The Hypothalamus in Schizophrenia Research: No Longer a Wallflower Existence

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Abstract: The hypothalamus is commonly believed to play only a subordinated role in schizophrenia. The present review attempts at condensing findings of the last two decades showing that hypothalamus is involved in many pathways found disturbed in schizophrenia (hypothalamus-pituitary-axis, hypothalamus-pituitary-thyroid axis, hypothalamus-pituitary-gonadal axis, metabolic syndrome, sleep-wakefulness cycle, and neuroimmune dysfunction). On the basis of this knowledge it is suggested to reconsider the place of the hypothalamus in the puzzle of schizophrenia.

Keywords: Hypothalamus, schizophrenia, hippocampus, depression, stress, neuroendocrinology, neuroimmunology.

1. INTRODUCTION

Schizophrenia is a severe, chronic brain disorder afflicting about 1% percent of the population. The disease mainly impairs multiple cognitive domains including memory, attention and executive function, and typically produces a lifetime of disability and severe emotional distress for affected individuals [1]. The clinical features of the disorder appear in the second to third decade of life. Normally, the age of onset is earlier in males than in females. The factors that give rise to the illness remain elusive. Intense clinical and basic research has shown that the nature of schizophrenia is complex [2, 3]. Like many other human diseases, the clinical syndrome recognised as schizophrenia may represent the termination of quite different pathogenic factors and pathways. Based on a plethora of neuroimaging, neuropathological, biochemical and genome studies over the last 25 years, it is clear that schizophrenia is not a pure functional disease without organic factors, and that both genetic susceptibility and environmental factors may contribute to its complex phenotype [4, 5]. In support of this, subtle brain structural and metabolic abnormalities have been found in almost all grey and white matter areas of the brain [5]. Moreover, the functional connectivity between different brain areas is known to be disturbed in schizophrenia [6-8]. There is evidence from several, replicated studies that the limbic system (especially the medial temporal lobe including parahippocampal gyrus, entorhinal cortex, and the amygdala), the heteromodal association cortices (dorsolateral prefrontal, cingulate, parietal and temporal cortex) and the thalamus show the most prominent structural and functional alterations in schizophrenia [9, 10]. Other brain structures are regarded to be less, or even only marginally, affected in schizophrenia. Until recently, the hypothalamus is thought to belong to the latter group. With this review we try to show that this important brain region is in many ways involved in the pathophysiology of schizophrenia, and that we therefore should reconsider the place of the hypothalamus in the puzzle of schizophrenia.

2. STRUCTURAL ABNORMALITIES OF THE HYPOTHALAMUS AND PITUITARY IN SCHIZOPHRENIA

2.1. Neuroanatomical Changes

The hypothalamus is a complex brain region encompassing numerous nuclei with different functions in the regulation of endocrine, autonomic and behavioural activities. The general organization of the hypothalamus is amazingly uniform in most mammalian species including man [11]. The hypothalamus forms the ventral part of the diencephalon and is connected with nearly every other brain area (including various limbic structures, brain stem nuclei, the thalamus, and the cerebral cortex) and the pituitary gland.

One of the well-known brain abnormalities in schizophrenia is the enlargement of the third ventricle, which already can be found in drug-naïve, first-episode patients, and which is therefore regarded to be of neurodevelopmental origin (reviewed in [12, 13]). This ventricle enlargement might be based on matter loss of the ventricle facing brain areas. Hence, hypothalamic structural abnormalities may exist in schizophrenia. However, the search for such structural deficits has yielded conflicting results. Early histological studies on postmortem brains of schizophrenics revealed a significant reduction of the thickness of periventricular grey matter [14], while recent neuroimaging studies demonstrate both decreased [15] and increased [16] total hypothalamic volumes. Only a few papers deal with the volumes of individual hypothalamic nuclei in schizophrenia. Using neuroimaging techniques, Goldstein et al.
[16] found increased volumes of the PVN nucleus and the mammillary bodies in schizophrenia, while postmortem investigations revealed decreased or unchanged volumes of these hypothalamic subregions [11, 17, 18]. The number of mammillary body neurons as well as the neuronal densities were significantly reduced in schizophrenia. This reduction was largely due to a decrease of the number of parvalbumin-immunoreactive neurons projecting to the anterior thalamus, which was reduced by more than 50% [18]. Interestingly, larger pituitary volumes were found in many patients with schizophrenia, which may be due to activation of the HPA axis (see below, [19-21]). Larger pituitary volumes in patients were found to be associated with less improvement in overall psychotic symptoms [21]. However, others have measured smaller pituitary volumes in first episode patients [22] and patients with established schizophrenia [19]. Reduction of the pituitary volume could be the consequence of repeated episodes of HPA axis hyperactivity [19]. It is currently not known, which cell populations are involved in pituitary volume changes in schizophrenia, but it has been assumed that volume increase is largely due to the effect of prolactin-elevating, neuroleptic drugs [20].

