ELSEVIER

European Journal of Pharmacology 405 (2000) 341–349

ejp

www.elsevier.nl/locate/ejphar

Psychoneurendocrinology: a science of the past or a new pathway for the future?

Francesca Brambilla *

Dipartimento di Scienze Neuropsichiche, Istituto Scientifico Ospedale S. Raffaele, Via Prinetti 29, 201279 Milan, Italy

Accepted 28 June 2000

Abstract

Psychoneuroendocrinology is a branch of neuroscience that developed in the beginning of the last century, which investigates the possibility of a cause–effect link between endocrinopathies and mental disorders — with these studies ending in negative results. Psychoneuroendocrinology was then used as a methodological approach for the investigation of neurotransmitter function, on the basis of the observation that neurotransmitters regulate neurohormone and peripheral hormone secretions. Data were obtained for hypothalamic noradrenergic, serotoninergic, dopaminergic, gabaergic and acetylcholinergic functions, which could not be automatically extended to higher brain centers whose impairments might be etiopathogenetically involved in the development of mental disorders. Future studies should focus on new methodological approaches to brain biochemistry, on investigation of genetic, molecular biology, brain imaging, psychoneuroimmunoendocrinology, neuropeptide and neurosteroid secretion in relation to brain endocrine function in mental diseases.

Keywords: Psychoneuroendocrinology; Psychoneuroimmunoendocrinology; Genetic; Molecular biology

1. Introduction

1.1. The history of psychoneuroendocrinology

The history of Psychoneuroendocrinology (PNE) has ancient roots, going back to the beginning of the century when clinicians and researchers looked for a possible link between disorders of brain biochemical functions and normal or pathological mentation. This was done in the hope to find a solid organic background for the development of mental disorders and for their pharmacological treatments.

In a first approach, a cause–effect link between peripheral well-defined endocrinopathies and similar nosographically well-defined psychopathologies was looked for. This was done on the basis of occasional observations that the development of hormonal disorders was often followed by the appearance of more or less evident changes of cognition, mood and behavior. Anecdotal data were reported, where it was actually shown that in single cases various mental diseases, mostly schizophrenia and depression, appeared after the development of endocrinopathies and disappeared after their therapeutic correction. What was intriguing was the fact that different endocrine imbalances were accompanied by the same types of psychopathologies and, vice versa, that the same endocrine imbalance was accompanied by different types of psychopathologies. No valid explanations were given for the phenomenon (Chatelanat, 1978; Brambilla et al., 1978; Fava et al., 1987).

These studies took place in the first decades of the century, and led nowhere since the erratic, inconsistent and not mandatory correlates were only anecdotal and possibly just artifactual. It was only suggested that the metabolic alterations could be one among multiple precipitating factors, acting in predisposed individuals as a stressing element to disclose a full-blown mental disease, or to modulate its symptomatological aspects and its course.

It was proposed, next, that psychoneuroendocrinology could be used as a methodological approach for the study of brain biochemistry. This was the time of the famous "window on the brain" proposed in the 1960s by Edward Sachar, one of the founders of psychoneuroendocrinology, in the tentative to find noninvasive, nontraumatic methods of approach to the study of brain biochemical function in relation to the development and characterization of normal and pathological mentation in humans (Sachar, 1976). The

* Tel.: +39-368-3017420; fax: +39-2-70122889.

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00564-1

hypothesis was not inappropriate, since researches in experimental animals were consistently demonstrating that the secretions of peripheral hormones are under the direct modulation of the hypothalamic releasing–inhibiting hormones, which in turn are stimulated or inhibited by centrally produced and secreted neurotransmitters and neuropeptides. Therefore, the study of the secretions of peripheral hormones could give information on the functional status of neurotransmitters–neuropeptides in the whole brain or in specific brain areas. When the neuroendocrine research was implemented by stimulatory–inhibitory tests, which used psychopharmacological drugs acting on the secretion of specific central neurotransmitters or on their pre–postsynaptic receptors to induce well-defined hormonal responses, the dream of the "window on the brain" seemed to have come true.

The mass of data obtained was enormous and extremely important. Alterations of functions of the hypothalamo-pituitary–adrenal axis, of the hypothalamo-pituitary–thyroid axis, of the hypothalamo-pituitary–gonadal axis, of the secretion of growth hormone, of prolactin, of endogenous opioids and of various neuropeptides were reported and considered specific for one or another psychopathology, even being considered as mandatory markers for the diagnosis of a disease and necessary for its nosographical definition (Shah and Donald, 1984; Brown et al., 1984; Halbreich, 1987; Schatzberg and Nemeroff, 1988; Holsboer, 1989; De Souza and Nemeroff, 1990; Musselman and Nemeroff, 1996).

Typical is the story of the hypothalamo-pituitary–adrenal function in Major Depressive Disorders (MDD). A plethora of data were reported, indicating that MDD were accompanied by hyperfunction of the hypothalamo-pituitary–adrenal system, with a disruption of the normal feedback and feedthrough mechanisms occurring not only during the symptomatologically active phases of the disease but sometimes also during the phases of remission, in the last cases representing an unfavourable factor for the responses to therapies and the prognosis of the disease (Holsboer, 1989). As mentioned before, each endocrine imbalance was considered as a signal of specific neurotransmitter alterations, able to indicate what type of brain biochemical impairment was responsible on the one side for the endocrine alteration and on the other for the psychopathology. Just to make an example, the hypothalamo-pituitary–adrenal hypersecretion so frequently occurring in MDD was considered as expression of noradrenergic or acetylcholinergic hyperfunctions or of serotoninergic hypofunction in the hypothalamus and possibly in higher brain centers, since both noradrenaline and acetylcholine are physiological stimulators of the hypothalamo-pituitary–adrenal axis and serotonin inhibits it (Muller et al., 1977). In other words, the pathogenesis of MDD was considered to be linked to noradrenaline or acetylcholine hyperfunctions or to serotonin hypofunction, occurring not only in the hypothalamus but possibly also in higher brain areas more specifically involved in the regulation of affectivity (Holsboer, 1989).

