INVITED VIEWPOINT

What future for neuroendocrinology in psychiatry?

Fabrice Duval *, Marie-Claude Mokrani, Marc-Antoine Crocq

Centre Hospitalier, Rouffach, France

Received 4 January 2013; received in revised form 16 April 2013; accepted 18 April 2013

KEYWORDS

Hormones; Peptides; Psychiatry; Neuroendocrine challenge tests; Psychophysiology; Endocrinology

Summary

In psychiatry, neuroendocrine techniques were initially considered a potential "window into the brain" by indirectly marking central nervous system limbic dysfunction. At present this conception has evolved, owing to significant progress over the last decades demonstrating direct involvement of neuropeptides and neurohormones in psychiatric diseases. In a synchronic perspective, neuroendocrine investigations evaluate a functional status at a given moment in the evolution of the disease, which results from both etiopathogenic processes and compensatory homeostatic mechanisms. These vital physiological changes appear to be potential targets for novel hormonally based pharmacotherapies. However, in the past few years, the interest for the study of neuroendocrine dysregulations in psychiatric patients has declined. In order to better understand this relative disinterest, this article will attempt to shed light on strengths and limitations of the neuroendocrine approaches in psychiatry. It is necessary to bear in mind that the usefulness of these techniques in the clinical, pathophysiological and therapeutic fields depends largely on the selectivity of stimuli and the appropriateness of the methodologies used. Owing to the complexity of the clinical phenomena, multifactorial approaches (combining several neuroendocrine challenge tests to imaging, immunological, neurophysiological, neurochemical and/or genetic techniques) are to be privileged in psychiatric investigations. Despite the inherent limitations of these approaches, due to their technical and ethical constraints, the neuroendocrine strategy can inform modern clinical practice and lead to new breakthroughs in future science and practice.

© 2013 Elsevier Ltd. All rights reserved.

What a long way since 1908, when Laignel Lavastine laid out the first concepts of endocrinological psychiatry in Dijon at a psychiatric congress entitled "Des troubles psychiques par perturbations des glandes à sécrétion interne" (mental disorders due to disturbances of endocrine glands). During the last third of the 20th century, the interest of psychiatrists and researchers shifted gradually from the study of mental disorders associated with endocrine diseases (such as Graves' disease, Cushing’s syndrome, Addison's disease), toward the study of endocrine symptoms as part of psychiatric disorders. This approach in turn generated enthusiasm followed by skepticism. Initial enthusiasm in the 1970s–1980s, as it seemed that paraclinical tests would become available to validate nosography, and that specific markers would be paired with clinical entities. A typical example is the dexamethasone suppression test (DST) for melancholia (Carroll et al., 1981). Skepticism followed, because it was quickly realized that it was impossible to validate a biomarker as long as...
as valid clinical definitions did not exist. Nevertheless, in the same way that high blood glucose is the biological criterion for diabetes mellitus, it was expected by some authors attempting to construct a more "scientific" psychiatric nosology (Kendler, 1990), that specific neuroendocrine abnormalities could have their place in future diagnostic algorithms. Unfortunately, their hopes have been disappointed.

Presently, the objectives of neuroendocrinology in psychiatry have become more pragmatic, even though a number of psychiatrists are still mourning a certain magical thinking which led to believe that biological investigations would be able to make the diagnosis. In our current state of knowledge, developing a "biological symptomatology" is out of the question. Biology cannot substitute for clinical observation, and is only meaningful when interpreted in a clinical context. It is therefore essential to keep in mind that neuroendocrine investigations remain valuable tools, available to clinicians and researchers, but that their relevance depends on the clinical context in which they are used. Despite the progress in biotechnology, it is obvious that neuroendocrine investigations are currently becoming less and less used in psychiatry. One might well wonder why and whether this disinterest is justified.