2.2. Cell Chemical Changes

The hypothalamus is known to be rich in various regulatory neuropeptides and other neuromodulators, of which some have been implicated in schizophrenia [11, 23]. Hence, efforts have been directed towards identifying alterations in the disease-related cellular expression of these chemical compounds in the hypothalamus. Pioneer work in this field was done by Mai et al. [24], who demonstrated reduced neurophysin immunoactivity in PVN neurons in schizophrenia. Since neurophysin is the carrier protein of the oxytocin and vasopressin, their results could be taken as a first hint for an involvement of the classical hypothalmo-hypophysial neuropeptide system in schizophrenia. However, further research revealed that both the number of vasopressin-expressing SON neurons and the hypothalamic concentration of this peptide are normal in schizophrenics without polydipsia [25]. Enhanced vasopressin secretion can be observed in schizophrenia patients suffering from polydipsia [26]. Unfortunately, no studies are yet available with regard to cellular oxytocin expression in schizophrenia, although several lines of evidence point to an important role of this hormone in social behaviour in schizophrenia [27]. The hypothalamic expression of the oxytocin/vasopressin degrading enzyme insulin regulated aminopeptidase is significantly reduced in schizophrenia (unpublished data). The densities of beta-endorphin immunoreactive arcuate nucleus neurons and of beta-endorphin-innervated PVN neurons were found to be reduced in schizophrenia [28]. Interestingly, we recently could show that in post-mortem brains of haloperidol-treated subjects with schizophrenia the cysteine protease cathepsin K is strongly upregulated. This seems to be a result of medication [29]. This enzyme is capable of selectively liberating enkephalin from beta-endorphin, which (1) may have consequences for the metabolism of endogenous opiates in schizophrenia, and (2) is reflected in the hypothalamic distribution pattern of beta-endorphin immunoreactivity [30]. In a series of papers our group dealt with the expression of nNOS in hypothalamic neurons in schizophrenia. Nitric oxide is an important player in the pathophysiology of schizophrenia [31] and is involved in the control of the release of some hypothalamic neuropeptides [32]. We could show that the density of NOS-immunoreactive PVN, but not SON, neurons is reduced in schizophrenia [11, 33]. This might have consequences for our understanding of HPA axis abnormalities in schizophrenia (see below). Later, we studied nNOS-immunoreactive neurons in the SCN nucleus and also found a decreased numerical density in schizophrenia [34, 35]. Lastly, we performed a morphometric analysis of beacon-ubiquitin-5 like immunoreactive neurons, a peptide which is involved in the regulation of energy metabolism, food intake, and obesity. We found an increased neuronal expression of beacon in the PVN and SON nuclei of schizophrenics. However, a significant increase in beacon-expressing SON neurons was also seen in adipose, non-psychotic individuals in comparison with normal-weight controls [36]. Thus, beacon is currently the only neuroactive compound that was found increased and not reduced in its hypothalamic expression in schizophrenia. A yet unanswered question is, whether the reduced expression of a certain peptide or protein in schizophrenia is due to the loss of generating cells, or if the decrease happens because still existing neurons are functionally compromised. Interestingly, many of the above described changes are not schizophrenia-specific, but can also be found in hypothalamic neurons of individuals with major depression, where they may appear even more pronounced than in schizophrenia (summarised in the Table 1).