The same deductions were proposed for the other psychopathologies and neuroendocrine dysfunctions, which sometimes concurred in the suggestion of a specific neurotransmitter pathology, and sometimes were discordant. We could mention the blunted thyroxine-releasing-hormone responses to thyrotropin-releasing hormone stimulation, the impaired prolactin and cortisol responses to serotoninergic probes, the altered growth hormone responses to noradrenaline, dopamine, serotonin, acethylcholine and γ-aminobutyric acid (GABA) stimulations, all of which were observed in MDD, schizophrenia, anxiety disorders, eating disorders, personality disorders, and so on (Brown et al., 1984; Checkley and Arendt, 1984; Pandey et al., 1984; Loosen, 1987; Nash and Meltzer, 1991; Brambilla, 1999).

In the meantime, the study of circadian rhythms of hormonal secretions were offering a deeper insight in the brain biochemistry. Circadian rhythms of hormonal secretions are regulated by "clocks" located in the hypothalamus but also in higher brain areas. All the neuroendocrine data that were obtained in basal or pharmacologically stimulated–inhibited conditions pointed to neurotransmitter functions only in the hypothalamus, while the study of the circadian rhythms of hormonal secretions referred also to suprahypothalamic areas. These researches revealed impairments in circadian rhythmicity with advanced or delayed phases or with total disorganization occurring in various psychopathologies, as expression of hypothalamic–suprahypothalamic alterations (Wehr and Goodwin, 1983; Monteleone et al., 1999).

At this point, the interpretation of the mass of data that were sometimes concordant and sometimes discordant in their immediate meaning, pointing to one or another type of biochemical brain pathology for each mental illness, became a real problem. Doubts started to rise on the consistency and validity of this diagnostic and prognostic approach. Psychoneuroendocrinology did not seem to offer the biochemical "target" for each psychopathology, but, rather, made the history of etiopathogenesis, nosography, prognosis and therapeutic choices of mental disorders so confused and intriguing that authoritative researchers suggested to abandon it, the observed hormonal pathologies being defined as aspecific, casual, nonvalidable, and, in all, insignificant and meaningless for the understanding of the etiopathogenesis of mental disorders.

What had happened? It was evident from most of the reports that none of the hormonal alterations were consistently present in each patient suffering from any one of the mental disorders. Rather, they generally occurred in a relatively small percentage of subjects, without apparent main symptomatological and demographic differences being demonstrable between patients who did and those who did not had the endocrine imbalance. It could also be observed that within the same mental disease, one group of patients had one neuroendocrine alteration, while another

group of apparently similar patients could have exactly the opposite impairment or even absolutely normal hormonal secretions. Moreover, the same neuroendocrine disorder was observed in more than one totally different psychopathology and sometimes even in physical diseases that were not accompanied by concomitantly impaired mentation. Pharmacological manipulations revealed very controversial responses related to the same neurotransmitter function, with hyperresponses of one hormone and hyporesponses of another to the same probe. Finally, most of the biochemical impairments were present during the symptomatologically active phases of the diseases to disappear during their remission, which suggested that they could be the consequence and not the cause of mental illnesses.

Even taking into account all these drawbacks, are we really convinced that the hormonal alterations observed are unspecific, casual, nonvalidable, and especially meaningless? Or, as often happens in the history of science, have we used psychoneuroendocrinology inappropriately, and because of that, obtained results that we do not know how to interpret and, even less, how to use?

1.2. Critical revision of past psychoneuroendocrine researches

If we make a critical review of all the data reported in the literature, it is clear that psychoneuroendocrinology has used an array of static and dynamic neuroendocrine tests, which encompass the entire function of the hypothalamo-pituitary–peripheral glands including all basal hormonal secretions, their responses to pharmacological stimulations–inhibitions, and the sensitivity of their pre–post-synaptic receptors. But looking at the meaning of these data, it is evident that they refer mostly to the function of the hypothalamus, and that alterations of higher brain centers possibly involved in the etiopathogenesis of mental disorders can only be inferentially proposed. Unfortunately, inferential hypotheses are not sufficient nor sufficiently validable, and could be a first source of confusion in the interpretation of the meaning of the data obtained, leading to hazardous theories. In other words, the psychoneuroendocrine tests can be used, always remembering that they give validable information only on the function of the hypothalamus, and not of higher brain areas whose impairments are possibly etiopathogenetically responsible for the development of mental disorders. Even with this point in mind, however, it is worth to suggest that the biochemical alterations occurring in suprahypothalamic areas must influence the hypothalamic function because of the projections existing between the various brain nuclei, and therefore it cannot be excluded that the hypothalamic impairments reflect those of higher brain centers.

