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INVITED VIEWPOINT

What future for neuroendocrinology in psychiatry?

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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.

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

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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

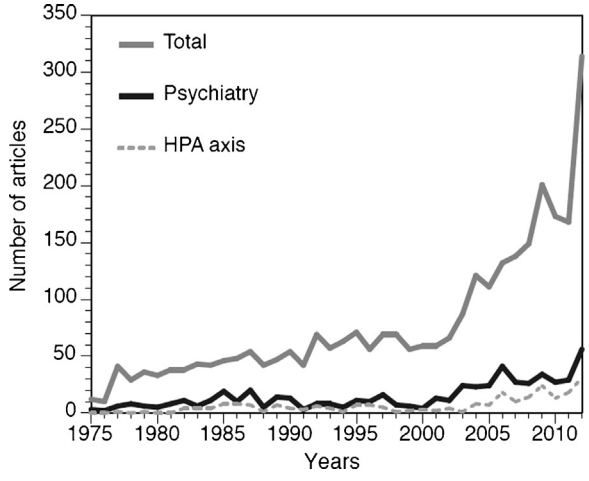

Figure 1 Number of articles published in psychoneuroendocrinology. Total: means the total number of articles; psychiatry: means the number of articles concerning studies carried out in psychiatric patients; HPA axis: means the number of articles studying hypothalamic-pituitary adrenal axis activity in psychiatric patients.

(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 melatonergic 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 (Souêtre 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, antiglucocorticoids (such as anti-corticotropin-releasing hormone CRH_1 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 CRH_1 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