3. STRESS, THE HPA AXIS, AND SCHIZOPHRENIA

An association between psychosocial stress exposure and schizophrenia has long been documented (reviewed in detail in [3, 23] and many others). By governing a cascade of hormonal events, the HPA axis mediates the biological response to stress and the regulatory feedback inhibition to the brain. In response to several stressors, CRH is released from the PVN of the hypothalamus. CRH triggers the secretion of ACTH from the pituitary, which in turn provokes the secretion of glucocorticoids from the adrenal glands. Glucocorticoids (with cortisol being the most important in humans), are multitaled hormones, which modulate a plethora of physiological events that include cardiovascular function, immunity, cell metabolism and various brain functions. In man, cortisol acts to synchronise other components of the stress response and alter the excitability of neural networks [3, 37, 38 and others]. Interestingly, the administration of corticosteroids for therapeutic reasons is associated with increased risk for psychosis [3]. Since the highest concentrations of glucocorticoid receptors are found in the hippocampus and other limbic structures [37, 38], the interaction between these brain regions and the hypothalamus (and the CRH-producing PVN neurons in particular) is assumed to be central to a proper regulation of HPA axis activity during stress. With regard to the functional feedback loop, cortisol overproduction may result in a disturbed interplay between stressed (partially injured?) limbic areas and the hypothalamus (sometimes referred to as the “glucocorticoid cascade hypothesis”, [3, 37, 39]). Persistently elevated cortisol levels are neurotoxic, and the hippocampus may be especially sensitive to these effects. Increased glucocorticoids lead, for example, to an inhibition of hippocampal neurogenesis, re-
duction of neuronal dendrites, and increased neuronal death, which may functionally compromise this brain region [3, 39]. This damage to the hippocampus may have far-reaching consequences with regard to cognitive processes which are known to be disturbed in schizophrenia [3, 40] and for its interaction with the hypothalamus. So, there is direct evidence that suppression of adult hippocampal neurogenesis leads to an increased HPA axis response [41]. And indeed, there is evidence that neurogenesis (or more precisely, neural stem cell proliferation) is reduced in post-mortem brains of subjects with schizophrenia [42]. A major outcome at the level of the hypothalamus is that CRH production (and the subsequent ACTH release) are not dampened, and the HPA axis continues to be overactive [3]. The aforementioned altered pituitary volumes may be a morphological correlate of this persistently hyperactive HPA axis. The functional dis-

<table>
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<th>Parameter</th>
<th>Schizophrenia</th>
<th>Affective disorder</th>
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<tr>
<td>Total Volume</td>
<td>decreased [15]</td>
<td>decreased [99]</td>
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<tr>
<td>Volumes of individual nuclei</td>
<td>increased [16]</td>
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<td>Periventricular grey</td>
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<td>Cell densities</td>
<td>in mammillary bodies reduced [18]</td>
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<td>in PVN, SON unchanged [11]</td>
<td>in PVN, SON reduced [100]</td>
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<td>Cell expression patterns</td>
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<td>Pituitary volume</td>
<td>increased [19, 20, 21]</td>
<td>unchanged in medication-free patients [103]</td>
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<td>decreased [19, 22]</td>
<td>increased in bipolar disorder [104]</td>
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Table 1. Comparison of Hypothalamic Abnormalities in Schizophrenia and Affective Disorder

Although typically associated with affective disorder, there is compelling evidence for hyperactivity of the HPA axis with hypercortisolism also in schizophrenia (for recent reviews see [3, 23, 46, 47]. An increased baseline cortisol secretion (and elevated ACTH) can be measured in patients
with schizophrenia not only as a result of antipsychotic medication, but already in first-episode, drug-naïve patients [3, 46, 48-50]. Interestingly, comparison of pre-drug cortisol levels reveal that patients who are most responsive to neuroleptics manifest higher pretreatment cortisol than those who are not responders [51]. The question is: Are these changes triggered by elevated CRH or other hypothalamic peptides as it is to be expected under the influence of stress? Unlike in depression, only few papers directly deal with this topic in schizophrenia. Early work has shown that the concentration of CRH in the CSF is slightly but significantly higher in schizophrenic patients than in control subjects [52]. CRF concentrations are not significantly related to severity of psychosis and further rise when haloperidol is withdrawn or replaced by placebo [53]. Genetic variations in CRH binding proteins have recently been reported to be linked to suicidal behaviour of schizophrenics [54].

