The importance of glutamate in the neuro-endocrinological functions in multiple sclerosis, related to fatigue

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Summary. Multiple sclerosis is an inflammatory disease, which still today affects the Northern-hemisphere population, generating a socioeconomically burden. One of the most unfavorable symptoms in this chronic disorder is fatigue. In this review, we favor and sustain a main alteration of the hypothalamus-pituitary-axis complex and its physiopathologic consequences, mostly related to glutamate and corticoid levels. We try to sustain our hypothesis in what is already reported, corroborating that the inflammatory cells release mainly glutamate, a neuro-toxic substance which leads to a demyelinating effect and as a main result fatigue as a symptom. When this hypothesis is demonstrated, we could trace therapeutic targets to stop the release of glutamate of these immunologic cells, in order to avoid fatigue in multiple sclerosis patients.

Key words. EAAT2. Fatigue. Glutamates. Hypothalamus. Magnetic resonance imaging. Multiple sclerosis.

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Accepted:
27.04.18.

How to cite this paper:
Pedraz B, Sammer G. The importance of glutamate in the neuro-endocrinological functions in multiple sclerosis, related to fatigue. Rev Neurol 2018; 67: 387-93.

Versión española disponible en www.neurologia.com

Introduction

Multiple sclerosis (MS) is a chronic disease that is characterized by inflammation and demyelination, whose etiology involves a relationship of unknown environmental factors and genetic vulnerability mainly in European population [1-4]. As a consequence of the physiopathology, there is an axonal injury and gliosis that can involve the central nervous system (CNS) and other peripheral nerves (i.e. optical nerves) [1,2].

This disease is common in northern European population and it mostly affects female population [2]. Epidemiologically, the disease attacks mostly young adults (between 20 and 40 years old), and it is estimated that around 2.5 millions of people suffer from this chronic disorder [4,6].

The incidence in Europe and North America is from 4-8 per 100,000 from the population, and the prevalence 60-100/100,000 [4]. The ratio between female and male subjects is from 2 to 1, being the female subjects more exposed to the disease [1,4,6,7].

Summarizing the genetic features of MS, most population studies have shown an association between the linked class II MHC alleles (DR15 and DQ6) with determined genotypes [3,4]. Other studies have identified genes that confer a significant increase of the disease risk: the interleukin receptor related genes IL2RA and IL7RA, and possibly genes as HLA-C, TKY2 and CD58 [3,4].

What concerns to the immunological factors, in brief summary, it is believed that interferon γ, tumor necrosis factor-α (TNF-α) and other pro-inflammatory cytokines such as interleukin-1 and 6, may mediate MS, specifically symptoms like fatigue [7].

The distribution of the disease and the susceptibility can be explained by the environmental effect conferred by variable light exposure and vitamin D status, albeit there are several theories that postulate the influence of viral exposure and disease susceptibility for MS (i.e. measles, mumps, rubella or Epstein-Barr virus) [3].

Most of the symptoms and signs of MS are not specific and it requires a deep clinical and auxiliary investigation to define the diagnosis in the patient who suffers from MS. Usually symptoms and manifestations are subordinated to the localizations in the brain and spinal cord [8].

The most common symptom in MS, being also the first one of the most disabling symptoms, is fatigue, which affects the 50-80% of the patients [7,9]. Fatigue is defined as 'a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities' [8]. This symptom may interfere with the daily activities in patients with MS, even if the physical disability still is not a major concern [7,9]. This symptom may be associated with a peripheral or central nervous system inflammation related to leukocytes [10].

Although we know that there are strongly and clearly relationships between inflammation related to leukocytes and MS, we have found surprising information concerning the structural disruption of the hypothalamus, and it's relationship with the hypothalamic-pituitary-adrenal axis (HPA axis) regarding fatigue in MS [11].

What is the most interesting part of this founded information, and also what has brought to write this review article, is the role of glutamate regarding the neuronal damage of determined areas of the CNS, but most specifically of the hypothalamus. Many studies have pointed out also, that there must be a relationship between the neuropsychological symptoms (i.e. fatigue) and the disruption of the HPA axis [11,12].

The main objective of this review is to point out the relationship between MS, HPA disturbance and glutamate. We will try to and explain all what concerns to these main variables. With the purpose of supporting this review, we will try also to join all this three areas of interest in order to get a feasible idea of the model and mechanism of fatigue in MS using glutamate as trigger and HPA as affected structure. This article is only a preview for future studies regarding the neuro-pathways of glutamate altering the hypothalamic neurons, and lastly generating a disruption in the normal functioning of the HPA axis. What are we trying to do is to explain this neuropsychological symptoms through a psychoneuroendocrine orientation.