A second point that must be taken into consideration is that most of the psychoneuroendocrine studies had been programmed on the hypothesis that each mental disorder is based on a single neurotransmitter impairment, possibly occurring in the entire brain. Typical examples of this theory are the hypotheses of an increased dopamine secretion in the whole brain, responsible for schizophrenia, that of noradrenergic hypo- or hypersecretion and of acethylcholinegic hypersecretion for MDD and anxiety disorders, of serotoninergic hypofunction for MDD, of gabaergic alterations for anxiety disorders and of specific neuropeptide impairments for many diseases (Siever, 1987; Jimerson, 1987; Janowsky and Risch, 1987; Meltzer and Lowy, 1987; Losonczy et al., 1987; Hommer et al., 1987).Today, nobody would still support this theory, since in the meantime it has been amply demonstrated that plasticity phenomena occur in the brain, leading to changes of multiple neurotransmitter–neuropeptide functions as a consequence of the primary impairment of one of them. In other words, an array of biochemical alterations has been demonstrated to concomitantly occur in each psychopathology, some of them possibly representing reactive phenomena one to another, but each of them concurring in the development, course and prognosis of each psychopathology. This would lead to complex peripheral hormonal responses to the administration of centrally acting probes, whose results can seem contrasting one to another for various reasons. First, each probe may act simultaneously on multiple neurotransmitters or on different neurotransmitter receptors responsible for the contrasting peripheral hormonal responses. Or, by acting contemporarily on different brain nuclei each probe may start cascades of events leading to multiple hormonal responses. The problem of the choice of pharmacological probes is extremely important, since unless we start to use probes extremely pure, acting only on one neurotransmitter system in a specific bran area, we will have always to confront the problem of the significance of the results of the tests applied.

A third point worth to remember is that most of the subjects who come to the observation of clinicians and researchers have previously been treated with psychotropic drugs, which modify central neurotransmitter–neuropeptide functions and central–peripheral endocrine secretions and capacity to respond to stimuli acting through neurotransmitter systems. Many of the psychoneuroendocrine impairments reported in the literature are not primary, but secondary to psychopharmacological therapies. This does not automatically exclude their importance in the pathogenesis of mental illnesses. In fact, a mental disorder is not a constant pathology in regard to symptomatological and biological aspects from its beginning to its end, but is a continuous pathoplastic event with an alteration leading to buffering situations, which in turn start cascades of events, all of them concurring in the modulation of the course of the diseases. When we investigate the biochemical bases of mental disorders, it is very important to look for factors which can be etiopathogenetically involved in their development, but it is equally important to know the pathological factors which occur during the course of the diseases,

modulating or changing their symptomatological aspects, their capacity to respond to therapies and therefore their prognosis. Thus, even to define biochemical pathologies which are secondary to psychopharmacological treatments is extremely important, as long as we are well aware that they are not primary but artificially induced by our therapeutic interventions.

A fourth point must to be taken into consideration. In the hope to find the biochemical background of each major mental disorder, there has been an attempt to correlate neuroendocrine impairments to one or another psychopathology defined according to the Diagnostic and Statistical Manual of Mental Disorders, III or IV editions (DSM III or IV; American Psychiatric Association 1980 and 1994) criteria, often with disappointing results. Maybe, this is where we have made another mistake. Possibly, the neuroendocrine alterations that we have found in mentally sick subjects do not refer to any nosographically well-defined Axis I mental disorder, like for instance MDD or schizophrenia, but to specific personality characteristic present in the patients, which might not necessarily be part of the predominant mental disorder. Personality characteristics and consequential behaviors are modulated by biochemical mechanisms, the neuroendocrine ones often being mandatory for their development and their patterns. A typical example is that of aggressiveness, which is normally initiated and sustained by the secretion of testosterone and possibly of other androgens, under the stimulatory regulation of noradrenaline and the modulatory one of serotonin (Gerra et al., 1996; Finkelstein et al., 1997). Normal, high or low levels of testosterone correlate with normal, high or low levels of aggressiveness, which can be the background for the development of pathological aggressiveness when the serotonin secretion is reduced and its modulatory activity is missing. Testosterone secretion inhibits serotonin secretion and stimulates the noradrenergic ones, the latter being a stimulator of aggressiveness by itself. The reduced serotonin secretion and the increased noradrenaline one might be the basis for the development of MDD or anxiety disorders in predisposed individuals. In other words, a higher than normal or even a high–normal testosterone secretion might be the basis on the one side for a increased aggressiveness and on the other for neurotransmitter(s) alterations, which can be mandatory for the development of an Axis I mental illness. The testosterone alteration, by itself, is only responsible for aggressiveness, but in that it modifies noradrenergic and serotoninergic functions it may concur to the development of major mental disorders in patients genetically or metabolically predisposed to them. It is obvious, therefore, that an alteration of noradrenergic and serotoninergic functions and of the related hormonal secretions observed in patients with MDD or anxiety disorders might, occasionally, be linked to the presence of aggressiveness and its biological background. In this case, we will see in the patients the biochemical changes which are related to aggressiveness and which may not be present in any other MDD or anxiety disorders patient.

A fifth point pertains to the fact that many external factors can intervene in modulating brain biochemistry and the related peripheral hormonal secretions. These include nutrition, drinking, sleep, exercise, concomitant physical pathologies, changes of external/internal temperature, life events, multiple drug consumption, and geographically or socially-linked variations of biological circadian rhythms. Each one of these variables may interfere with the secretions of neurotransmitters–neuropeptides and therefore, obscure the biochemical characteristics of the mental disorders and their etiopathogenetic meaning. In the meantime, they may be among the "primary" factors responsible, in predisposed individuals, for the pathogenesis of specific psychopathologies. In this regard, Van Praag (1996) has suggested an intriguing hypothesis for the pathogenesis of MDD, linked to a genetic predisposition to affective disorders and to intrinsic liability of the hypothalamo-pituitary–adrenal axis with difficulties in coping with external and internal stimulations. In these subjects, superimposed activating stressful events may lead on the one side to the development of specific hypothalamo-pituitary–adrenal-dependent psychopathological symptoms, including anxiety and worsening of the coping difficulties, and on the other to a hypothalamo-pituitary–adrenal stimulation, and as a consequence to a hypothalamo-pituitary–adrenal-dependent inhibition of central serotoninergic function, MDD being the final breakdown of the converging biochemical and mental homeostatic capacities of the individual. In this case, life events have been mandatory for the development of the disorder, obviously in genetically predisposed individuals. The alterations of the hypothalamo-pituitary–adrenal axis of these patients may not occur in others with better functioning biological and psychological coping systems.

