11. Neuropeptides and Affective Disorders

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Pituitary hormones regulate the endocrine organs, are involved in many homeostatic mechanisms in the body, and have direct effects on processes in the central nervous system. The latter was initially demonstrated by animal behavioral experiments¹ and confirmed by neurochemical and electrophysiological studies in animals.² Fragments of pituitary hormones may have similar effects on behavior as the parent hormones, but interestingly they hardly elicit the classical endocrine actions of the parent hormones. The central effects of pituitary hormones and their fragments indicate that they belong to the category of neuropeptides, which are peptide molecules that affect nerve function and/or are present in nerve tissue. Research during the last decade has disclosed that many peptide molecules, including the pituitary hormones, are present in the central nervous system, and that they are presumably located in neuronal pathways. They are synthesized in large proteins, and several are formed in the same molecule. A cascade of processes evolve in peptidergic neurons to express the genetic information into biologically active neuropeptides. These processes control the quantities of neuropeptides synthesized as well as the nature of their biological activity through size, form, and derivation of the end product. In this way sets of neuropeptides with different, opposite, and more selective properties are formed from the same precursor.

The symptomatology of affective disorders is heterogeneous. Prominent are mood changes and disturbances in appetite, sleep, libido, energy, and circadian rhythms. Some of these functions are controlled by brain centers located in the hypothalamus and lower brainstem, and they are innervated by particular peptidergic neurons. Neuroendocrine dysfunctions have been demonstrated in patients with affective disorders, such as diminished suppression of cortisol after dexamethasone administration³ and a blunted thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH).⁴ Cognitive dysfunctions may accompany the mood disturbances in affective disorders. Interestingly, neuropeptides related to adrenocorticotropic hormone (ACTH) and vasopressin have been implicated in cognitive processes; and the opioid peptide β-endorphin, which like ACTH is derived from proopiomelanocortin, may be involved in mood changes. These findings and suggestions may indicate a relation between affective disorders and neuropeptides, especially those related to pituitary hormones and the hypothalamic peptides controlling the release of these hormones.
Animal Studies

Three strategies can be followed in animal experiments to search for potential antidepressant entities, i.e., physiological, pharmacological, and pathological approaches. These strategies may also contribute to the unraveling of possible relations between endogenous substances, including neuropeptides, and affective disorders.

The physiological approach determines physiological processes in the brain that are disturbed in affective disorders. These processes may be related to one or a set of symptoms characteristic for the disease. Knowledge about the substances involved in the regulation and control of these processes may lead to prediction of entities with antidepressant action. Information about brain processes disrupted in affective disorders, however, is limited. The symptomatology of affective disorders is rather heterogeneous, and key symptoms can hardly be designated. One characteristic feature is mood changes. It has been suggested that intracranial self-stimulation behavior in animals, investigating the brain systems that mediate reward, may bear some relation with mood in humans. This behavior procedure also fulfills other validating criteria for an animal model related to depression, including that under certain conditions subchronic treatment with antidepressants facilitates reward.\(^5\)

Research so far has mainly been concentrated on the pharmacological approach, which determines the actions in animals of drugs known to be effective in treating affective disorders. However, little information about the relation between such actions and the therapeutic effect of the antidepressants is available. Not all antidepressant treatments, including the second generation of antidepressants and electroconvulsive shock, share the same effects in these models. Furthermore, most of these models deal with acute effects of antidepressants, whereas their therapeutic action is visible after chronic administration only. Thus until now the pharmacological approach—including, for example, yohimbine, dopa, or amphetamine potentiation, reserpine reversal, olfactory bulbectomy, and kindling—has not yielded new classes of antidepressants. One interesting lead has, however, been explored during the last decade, suggesting that chronic treatment with antidepressants may desensitize hypersensitive adrenoceptors.\(^6\)

The pathological approach, which tries to mimic the pathology of affective disorders in animals, is hampered by the fact that the pathological process underlying affective disorders is unknown. Most animal studies in this respect have concentrated on phenomena related to stress. They include the responses of infant monkeys to maternal separation, reversal of the light-dark cycle in rats, the exposure of rodents to chronic unpredictable stress, the performance deficit in learning tasks after exposure to uncontrolled stress (learned helplessness), and the enhanced immobility after a previous experience of an unsuccessful escape attempt (behavioral despair). In most of these models an activation phase is followed by an inhibition phase. Interestingly, in three of these models the inhibitory phase has been shown to be associated with a decrease in positively reinforced behavior, which characterizes the intracranial self-stimulation model.\(^3\) (Sub)chronic treatment with antidepressant alleviates the induced behavioral changes in these models, but the specificity of some of these tests for antidepressants has been questioned. It has been proposed that in depressed patients \(\alpha_2\) - and \(\beta\)-adrenoceptors are supersensitive. However, a valid animal model mimicking this pathology is not available.