Some facts

When analyzing the number of articles published in psychoneuroendocrinology since 1975, it appears that the percentage of work carried out in psychiatry — i.e., conducted among inpatients or outpatients — has declined drastically in recent years (down to about 15% in 2012). In the 1980s, the "golden age" of psychiatric neuroendocrinology, the proportion was about one third of the articles (Fig. 1). One can also notice that over half of the articles currently published in psychoneuroendocrinology in the field of psychiatry concern, at least partly, investigations of the hypothalamic-pituitary-adrenocortical (HPA) axis. Given the role of stress in precipitating psychiatric illnesses, is the HPA stress axis the Holy Grail of psychobiology? The question is therefore whether the applications of neuroendocrinology in psychiatry have already been exhaustively covered; in other words, is there still something to find in this field? One would be tempted to reply "no," since, at first sight, "neuroendocrinology" has nearly disappeared from the list of topics at psychiatric meetings.

Paradoxically, hormones have never been so much "in fashion," both in the general public (with the sometimes reckless use of hormonal dietary supplements such as androgenic steroids, dehydroepiandrosterone [DHEA], testosterone "boosters," etc.), and in medical therapy (e.g., estrogen, testosterone, gonadotropin-releasing hormone agonists, oxytocin, melatonin, etc.). In the treatment of major depression, the effectiveness of adjuvant therapies based on thyroid hormones is well documented (for review see Joffe, 2011). Recently, agomelatine, a melatonic agonist (MT1 and MT2 receptors) and serotonin 5-HT2C receptor antagonist, has been marketed as an antidepressant (Hickie and Rogers, 2011). However, studies that are cited by the pharmaceutical company (Hajak, 2012) to argue for the involvement of melatonin in depression date back to the late 1980s (Souët et al., 1989), whereas a more recent study failed to show a difference in the mean nocturnal secretion of melatonin between controls and depressed patients (Crasson et al., 2004). This highlights the need for further studies on melatonin secretion during depressive states and recovery. On the other hand, anti-glucocorticoids (such as anti-corticotropin-releasing hormone CRH1 receptors), which are still under development, may lead to new opportunities in the treatment of affective disorders by rectifying HPA disturbances (Ising and Holsboer, 2007), although, the only controlled study investigating a CRH1 receptor antagonist was negative (Binneman et al., 2008). Moreover, resonating with some recent studies (Duval et al., 2010), thyrotropin-releasing hormone (TRH) agonists, administered via a nasal spray (Kubek et al., 2009), might be used, in the near future, in suicide prevention.

Neuroendocrine investigations in psychiatry: pros and cons

Which strategy to choose?

Basically, hormones in psychiatry may be assessed by measuring their "unstimulated" concentration in the urine, saliva, cerebrospinal fluid, or blood — the latter two being rather invasive investigations. The "one sampling strategy" is hindered by the fact that plasma hormone concentration reflects the interaction of several related rhythmic variables like hormone synthesis, secretion, transport and metabolism, and will vary according to the stage of each variable at the time of measurement (Haus, 2007). Thus, repeating sampling is preferable in order to take into account chronobiological variations. For instance, while depressed patients do not usually show obvious thyroid disease, it has been consistently found that circadian thyrotropin (TSH) secretion is lower in such patients than in control subjects, especially in the evening and at night (Jackson, 1998). However, to be valid
such chronobiological approaches require a synchronization of the patients’ environments, since many factors, both internal and external (i.e., “masking” factors), can influence biological rhythms. These stringent experimental protocols can only be performed in hospital.

There is considerable evidence that the secretion of the hypothalamic hypophysiotropic hormones is controlled by the classical neurotransmitters including serotonin (5-HT), norepinephrine (NA), dopamine (DA), and acetylcholine (ACh), all previously posited to play a preeminent role in the pathophysiology of affective, anxiety, and psychotic disorders. Given the links between the limbic system and the pituitary through the hypothalamus, it is logical to assume that the biological abnormalities that affect the activity of the limbic system produce neuroendocrine abnormalities—which are measurable by more and more efficient laboratory assays. Nevertheless, despite those highly sensitive assays, it is rare, under “unstimulated” conditions, to find hormonal levels outside of the normal range in psychiatric patients.