The sixth point refers to the very intriguing observation, mentioned before, that the same neurotransmitter–neuropeptide impairment can occur in psychopathologies which are pathogenetically and symptomatologically completely different. Just to make some examples, serotonin deficiency and noradrenaline and corticotropin-releasing-hormone hypersecretions can occur in MDD, but also in Generalized Anxiety, in Obsessive–Compulsive Disorder, in Panic Disorders, in Posttraumatic Stress Disorders, in Eating Disorders and possibly in other psychopathologies (Schatzberg and Nemeroff, 1988; Lynn-Brown and Van Praag, 1991). How can the same impairment be at the basis of different mental illnesses? It may be that a neuroendocrine pathology which is constantly or at least very frequently present in totally different mental disorders might not be the primary cause or the correlate of any one of these disorders, but the cause or the correlate of a specific symptomatology common to each of the pathologies, which, because of that, share the same hormonal abnormalities as expression of a common brain alteration.

This does not mean that the neuroendocrine impairments are only an expression of symptomatic phenomena that are marginally related to the nosography and etiopathogenesis of mental disorders, but that they could be the expression of symptoms which are actually part of any one of them. Another possible explanation is that a specific brain biochemical impairment expressed peripherally by a hormonal alteration and clinically revealed by a symptom or a group of symptoms that can appear in different mental disorders, may be in one case the starting point for a cascade of biochemical events etiopathogenetically leading to one psychopathology and in the meantime be only temporarily involved in the modulation of the course of other psychopathologies. As an example, thyroid dysfunctions can be only a precipitating factor for the development of MDD in genetically predisposed individuals, through the effects of thyroid hormones on noradrenaline, dopamine, and serotonin systems. In the meantime, the thyroid-linked monoamine alterations can worsen characteristics, which are normally modulated by the hypothalamo-pituitary–thyroid system like anxiety, leading to a full-blown anxiety disorder. The same could be suggested for other personality characteristics, which are normally modulated by the hypothalamo-pituitary–thyroid axis, like pathological aggressiveness, impulsiveness or sensation seeking.

All these aspects of psychoneuroendocrinology must be taken into account to explain the apparently contradicting results of this branch of investigation, and to validate its meaning and usefulness. All the data reported in the literature should be revisited with these criticisms in mind, thus making it possible to offer a real "mirror" of brain functions and dysfunctions.

2. The future of psychoneuroendocrinology

Where do we go from here?

Studies in experimental animals are steadily opening new pathways of research and day by day clarifying the mechanisms of brain functions in normal and abnormal situations. Studies in humans lag far behind due to ethical reasons, methodological difficulties, lack of compliance, and, as mentioned above, interferences of an array of external–internal factors that can be carefully avoided in animals but not always in humans. All these drawbacks make studies of human brain function still extremely difficult, and the search for acceptable, non-invasive methods of investigation mandatory. In this regard, psychoneuroendocrinology can still be an important branch of investigation, as long as it takes new innovative steps, indispensable to validate its meaning and its significance.

2.1. Methodological proposals

A first point, which should be taken into consideration, is the fact that psychoneuroendocrinology has always used pharmacological probes to stimulate or inhibit neurotransmitter, neuropeptide, neurohormone secretions and their receptor sensitivities to investigate the brain capacity to confront the everyday life or new events. Even though this type of investigation has a rationale, in that the drugs used were as much as possible specific modulators of each biochemical brain activity, they have always been administered without real knowledge of how much drug should have been used to define the state of function of each brain system in a physiological situation. Most of the time, we have probably used stimuli that were pharmacological rather than physiological, and, in all, probably too massive resulting in responses which could hardly mimic the normal brain activity. This might have obscured the real capacity of the brain biochemical system to adapt to every day situations. Difficulty in coping with external and internal stimuli seems to be one of the core symptoms of most, if not all, psychopathologies. We are not even talking about coping with severe life events, but with the changes that occur during everyday life and require modest mechanisms of adaptation. The dynamic tests we have used up to now to study the coping capacities of mentally sick patients can certainly reveal severe pathologies of the various systems that are involved in adaptation, but not the minor ones that might not be clinically evident but are certainly of great importance for the brain's homeostatic mechanisms and for the patient's social life.

At this point, we should investigate the brain regulatory system by using stimuli that would mimic everyday situations, using on the one hand physical stimulations (e.g., feeding, drinking, adaptation to high and low temperature, exercise, sleeping) and on the other, mental situations (e.g., execution of mental tests, of work, of study, of public speeches, etc.). This type of investigation might reveal specific biochemical alterations of the adaptation systems, including the secretory tonus of classical neurotransmitters, neuropeptides, neurohormones and peripheral hormones, whose impairments might underlie the coping difficulties of the subjects and might be the basis for subsequent psychopathological features.