Dynamic challenges of the HPA have provided conflicting results, but the dexamethasone suppression test (normally inhibiting ACTH and cortisol secretion) is abnormal in 50% of subjects with schizophrenia (reviewed in [49]). These findings aside, there is yet no direct evidence in favour of an increased expression of CRH in hypothalamic neurons, or elevated hypothalamic concentrations of the peptide, in schizophrenia. Vasopressin and oxytocin are other neuropeptides that may influence ACTH release, and thereby may contribute to HPA axis hyperactivity. While there is clear evidence that the cellular expression of these neurohormones is upregulated in depression [55], vasopressin concentrations, secretion and hypothalamic cell number appear to be normal in schizophrenia [25, 26]. However, the application of metoclopramide (a selective stimulator of vasopressin release) induces an elevated ACTH secretion in patients with schizophrenia, indicating an increased pituitary responsiveness to vasopressin [49]. Nitric oxide is able to inhibit the release of CRH, oxytocin and vasopressin. Hence, the observed significant reduction of the NO-generating enzyme NOS expression in schizophrenia [11] may contribute to a disinhibition of all three hormonal components which are under suspicion to trigger HPA overactivity: CRH, vasopressin and oxytocin [44]. Plasma oxytocin levels are diminished in schizophrenia patients with neuroendocrine dysfunction and emotional deficits [56]. Interestingly, oxytocin has been suggested to act as an endogenous antipsychotic, and oxytocin knockout mice are a good animal paradigm for schizophrenia [57].

In sum it can be said that the HPA axis is deflected in schizophrenia, probably as part of a long-lasting, deviant stress response. The age of onset of this stress may be very early – even during fetal development [3, 58, 59]. The fatal consequences of elevated cortisol, however, are more pronounced in the hippocampus and other limbic structures than in the hypothalamus itself, where the problems most probably originate.

4. OTHER NEUROENDOCRINE HORMONE AXES COMPROMISED IN SCHIZOPHRENIA

Thyroid dysfunction is relatively common in patients with schizophrenia, which is possibly related to a genetic linkage of the disorders and to antipsychotic treatment [60]. The thyroid gland is the endpoint of another neuroendocrine hormone cascade which begins in the hypothalamus, the

HPT axis. There, the tripeptide TRH is synthesised in a subpopulation of neurons. The main function of TRH is to stimulate the release of TSH from pituitary thyrotophs. A blunted TSH response to intravenously administered TRH has been consistently observed in many patients with major depression and some patients with schizophrenia [61]. It has been suggested that a blunted TSH response predicts a good therapeutic response to haloperidol in schizophrenia. CSF concentrations of TRH were found to be normal in patients with schizophrenia [52, 62], but elevated in patients with schizoaffective disorder [62]. Remarkably, many schizophrenic patients have anti-thyroid antibodies [63]. Thus, possible disturbances within the HPT gland axis in schizophrenia are likely to be at the level of the pituitary or the thyroid rather than the hypothalamus itself.

The typical onset of schizophrenia during late adolescence and early adulthood has stimulated interest in the potential contribution of HPG axis abnormalities to this disorder. While some investigations of reproductive hormone function in men with schizophrenia suggest diminished activity of the HPG axis, it was later found that schizophrenic patients do not show significant differences from healthy volunteers with respect to LH pulsatility, response to GRH challenge, and testosterone secretion [64]. However, plasma levels of testosterone and free testosterone in the patients with negative symptoms were significantly lower than those in normal controls. Furthermore, plasma levels of FSH and LH, in the patients with predominant negative symptoms were significantly lower than those in the normal controls [65]. Interestingly, treatment of patients with hypothalamic GRH hormone has beneficial effects on positive and negative symptoms of schizophrenics [66, 67].

A particular aspect of the influence of hypothalamic factors on sexual and other body functions is the well-known hyperprolactinaemia of patients with schizophrenia. It is established that hyperprolactinaemia causes suppression of the reproductive endocrine axis (menstrual dysfunction) and consequent bone mineral density loss. Most antipsychotic agents antagonise the actions of endogenous dopamine (DA) at DA-2 receptors in the brain. The propensity of antipsychotic agents to cause hyperprolactinaemia is related to their potency in antagonising DA-2 receptors on the lactotroph cells of the anterior pituitary (for review see [68-70]). Thus, hyperprolactinaemia in schizophrenia should be regarded an unwanted side-effect of antipsychotic medication.