Dynamic neuroendocrine tests (Table 1) have the advantage over “static” investigations to assess the functionality of target biosystems since they destabilize the homeostatic balance and, therefore, may be used to better characterize heterogeneous bio-clinical states. This characterization may lead to different therapeutic strategies. For instance, according to many studies in depression, the presence of a positive (or abnormal) neuroendocrine test suggests the need for antidepressant somatic therapy. However, most studies have examined a single hormonal response to a single neuroendocrine challenge; this strategy cannot be considered sufficient in the evaluation of the functional state of the endocrine system in psychiatric diseases. Combining a series of neuroendocrine challenge tests represents a multisystem approach to the study of endocrine abnormalities in psychiatry (Amsterdam et al., 1983; Mokrani et al., 1997; Duval et al., 2006). This strategy may provide important information on pathophysiology, and offers an opportunity to identify patterns of hormonal response abnormalities in subgroup of patients. While patients (especially depressives) easily give their informed consent to such investigations, which are perceived as a means to objectify their disease process, neuroendocrine tests are rarely performed routinely in most psychiatric units, since they need to be conducted by suitably trained staff. This is why the more sophisticated procedures are restricted to devoted research units, in particular when nocturnal tests are performed such as the 2300 h TRH (protirelin)-TSH/prolactin (PRL) stimulation test, and the light-induced melatonin suppression test.

One may remark that neuroendocrine investigations in psychiatry may find applications in three different contexts: (1) clinical, in order to identify trait or state markers of clinical entities and/or behavior such as suicidal behavior (Coccaro et al., 1989; Corrêa et al., 2002); (2) pathophysiological, to evaluate the neurobiological mechanisms involved, depending on the stimuli used; and (3) therapeutic, to monitor the evolution of state-markers (Bowie and Bealini, 1985; Duval et al., 1996), to assist in the therapeutic choice via predictive markers (Ansseau et al., 1988; Ising et al., 2007; Duval et al., 2013), and to study the “in vivo” mechanisms of action of psychotropic drugs in humans — via studies performed before, during and after treatment (Mölle et al., 1984; Shapira et al., 1989; Duval et al., 1993; Schüle et al., 2009). In the medium term, one may hope that it will be possible to rationalize the choice of pharmacotherapy taking into account not only the clinical features but also the “biological state” since it may influence therapeutic response. Moreover, neuroendocrinology could improve the drug development process. With respect to the HPA axis, a large body of research now suggests that normalization of impaired corticosteroid receptor signaling — as evidenced by an exaggerated ACTH/cortisol response to the combined dexamethasone (DEX)/CRH test — could be a final common pathway of antidepressant drug action (Holsboer, 2000).

### Table 1 Dynamic neuroendocrine tests in psychiatry.

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Hormones Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dexamethasone suppression test (DST)</td>
<td>Cortisol, ACTH, PRL, TSH, GH</td>
</tr>
<tr>
<td>2. Corticotropin-releasing hormone stimulation test (CRH)</td>
<td>ACTH, Cortisol, Aldosterone</td>
</tr>
<tr>
<td>3. Combined dexamethasone/CRH stimulation test (DEX/CRH)</td>
<td>ACTH, Cortisol</td>
</tr>
<tr>
<td>4. Protirelin stimulation test (TRH)</td>
<td>TSH, PRL, L-dopa</td>
</tr>
<tr>
<td>5. GH stimulation tests</td>
<td>GHHR, Clonidine, Apomorphine, Insulin</td>
</tr>
<tr>
<td>6. PRL suppression tests</td>
<td>Apomorphine, Bromocriptine, L-dopa, Amphetamine</td>
</tr>
<tr>
<td>7. “Serotonergic” tests (stimulation of PRL, ACTH/cortisol, GH secretion)</td>
<td>L-tryptophan, 5-hydroxytryptophan, m-Chlorophenylpiperazine, Clomipramine, 5-HT1a receptor agonists</td>
</tr>
<tr>
<td>8. “Cholinergic” tests (stimulation of ACTH/cortisol secretion)</td>
<td>Arecoline, Physostigmine</td>
</tr>
</tbody>
</table>