A second point worthy to be taken into consideration is the fact that any single psychoneuroendocrine test can give contradictory responses, resulting in the contemporaneous suggestion of hyperactivity and hypoactivity of a neurotransmitter system according to the type of neuroendocrine axis used as a mirror of the brain situation. This may be due to the fact that a pharmacological probe can act in different brain areas in which the same neurotransmitter evokes different secretory cascades, which are modulated in turn by multiple neurotransmitters/neuropeptides with ensuing apparent conflicting peripheral results. Alternatively, it may be due to the fact that a probe used to investigate a specific neurotransmitter function can act on different receptors each of which has different peripheral effects, and therefore induces apparently opposite downstream responses.

To differentiate between these possibilities and recognize the real significance of the responses obtained, we should use, contemporaneously or subsequently, multiple psychoneuroendocrine tests that could differentiate between the brain areas on which the probe(s) is acting and between the responses of various receptors for each neurotransmitter and neuropeptide. This approach may seem to make the investigations too complicated and not acceptable to the patients, but this is not necessarily so. In fact, a single test can include a probe stimulating one receptor and another inhibiting another receptor, or one stimulating the secretion of a neurotransmitter and another stimulating another neurotransmitter, or one acting on a neurotransmitter and another blocking the effects of a modulatory neuropeptide, or one acting on one type of receptors and the other on another receptor for the same neurotransmitter. Such combinations have already been used with excellent results. Just as an example, the combination of the dexamethasone or the metopyrone suppression tests with the corticotropin-releasing hormone stimulation test has greatly clarified the type and magnitude of the secretory alterations of the hypothalamo-pituitary–adrenal axis in MDD, in anxiety disorders, in Eating Disorders, alcohol addiction, and normal or pathological aging (Van Bardeleben et al., 1988). The combination of the tests has been especially helpful in pointing out the level(s), and therefore the brain area, where the impairments take place and, as a consequence, the possible etiopathogenetical role of the hypothalamo-pituitary–adrenal dysfunctions in the development of the above mentioned disorders.

2.2. Molecular biology studies

So far, psychoneuroendocrinology has directed its attention to the investigation of the first and second steps of the biological activities of the brain, including the secretion of neurotransmitters–neuropeptides–neurohormones–peripheral hormones and the sensitivity of their pre- or postsynaptic receptors. Very little has been done to study the possible importance of alterations of neuronal membrane, or of second messenger production and function and, in general, on the cascade of events that precede the secretion of neurotransmitters, neuropeptides and hormones, or follow the stimulation–inhibition of their receptors.

Today, molecular biology in experimental animals has furnished data vital for the knowledge of the cellular activities involved in normal and pathological physical and brain life. Not much is known in humans, however, regarding the reciprocal influences of extra- and intracellular components and activities of neurons and endocrine cells for the development of mental disorders.

Some work in this regard has been done in experimental transgenic animals, in whom genetic deoxy-ribonucleic acid-linked alterations of specific hormonal functions have resulted in significant brain alterations and consequent behavioral changes (Marchetti et al., 1997). This suggests that similar spontaneously occurring alterations in humans may lead to specific psychopathologies. Obviously, the study of neuronal molecular biology in living humans seems to be impossible. However, it has been suggested, and sometimes demonstrated, that some peripheral cell functions mimic the neuronal ones. For instance, peripheral blood mononuclear cells have been observed to secrete neurotransmitters and neurohormones and to possess their specific receptors similarly to what occurs in the hypothalamus. Platelets have been reported to display pre- and postsynapyic receptors for some neurotransmitters acting like those of central neurons. It has never been properly investigated in experimental animals, and much less in humans whether or not central and peripheral neurons have similar intra- and extracellular components and functions. This field should be developed to offer new possibilities of understanding the mechanism of central neuronal functions in regard to psychoneuroendocrinology.

2.3. Psychoneuroimmunoandocrinology

In the last two decades, numerous investigations have revealed that the immune and the neuroendocrine functions amply interrelate in regulating the mechanisms of adaptation to internal and external stimuli. More recently, the central nervous system (CNS) has been observed to be part of a triangle that includes the neuroendocrine and the immune system, each of which maintains a strict control of the function of the others. Most of the work that has been done, however, regards the effects of the CNS on the immune and the endocrine system and much less on the contrary. In particular, the effects exerted by the immune system on the hypothalamus and suprahypothalamic centers are still poorly understood.

Some data obtained in experimental animals suggest that concomitant immune and neuroendocrine dysfunctions occurring during the pre- or postnatal life can result in anatomical alterations in the CNS with ensuing behavioral impairments. In humans, pre- or immediately postnatal immune alterations have been suggested to alter brain development and functions specifically leading to schizophrenia (Waksman, 1990; Ader et al., 1991). Data on the development of other psychopathologies are lacking and worth of further investigations.

In experimental animals, many studies have been done on the effects of pro- and anti-inflammatory cytokines on behavior, ranging from modulation of hunger, satiety, drinking, sleeping, sexual activity, socialization, exploratory behavior and avoidance (Ader et al., 1991). For humans, very few studies of the effects of cytokine on mentation and on behavior have been reported. However, alterations of cytokine secretion occurring in parallel with multiple hormonal impairments have been found in affective disorders, anxiety disorders, and in schizophrenia (Waksman, 1990; Muller and Ackenheil, 1998; Maes and

Van West, 1999), suggesting that they are possibly involved in the modulation of mental disorders.