5. METABOLIC ABNORMALITIES IN SCHIZOPHRENIA AND THE HYPOTHALAMUS

Patients with schizophrenia often suffer from the so-called “metabolic syndrome” which is characterized by visceral obesity, type 2 diabetes, elevated lipid levels and hypertension, and decreased sensitivity to insulin (for review see [71]). Treatment with atypical (but not with classical) neuroleptics either initiates or further increases the metabolic problems of many (but not all) schizophrenics. This comorbidity contributes to an increased risk of cardiovascular diseases in mentally ill patients [72], and is a major reason for non-compliance of patients [73]. Interestingly, drug-naïve schizophrenics may already show symptoms of the metabolic syndrome [49, 74, 75]. There is now some evidence in
favour of stress being a common mediator of overactivity of the HPA axis (see above) and metabolic abnormalities in patients with schizophrenia and the metabolic syndrome [49, 74, 75]. Weight gain in patients suffering from schizophrenia is very often accompanied by increased food intake. There are three primary neuroendocrine components that control food intake: (1) the afferent peripheric system that is stimulated in response to a meal, (2) the CNS food intake integrating unit, and (3) the efferent system [76]. Hormonally, feeding behavior and body weight are homeostatically regulated by several peptide factors released from sites in the periphery (insulin, leptin, ghrelin) as well as from neurons in the hypothalamus (neuropeptide Y, CRH, orexins/hypocretins, cocaine- and amphetamine-regulated transcript, agouti-related peptide melanocortin, VGF and others; for overview see [77-79]. Most of these peptides have never been tested with regard to alterations in schizophrenia. In search of novel hypothalamic factors involved in the regulation of energy metabolism, Collier et al. [80] identified a gene which they termed beacon, in the Israeli sand rat (Psammomys obesus). Strongly increased beacon mRNA was measured in hypothalami of obese sand rats in comparison to lean littermates [80]. Moreover, intracerebroventricular administration of beacon to sand rats increases food intake, body weight and neuropeptide Y gene expression in the hypothalamus, suggesting that the peptide may, possibly via the neuropeptide Y circuitry, regulate energy balance and feeding [81]. Genetic linkage studies have shown that chromosome locus 19p13 encoding beacon-like/ubiquitin-5-like protein in humans, is associated with increased risk for schizophrenia [82, 83]. Beacon-like immunoreactivity is expressed in hypothalamic neurons. As outlined above, we recently could show that beacon is indeed upregulated in the hypothalamic neurons of schizophrenics [36], while for the other neuropeptides putatively involved in the regulation of energy balance (including neuropeptide Y, ref. [84] data are inconclusive with regard to altered hypothalamic expression. Here, research is still at the very beginning. Currently, we investigate further promising candidate peptides for playing roles in the metabolic dysregulation in schizophrenia (VGF, urocortin, agouti-related peptide, see Fig. 1).

6. SLEEP DISTURBANCES IN SCHIZOPHRENIA AND THE HYPOTHALAMUS

Patients suffering from schizophrenia commonly have sleep disturbances (including poor sleep efficiency, increased sleep-onset latency, and decreased REM sleep latency). Psychotic agitation is often associated with profound insomnia, while negative symptoms are accompanied with slow wave sleep deficiency [85]. These alterations in the sleep/wake pattern point to a prominent involvement of the hypothalamus. Endogenous circadian rhythms are under control of the SCN nucleus. This tiny nucleus has nearly completely been overlooked by schizophrenia research, however [34, 86, 35]. When mapping human hypothalamic nuclei for the expression of nNOS in different neuropsychiatric disorders, we found that in subjects with schizophrenia the total number of NOS-expressing SCN neurons was greatly reduced in com-

![Fig. (1). Immunohistochemical localization in the human hypothalamus of different neuropeptides with potential relevance for energy metabolism, food intake and obesity.](image-url)

A. Beacon-ubiquitin-5 immunoreactive neurons. Beacon was found to be increased in schizophrenia [36].

B. VGF neurons in the PVN of an individual with schizophrenia. Our preliminary results show that hypothalamic VGF expression is normal in schizophrenia.