a. Large application.  
b. Specific investigation.  
c. Limited application.
During antidepressant treatment neuroendocrine response to DEX/CRH test attenuates. This attenuation could predict (1) acute antidepressant response after 2-3 weeks of treatment (Ising et al., 2007), and (2) medium-term outcome in depressed patients: non-suppression in the DEX/CRH indicates a higher relapse risk within 6 months in patients tested at discharge (Zobel et al., 2001), and in outpatients tested after 8 weeks of treatment (Appelhof et al., 2006). Comparable results have been reported with the HPT axis after 2 weeks of antidepressant treatment: (1) an abnormal ΔTSH test (i.e., difference between 0800 h and 2300 h TSH response to TRH tests on the same day) could predict non-remission, and (2) ΔTSH normalization is associated with subsequent remission (Duval et al., 2013). Taken together these findings suggest that, when available, reliable biomarkers could help to judge the efficacy of a novel drug candidate (Ising et al., 2007).

Although these three contexts — diagnostic, pathophysiological and therapeutic — are inseparable in practice, it may happen that a marker is relevant in one of them (e.g., therapy) but not in another (e.g., diagnosis). This is also a further justification for neuroendocrine test batteries in psychiatry, the sequence of the tests being carefully determined in order to minimize bias due to interferences between the tests (e.g., the DST should be performed after the TRH test as cortisol inhibits the secretion of TSH). This multivariate approach, which is the most suitable in theory since the pathogenesis of major psychiatric disorders is likely multifactorial, is not without raising a number of practical constraints. Here we touch other limitations of this type of explorations that are ethical and technical but also economic. For example, the cost for a human CRH dose (100 µg) is about 300 € — in comparison a protirelin ampoule of 200 µg (for the TRH test) is much more affordable (ca. 15 €).

It is undeniable that the neuroendocrine strategy can characterize the hypothalamic-pituitary and pineal dysfunction of certain clinical entities, and evaluate the functionality of some neurotransmitter systems by using appropriate pharmacological stimuli. However, it appears necessary, in order to generate and validate new pathophysiological hypotheses, to associate neuroendocrine investigations to other paraclinical approaches (e.g., neurochemistry, neuroimmunology, genetics, molecular biology, neurophysiology, nuclear magnetic resonance spectroscopy, other types of neuroimaging, etc.) (van Honk and Pruessner, 2010). Indeed, most psychiatric diseases do not have defined single causes, and it is believed that multiple genes or gene families may trigger disease manifestation while non-genetic factors may play a key role in the development and progression of the illness. Endocrine secretions represent one of the principal links between the environment and the genes, and it has been suggested that endocrine alterations in psychiatric patients could be linked to genetic polymorphisms. For instance, Menke et al. (2013) showed that plasma cortisol, ACTH, and dexamethasone levels in major depression might be influenced by genetic polymorphisms in the FKBP5 binding protein, which interacts with the glucocorticoid receptor. Among the other paraclinical approaches, neuroimaging, despite promising structural and functional findings in patient groups, has currently provided no valuable biomarkers for a given psychiatric patient (Savitz et al., 2013). Thus, using neuroendocrine information in conjunction with genetics and brain imaging data is expected to significantly improve our understanding of both normal and pathological variability of brain organization. This multivariate approach should lead to the development of biomarkers most relevant in view of a future personalized medicine.

Limiting factors

A number of factors may compromise the reliable and valid assessment of hormones in psychiatric conditions. In brief, such factors include unreliable clinical diagnosis, the contribution of extraneous variables (age, sex, weight loss or gain, menstrual status), the non specific effect of stress or hospitalization, the confounding effect of intercurrent medical illness, the direct biological effects of medication, treatment or withdrawal from drugs or alcohol (Kupfer and Thase, 1989). Given the difficulty to control all these factors, it is not surprising that so many false leads and unreplicated findings plagued psychoneuroendocrinology.