2.4. Psychoneuroendocrinology of personality characteristics

As mentioned above, the study of the effects that neuroendocrine secretions exert on the development of personality characteristics in so-called normal subjects is mandatory to understand the modulatory importance of physiological hormonal fluctuations along a wide range of normal values, as the basis and core of possible subsequent psychopathologies. This type of study should define the background for the development of apparently minor personality variations, on the one side, and of feedback biochemical impairments, on the other, the two components possibly leading toward mental disorders. In other words, it should first be defined which psychological aspect is modulated by which hormonal secretion, starting from the wide range of hormonal and psychological variations in normal individuals, and then proceed to investigate their influences on the etiopathogenesis of mental disorders. Earlier, we have mentioned the example of testosterone modulation of aggressiveness. Most of the studies in the literature deal with highly pathological aggressiveness, or with other personality disorders and their possible biological background, but still too little is known about the normal fluctuations of personality characteristics in every day life and their relation to every day brain biochemical changes of function. This investigation should be extended to each personality characteristic of "normal" individuals, since each one of them can represent, even when minimally impaired, one of the basis or, at least, a very important component of successive psychopathologies. This type of study should be of importance in the field of prevention of mental disorders and in that of pharmacological correction of minor personological changes before they reach clinically significant levels.

2.5. Genetic studies

In the past decade, studies of the genetic background of mental disorders have been flourishing, being especially centered on the research of specific impairments of secretion of the main neurotransmitters and of their receptor sensitivity. Very scarce or no data are reported regarding the genetic regulation of neurohormones and neuropeptides both in normal and pathological mentation. This type of investigation should be developed, since it is well known that neurohormones and neuropeptides intervene in the development of mental disorders, possibly not only by acting as modulators of neurotransmitter functions but also as neurotransmitters by themselves, acting on their specific receptors. Genetically conditioned alterations of the physiological functions of neurohormones may be at the basis of the incapacity to adapt to internal and external events. This has been proposed to occur for the hypothalamo-pituitary–adrenal function in MDD by Van Praag (1996), as mentioned above, but it could be present in any other brain hormonal function, being responsible not only for specific endocrinopathies but also for psychopathologies.

2.6. Brain imaging

Researches using brain imaging techniques for the investigation of anatomical aspects and functions of whole brain and of specific brain nuclei are steadily growing, leading to a better understanding of CNS development and its physiological activity, and of the connections between various brain areas. Recently, these techniques have been applied to the studies of psychopathologies, in the hope to better clarify their brain pathological aspects. Electrical activities, blood flow and few data on distribution and function of neurotransmitter secretion and their receptor activities have been reported. But, again, no data exist on the secretion of neurohormones, neuropeptides and neurosteroids, and on their receptor functions.

2.7. Hormonal therapies

A psychoneuroendocrine field that should be developed further is that of hormonal or antihormonal therapies, as single or multidrug treatments of psychopathologies. The rational for this therapeutic approach is based, on one hand, on the observation that multiple hormonal impairments occur during mental disorders, and, on the other, that hormones may act as neurotransmitters or as modulators of neurotransmitter functions in the CNS — in both cases, being possibly involved in the pathogenesis of mental disorders.

In the past, hormonal therapies have been used as single treatments of mental disorder with very poor results. This was due to the scarce and approximate knowledge of the biochemical background of psychopathologies, the effects of hormones on CNS activity, and also to the lack of pure hormonal preparations. Recently, hormonal therapies have been tried again, but most of the therapeutic trials were not blind and controlled by placebo, and therefore their validity are still questionable.

Estrogens, androgens and thyroid hormones have been used in MDD in conjunction with classical psychotropic drugs to increase the receptor sensitivity of neurotransmitters, and therefore to potentiate the effects of antidepressants (Kleiber et al., 1979; Oppenheim, 1983; Halbreich, 1996; Aronson et al., 1996; Callahan et al., 1997). Glucocorticoids, antiglucocorticoids, endogenous opioids and anti-opioids, gonadal hormones, antigonadotropin drugs have been used in MDD, and colecystokinin, endogenous opioids and anti-opioids have been used in schizophrenia and in autism, with uncertain results (Crammer, 1986; Murphy et al., 1991; Wolkowitz et al., 1993). This field, however, is worth further investigation

with protocols that should take into consideration: (i) the specific neurohormone, neuropeptide, neurosteroid alterations of each type of mental pathology taken into consideration, and (ii) the effects that hormones can exert not only at the level of neurotransmitter secretions and receptor sensitivities but also on second-messenger function and intracellular component in general. The correction of a neurohormonal impairment can be mandatory for the prognosis of mental disorders, since it has already been amply demonstrated that the persistence of hormonal impairments in the course of mental disorders is an unfavourable prognostic parameter.

2.8. Neuropeptide and neurosteroid secretions

The actions exerted by neuropeptides and neurosteroids on CNS have been amply investigated in experimental animals, but are still poorly confirmed in humans.

It is well known that in experimental animals, neuropeptide and neurosteroids are secreted by the CNS and act in some cases and some areas by stimulating and inhibiting their specific receptors, and in other cases and other areas by modulating secretion and receptor sensitivity of classical neurotransmitters. This has been hardly controlled in humans, because of ethical reasons, poor feasibility, lack of compliance, lack of appropriate methodologies, and so on. However, it is extremely important to extend the animal studies to humans since neuropeptides and neurosteroids modulate cognition, affectivity and behavior in experimental animals and they might do the same in men. The effects of corticotropin-releasing hormone on mood, anxiety and psychological coping with stress (Holsboer, 1989), of vasopressin and oxytocin on learning and memory (De Wied, 1990), of neurosteroids on anxiety and depression (Rupprecht and Holsboer, 1999a,b), are well known for animals but not fully demonstrated in humans.