C. Agouti related peptide immunoreactive neurons.

D. Urocortin immunoreactive neurons in the SON.
parison to controls [34]. This situation is very similar to what can be found in the SCN of patients with major depression, who also frequently suffer from disturbances of the sleep-wake cycle. Neuronal NOS accounts for more than 90% of the cerebral NO production. This gas has multiple functions in the brain and seems to be prominently involved in the pathophysiology of schizophrenia [31]. In particular, NO is prominently involved in sleep regulation. Interestingly, both nNOS inhibition and a NO scavenger were shown to prevent recovery sleep induction, while application of a NO donor during the spontaneous sleep-wake cycle increased sleep, thus indicating that NO is necessary and sufficient for the induction of recovery sleep [87]. Moreover, in nNOS knock out mice REM sleep is substantially reduced [88]. Thus, reduced cellular expression of nNOS in the SCN neurons in schizophrenia might be part of a disturbed signalling cascade finally leading to the profound sleep disturbances as summarised in a recent paper of Trbovic [86]. Other hypothalamic factors with known effects on sleep architecture as hypocretin-1 are apparently normal in patients with schizophrenia [89].

### 7. NEUROIMMUNE DISTURBANCES IN SCHIZOPHRENIA AND THE IMPACT OF THE HYPOTHALAMUS

Several lines of evidence suggest a crucial role for the immune system in the multifactorial pathogenesis of schizophrenia. Infection during pregnancy in mothers of offsprings later developing schizophrenia has been repeatedly described. The immune response, itself, of the mother may be related to the increased risk for schizophrenia in the offspring [90]. Indeed, increased IL-8 levels of mothers during the second trimester were associated with an increased risk for schizophrenia in the offspring [3, 90]. A five-fold increased risk for developing psychoses later on, however, was also observed after infection of the CNS in early childhood. Moreover, several signs of inflammation including activated microglia have been found in brains and bodily fluids of schizophrenics (for reviews see [91-95]). Although the hypothalamus is central to the regulation of psycho-neuro-immunological processes amazingly little is yet known about the involvement of this brain region in the assumed immune/inflammatory response in schizophrenia. Hypothalamic neurons prominently express ILs [96] and may release them. Recently, a strong activation of brain Il-1beta was found in schizophrenia [97]. There are indications for a beneficial effect of antipsychotic medication on cytokine dysregulation in schizophrenia [92]. However, some authors believe that the inflammatory response system in schizophrenia is activated because of the cortisol-driven dysfunctioning of the HPA axis [92, 98], and that therefore the observed increased release of immune mediators like IIs or other cytokines is a late consequence of the disease process. Further studies on drug-naïve, first episode patients should help reveal the actual impact of immune processes in schizophrenia, and the possible contribution of the hypothalamus to them.

### CONCLUSION

The present survey shows that the hypothalamus is in many ways involved in the pathophysiology of schizophrenia. However, some of the observed changes perhaps result from long-lasting stress, or are the consequence of antipsychotic medication. Amazingly little is still known about alterations in the hypothalamus itself. Hence, an important task for future research will be to reveal structural and functional changes within the hypothalamus in order to better understand the basis of these changes in schizophrenia.

### ABBREVIATIONS

- ACTH = Adenocorticotropin
- CNS = Central nervous system
- CRH = Corticotrophin releasing hormone
- CSF = Cerebrospinal fluid
- FSH = Follicle stimulating hormone
- GRH = Gonadotropin-releasing hormone
- HPG = Hypothalamus-pituitary-gonadal
- HPA = Hypothalamus-pituitary adrenal
- HPT = Hypothalamus-pituitary thyroid
- IL = Interleukin; LH: luteinizing hormone
- nNOS = Neuronal nitric oxide synthase
- SCN: PVN = Paraventricular nucleus
- REM = Rapid eye(s) movement
- SON = Supraoptic nucleus; suprachiasmatic nucleus
- TRH = Thyrotropin releasing hormone
- TSH = Thyroid stimulating hormone
- VGF = Is not an acronym

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