Among the solutions, it has been proposed to carefully match patients and controls, and to perform the tests after a relatively long medication-free washout period. The latter point raises an ethical issue (especially when the suicide risk is obvious), although an insufficient washout period is a major confounding factor in assessing neurotransmitter function. For instance, in the assessment of the functionality of the α2-NA postsynaptic receptor by means of the growth hormone (GH) response to clonidine (CLO; an α2-NA receptor agonist), the results depend to a large extent on the quality of prior therapy withdrawal. In depressed patients, the GH response to CLO is often blunted (Siever and Uhde, 1984). However, antidepressants (especially tricyclics), owing to their mechanism of action, induce a sustainable hyposensitivity of α2-NA receptors. In order to rule out the potential long-lasting effects of antidepressant treatment, it has been suggested that a washout period of at least 3 weeks is necessary (Schittekat et al., 1989); this constraint limits the use of the CLO test as a NA probe in psychiatry. In fact, this consideration can be extended to other challenge tests, such as the apomorphine test (APO; a direct DA receptor agonist), whose results depend directly on the quality of antipsychotic withdrawal (Mokrani et al., 1995). Nowadays, it is rare to have the opportunity in psychiatry to evaluate psychotropic drug-naïve hospitalized patients, this is probably the major limiting factor in the use of neuroendocrine strategy in the assessment of specific neurotransmitter function.

Another important issue, is the lack of strict standardization of the challenge tests (e.g., with regard to the dose of the compound administered, assay used to measure hormones, threshold for abnormal response, and the moment in the day when the test is performed) that limit the comparability of results from different studies. At present, it seems hardly possible to create international databases in psychiatry from the results of neuroendocrine tests, contrary to what is achieved in other branches of medicine. This explains why the introduction of endocrine parameters in diagnostic algorithms, although theoretically desirable, is not feasible because of methodological obstacles inherent to these
investigations. Moreover, when evaluating the neurotransmitter activity at postsynaptic receptor sites, the selectivity of the pharmacologic stimuli used is often questionable: this greatly limits the pathophysiologic value of the results. For instance, 5-HT activity has been evaluated with m-chlorophenylpiperazine (m-CPP), but this compound stimulates 5-HT1B/1D receptors, antagonizes 5-HT2A receptors, binds to α2, α1 and β-NA, DA receptors and stimulates the catecholamine release. Buspirone, gepirone, ipsapirone, as probes of 5HT1A function appear to be of limited value since the responses are also mediated by DA receptor blockade. Clomipramine (at low dose), like citalopram or its 5-enantiomer (escitalopram), inhibits 5-HT uptake; but since these compounds are not 5-HT releasers, the hormone responses are rather weak. Fenfluramine (FEN) promotes a rapid release of 5-HT and inhibits its uptake, and may function in 5-HT receptor agonist (via the 5HT1A/2 receptors). Both 5-TR and the racemate (dl-FEN) have been used, but the former was a more specific 5-HT probe, lacking the DA and NA action of dl-FEN. In depressed patients, especially those with a history of suicidal behavior, PRL and HPA-hormone responses were blunted, suggesting impaired 5-HT activity in such patients (Corrêa et al., 2002). However, dl-FEN and d-FEN were withdrawn from the market in 1997, and since that time clinicians and researchers have been waiting for specific and efficient neuroendocrine tests in the evaluation of 5-HT system in psychiatric patients.

So much to discover . . .

The brain is the most fertile of all endocrine organs, producing neuropeptide hormones within and beyond the boundaries of the endocrine hypothalamus. Although much as been learned about hormonal dysfunctions in major psychiatric diseases for the past 50 years, it is clear that there is no simple answer to the question of whether altered endocrine activity is directly related to the pathophysiology of the psychiatric illnesses, or acts as a vulnerability factor, or even may represent a compensatory mechanism.