3. Conclusions

Psychoneuroendocrinology — or better yet, psychoneuroimmunoendocrinology — has been demonstrated in the past to be a good type of approach for the knowledge of normal and pathological brain function, and should not be abandoned in the future. Obviously, it cannot be used today in the same way that it has been used in the past, since, as mentioned above, the methodological approaches adopted up to now have given already the maximum of possible responses and we will go nowhere by using the same techniques over and over again in the future. We need to develop new methodologies to open new pathways but, mostly, to bring psychoneuroendocrine investigations in the context of multiple brain biological researches. The impaired secretion of one single neurohormone or neuropeptide, taken as an isolated phenomenon, will be severely pressed to offer a complete pathogenetic hypothesis for the development of a mental disorder but can be mandatory in the context of a complex pathoplastic situation, where neurotransmitters, neuropeptides, neurosteroids, neurohormones and immune components all interplay in a game of reciprocal stimulation–inhibition phenomena resulting in final breakdowns of brain physiological functions.

The discovery of the temporal position — primary or secondary — of neurohormonal impairments in this pathological game may be of importance from an etiopathogenetic point of view. But equally important is the knowledge of the effects on perpetuation of a mental disease exerted by neurohormonal dysfunctions, regardless of whether or not they are the primum movens of the psychopathology. It is well known, for instance, that a persistent hyperfunction of the hypothalamo-pituitary–adrenal system seems to be pathogenetically mandatory for the persistence of MDD, its resistance to any therapy, and its tendency to relapse. Today, this is leading towards the search for therapeutic interventions centered on the inhibition of corticotropin-releasing hormone, which seems to be promising. But very little is known about all the other neuropeptides and neurohormones.

At this point, we must have the courage to look over all our old data, file away some of them to revisit later some researches and hypotheses under new perspectives, and, in the meantime, proceed along totally different pathways, as we have done so successfully in the past. In our lives we have seen the birth and the abandonment of many scientific branches of research, and many hypotheses. And after a period of rejection, many of them have been taken up under different perspectives and with different methodological approaches, resulting in the discovery of important aspects of animal and human lives.

The future is in front of us.

References

Ader, R., Felten, D.L., Cohen, N., 1991. Psychoneuroimmunology. Academic Press, San Diego, USA.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual for Mental Disorders. 4th edition (III and IV editions) American Psychiatric Press, Washington, DC, 1994.

Aronson, R., Offman, H.J., Joffe, R.T., Naylor, C.D., 1996. Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. Arch. Gen. Psychiatry 53, 842–848.

Brambilla, F., Bridges, P.K., Endroczi, E., Heuser, G., 1978. Perspective In Psychochobiology. Akademiai Kiado Press, Budapest Hungary.

Brambilla, F., 1999. Neurohormonal alterations in eating disorders and obsessive compulsive disorders: a common biological basis? In: Bellodi, L., Brambilla, F. (Eds.), Eating Disorders and Obsessive Compulsive Disorder: An Etiopathogenetic Link? Centro Scientifico ed., Torino, Italy, pp. 77–98.

Brown, G.M., Koslow, S.H., Reichlin, S., 1984. Neuroendocrinology and Psychiatric Disorder. Raven Press, New York, USA.

Callahan, A.M., Frye, M.A., Marangell, L.B., George, M.S., Ketter, T.A., L'Herrou, T., Post, R.M., 1997. Comparative antidepressant effects of intravenous and intrathecal thyrotropin-releasing hormone: confound-

