldosterone secretion, probably through inhibition of the renin-angiotensin system (Schlatmann et al., 1964) and that in rat it causes an atrophy of the glomerulosa layer (Mikolajczyk, 1965). In rat, heparin even depresses adrenocortical reactions to starvation, known to be one of the most powerful stress factors (Boulouard, 1963). The demonstration of specific binding sites for *angiotensin II* in the human zona glomerulosa (González-García and Keiser, 1990) works in favour of an involvement of this peptide in the aldosterone metabolism of man as well. Finally, two members of the interferon family appear to be involved in steroidogenesis with different effects. While in rats interferon-α stimulates corticosterone release (Gisslinger et al., 1993), in human fetal adrenal cells interferon-γ inhibits ACTH-induced IGF-expression (Ilvesmäki et al., 1993), suggesting a similar action to TNF-α on adrenocortical growth and differentiation.

Concluding remarks

The immunological and immunohistochemical presence of a multitude of compounds in the human adrenal cortex, that are derived from extrinsic and intrinsic nerve fibres, from cortical and medullary endocrine cells, from immune- and from mast cells, suggest a prominent participation of extrapituitary factors in adrenocortical regulation (Fig. 7). It is hypothesized, that nervous, paracrine, and autocrine mechanisms provide control and fine-regulation of basic adrenocortical stimulation by the endocrine axis.

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