This latter hypothesis may be illustrated by the HPT axis activity in depressed patients. A substantial body of evidence suggests that TRH acts as a homeostatic modulator in the central nervous system (for review see Gary et al., 2003). In depressed patients, TRH hypersecretion leading to downregulation of the TRH receptors of the pituitary thyrotrophs (Loosen and Prange, 1982) as evidenced by reduced TSH response to TRH may be seen as a compensatory mechanism in order to normalize 5-HT activity (Duval et al., 1999). We have hypothesized that a decrease in 5-HT function triggers an increased TRH secretion that secondarily normalizes 5-HT neurotransmission and also maintains normal thyroid hormone levels. Furthermore, we have also recently suggested that this compensatory mechanism is not effective in depressed patients with a history of suicidal behavior (Duval et al., 2010), which could play a role in the sustained 5-HT hypoactivity consistently linked to suicidal behavior (Mann and Currier, 2007). However, additional research is needed to precisely the biological processes underlying the failure of this compensatory mechanism (i.e., lack of increased TRH secretion in response to decreased 5-HT activity) in patients with suicidal behavior. The elucidation of such processes could lead to new psychopharmacological approaches.

The diathesis-stress model views major psychiatric disorders as the result of an interaction between genetic, personal, environmental and cultural factors. The HPA stress axis is undoubtedly the most extensively investigated system in the pathophysiology of mood disorders. Nevertheless, comprehensive studies on the relationships between HPA-axis dysregulation and 5-HT, DA, NA, ACH, γ-aminobutyric acid (GABA), glutamate, vasopressin, oxytocin, cytokine activity in psychiatric patients are still warranted. In depression, it has been hypothesized that cortisol would be the biological link between stressful life events and the onset of depression. However, increased cortisol secretion secondary to CRH oversecretion from both hypothalamic and extrahypothalamic neurons (Lloyd and NemeroB, 2011) is only reliably recorded in severe (Carroll et al., 1981) and often psychotic depression (Schatzberg et al., 1985). Most depression occurs with normal cortisol or even slightly reduced cortisol secretion (Stokes et al., 1984; Strickland et al., 2002). In mild depression, social stress, which plays an important etiological role, generally does not induce chronic hypercortisolism. Thus, it has been suggested that hypercortisolism would be a marker for brain vulnerability to depression and not the proximal cause of depressed state (Strickland et al., 2002). Moreover, despite many studies suggesting that lowering HPA activity and clinical response are related since HPA axis hyperactivity is generally considered as a “state” marker for depression — it has been reported that restoration of the HPA system dysfunction is neither a necessary nor a sufficient determinant for acute antidepressant treatment response (Schüle et al., 2009). Furthermore, some studies have reported that the combined dexamethasone/CRH test remains abnormal in remitted bipolar patients (Watson et al., 2004), suggesting that HPA axis dysfunction could be a potential “trait” marker in bipolar disorder. Taken together, studies of the HPA axis in psychiatry have raised more questions than can currently be answered and thus suggest avenues for further exploration over the next decade.

So far, our knowledge of other peptide and hormone systems (such as somatostatin, vasopressin, oxytocin, neurotensin, melatonin, gonadotropin-releasing hormone...) involved in mood disorders are sketchy, and other psychiatric disorders, including schizophrenia, anxiety disorders, eating disorders, suicidal behavior and personality disorders should also be systematically evaluated. In this context, the neuroendocrine strategy still offers new insight in biology and treatment by delineating more homogeneous subgroups from a bio-clinical and therapeutic viewpoint. However, its possible expansion depends in part on the development of specific pharmacologic tools in order to better investigate the activity of neuropeptoids and receptors for the endocrine target hormones. These advances will consolidate the strengths of the neuroendocrine strategy in elucidating the specific mechanisms by which hormones affect brain function, as well as mechanisms underlying hormone changes during psychiatric states in a diachronic perspective.

Role of the funding sources

The authors received no funding in support of this work.
Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

We are grateful to Prof. Robert Dantzer for his invitation to submit this commentary, and thank Dr. Rose-Marie Bluthé for her editorial support.

References