ing effects of tolerance and implications for therapeutics. Biol. Psychiatry 41, 264–272.
Chatelanat, P., 1978. Troubles mentaux symptomatiques d'affections médicales. Schweiz. Rundsch. Med. 67, 518–526.
Checkley, S., Arendt, J., 1984. Pharmacoendocrine studies of G.H., PRL, and melatonin in patients with affective illness. In: Koslow, G.M., Reichlin, S.H. (Eds.), Neuroendocrinology and Psychiatric Disorder. Raven Press, New York, pp. 165–190.
Crammer, J.L., 1986. Premenstrual depression, cortisol and estradiol treatment. Psychol. Med. 16, 451–455.
De Souza, E., Nemeroff, C.B., 1990. Corticotropin-releasing factor: basic and clinical studies of a neuropeptide. CRC Press, Boca Raton, USA.
De Wied, D., 1990. Neuropeptides — Basics and Perspectives. Elsevier, Amsterdam.
Finkelstein, J.W., Susman, E.J., Chinchilli, W.M., Kunselman, S.J., D'Arcangelo, M.R., Schwab, J., Demers, L.M., Liben, L.S., Lookingbill, G., Kulin, H.E., 1997. Estrogens and testosterone increases self-reported aggressive behaviors in hypogonadal adolescents. J. Clin. Endocrinol. Metab. 82, 2433–2438.
Fava, G.A., Sonino, N., Morphy, M.A., 1987. Major depression associated with endocrine disease. Psychiatr. Dev. 4, 321–348.
Gerra, G., Avanzini, P., Zaimovic, A., Fertonani, G., Caccavari, R., Delsignore, R., Gardini, F., Talarico, E., Lecchini, R., Maestri, D., Brambilla, F., 1996. Neurotransmitter and endocrine modulation of aggressive behavior and its components in normal humans. Behav. Brain Res. 81, 19–24.
Halbreich, U., 1987. Hormones and Depression. Raven Press, New York, USA.
Halbreich, U., 1996. Role of estrogens in depression of menopausal women. Proc. X World Congr. Psychiatr. pp. S1121–S1122.
Holsboer, F., 1989. Psychiatric implications of altered limbic–hypothalamic–pituitary–adrenocortical activity. Eur. Arch. Psychiatr. Neurol. Sci. 238, 302–322.
Hommer, D.W., Skolnick, P., Paul, S.M., 1987. The benzodiazepine/gaba receptor complex and anxiety. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 977–984.
Janowsky, D.S., Risch, S.C., 1987. Role of acetylcholine mechanisms in the affective disorders. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 527–534.
Jimerson, D.C., 1987. Role of dopamine mechanisms in the affective disorders. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 505–512.
Kleiber, E.L., Broverman, D.M., Vogel, W., Kobayashi, Y., 1979. Estrogen therapy for severe persistent depression in women. Arch. Gen. Psychiatry 36, 550–554.
Loosen, P.T., 1987. Thyroid hormones and affective state. In: Halbreich, U. (Ed.), Hormones and Depression. Raven Press, New York, pp. 357–383.
Losonczy, M.F., Davidson, M., Davis, K.L., 1987. The dopamine hypothesis of schizophrenia. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 715–726.
Lynn-Brown, S., Van Praag, H., 1991. The Role of Serotonin In Psychiatric Disorders. Brunner/Mazel, New York, USA.
Maes, M., Van West, D., 1999. Cytokine production in anorexia nervosa and obsessive compulsive disorder: a review. In: Bellodi, L., Brambilla, F. (Eds.), Eating Disorders and Obsessive Compulsive Disorder: An Etiopathogenetic Link? Centro Scientifico ed., Torino, Italy, pp. 111–124.
Marchetti, B., Morale, M.C., Gallo, F., 1997. Neurochemical, immunological and pharmacological assessments in a transgenic mouse model of the endocrine changes in depression. Aging Clin. Exp. Res. 4, 26–27, (suppl.).
Meltzer, H.Y., Lowy, M.T., 1987. The serotonin hypothesis of depression. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 513–526.
Monteleone, P., Catapano, F., Tortorella, A., Maj, M., 1999. Hormonal circadian rhythms in patients with eating disorders and in patients with obsessive–compulsive disorder. In: Bellodi, L., Brambilla, F. (Eds.), Eating Disorders and Obsessive Compulsive Disorder: An Etiopathogenetic Link? Centro Scientifico ed., Torino, Italy, pp. 99–110.
Muller, E.E., Nisticò, G., Scapagnini, U., 1977. Neurotransmitters and Anterior Pituitary Function. Academic Press, New York, USA.
Muller, N., Ackenheil, M., 1998. Psychoneuroimmunology and the cytokine action in the CNS: implications for psychiatric disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 1–33.
Murphy, B.E.P., Dhar, V., Ghadirian, A.M., Chouinard, G., Keller, R., 1991. Response to steroid suppression in major depression resistant to antidepressant therapy. J. Clin. Psychopharmacol. 11, 121–126.
Musselman, D.L., Nemeroff, C.B., 1996. Depression and endocrine disorders: focus on the thyroid and adrenal system. Br. J. Psychiatry 168, 123–128.
Nash, J.F., Meltzer, H.Y., 1991. Neurendocrine studies in psychiatric disorders. In: Lynn Brown, S., Van Praag, H.M. (Eds.), The Role of Serotonin in Psychiatric Disorders. Brunner/Mazel, New York, pp. 57–90.
Oppenheim, G., 1983. Estrogen in the treatment of depression: neuropharmacological mechanisms. Biol. Psychiatry 17, 721–725.
Pandey, G.N., Ali, S.I., Casper, R., Davis, J.M., 1984. Neuroendocrine studies in schizophrenia. In: Shah, N.S., Donald, G.D. (Eds.), Psychoneuroendocrine Dysfunction. Plenum, New York, pp. 503–548.
Rupprecht, R., Holsboer, F., 1999a. Neuroactive steroids: mechanisms of action and neuropharmacological perspectives. Trends Neurosci. 22, 410–416.
Rupprecht, R., Holsboer, F., 1999b. Neuropsychopharmacological properties of neuroactivesteroids. Steroids 64, 83–91.
Sachar, E., 1976. Hormones, Behavior And Psychopathology. Raven Press, New York, USA.
Schatzberg, A.F., Nemeroff, C., 1988. The Hypothalamic–Pitutary–Adrenal Axis: Physiology, Pathophysiology, and Psychiatric Implications. Raven Press, New York USA.
Shah, N.S., Donald, A.G., 1984. Psychoneuroendocrine Dysfunction. Plenum, New York, USA.
Siever, L.J., 1987. Role of noradrenergic mechanisms in the etiology of the affective disorders. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 493–504.
Van Bardeleben, V., Stalla, G.K., Muller, O.A., Holsboer, F., 1988. Blunting of ACTH response to human CRH in depressed patients is avoided by metyrapone pretreatment. Biol. Psychiatry 24, 782–786.
Van Praag, H.M., 1996. Serotonin-related, anxiety/aggression-driven, stressor-precipitated depression. A psychobiology hypothesis. Eur. Psychiatry 11, 57–67.
Waksman, B.H., 1990. Immunological Mechanisms in Neurologic and Psychiatric Disease. Raven Press, New York, USA.
Wehr, T.A., Goodwin, F.K., 1983. Biological rhythms in manic–depressive illness. In: Wehr, T.A., Goodwin, F.K. (Eds.), Circadian Rhythms In Psychiatry. Boxwood Press, Pacific Grove, CA, USA, pp. 129–184.
Wolkowitz, O., Resuss, V.I., Manfredi, E., Ingbar, J., Brizendine, L., Weingartner, H., 1993. Ketokonazole administration in hypercortisolemic depression. Am. J. Psychiatry 150, 810–812.