The HPA axis in multiple sclerosis

As far as we know, there are many components of the immune response related to the MS that are implicated on the pathophysiology, and these are also related with the endocrine system, specifically through the HPA axis [13,14]. It is thought, that the chronic hypersecretion of cortisol implied by these findings related to the pathophysiology of the MS would lead to a desensitization of corticosteroids, damaging many neurons, including the ones related to the regulation of the HPA axis [13]. Taking in consideration this information, many authors have described the role of the HPA axis disturbance in MS pathogenesis, disease progression and comorbid mood disorders [14-16].

Based on the fact that dehydroepiandrosterone (DHEA) levels are decreased and that biological responses to cortisol are decreased in patients with MS, many studies have reported the relationship with this phenomenon and fatigue [7]. That means, that there is evidence based on a deregulation of the HPA axis and neuropsychological symptoms in patients with MS and fatigue symptoms [7].

With the dexamethasone-corticotrophin releasing hormone test (Dex-CRH test), many researchers have previously shown and proved the hyperactivity of the HPA axis in patients with MS [13,14]. For that reason, in many other studies a correlation between abnormal function of HPA axis and clinical manifestations of MS was frequently mentioned in the scientific literature [13].

Other studies showed a chronic activation of the HPA axis in post-mortem patients with MS. The main indicators for this pathophysiological phenomenon were: enlarged adrenal glands, higher cortisol levels in the cerebrospinal fluid (CSF) and increased corticotrophin-releasing hormone (CRH) producing neurons co-expressing vasopressin (VP) in the hypothalamus [14-16].

Other authors mentioned that in patients with strong and severe MS manifestations, due to the neurodegenerative and inflammatory process, have more severe and active lesions that make the HPA axis hypoactive [14,17]. Whether there is a hyperactivation (in most patients with MS) or hypoactivation (in severe MS patients), what important is that there is a dysfunction of the HPA axis that is well described on the literature [14].

Other measured variable, reported in the literature, is the cortisol awakening response (CAR). This phenomenon is characterized by a pronounced increase of cortisol within 20 to 30 minutes after awakening, and is controlled specially by the limbic system [15].

It is known that when CAR is elevated, there is an hyperactive HPA axis activity, and that is also related to auto-immune diseases and emotional disorders [15,16]. What is interesting is that HPA axis hyperfunction is linked with radiological manifestations: increased cortisol response to CRH was associated with gadolinium enhancing lesions [15].

In a case report from a MS patient it was demonstrated that it was a partial insufficiency of the ACTH function [18]. Although there was a case report, what interested us is the deficiency of the ACTH function and its relationship with the HPA axis and MS [18].

Looking for summarizing all the information obtained in the literature, we searched through PubMed using the MeSH terms ('Adrenal Cortex Hormones'[Mesh] AND 'Multiple Sclerosis'[Mesh] AND 'Fatigue'[Mesh]). In our search, we grab the most important information of many studies related to our review, which is just above described. In

Table I. Summary of the studies from 2008 until now related to HPA axis, fatigue and MS.

Topic	Main findings
Levels of inmunological parameters and fatigue in patients with MS [19]	The plasmatic in vivo levels of TNF-α (7.6 ± 3.4 vs 23.9 ± 10.8 pg/mL; $p < 0.0001$) and IL-6 (25.5 ± 9.7 vs 214.9 ± 95.3 pg/mL; $p < 0.0001$) were significantly higher among MS patients with fatigue in comparison with healthy control groups. It was shown, also, that in patients with MS the hydrocortisone as drug was less efficient at reducing the release of pro-inflammatory cytokines by activated T cells in patients with fatigue
Cortisol level, disease duration and MS [20]	There was no statistical difference in the acute HPA stress response between MS patients and control subjects. However, in patients with relapsing-remitting MS, the relative maximum cortisol increase had a strong negative association between the times since diagnosis ($r = 0.67$; $p < 0.001$). This means that MS patients with shorter disease duration (2-12 months) expressed a significant higher cortisol stress compared to longer duration (14-36 months)
Cortisol levels, fatigue and MS types [21]	The cortisol awakening response (CAR), for cortisol output, is larger in people with relapsing-remitting MS (RRMS), than in healthy subjects. In patients with RRMS, fatigue was associated with a low waking cortisol level and grater post-awaking cortisol increases. Cortisol levels are likely to relate with present disease states, rather than neurological disability
Circadian levels, fatigue and patients with MS [15]	The circadian cortisol release significantly differed between groups ($F = 4.36$; $p = 0.015$), mostly pronounced in RRMS patients. MS patients reported significantly more depressive symptoms (i.e. fatigue) than healthy control subjects. RRMS express a significantly greater CAR, in comparison to healthy control subjects
ACTH/cortisol ratio, treatment and patients with MS [13]	In patients who remained without treatment, the ACTH/cortisol ratio decreased notoriously (increase of cortisol and decrease of ACTH secretion). In this study it is shown that MS appears to increase over time and changes from a central to an additional adrenal component. This component is shown its reduction through immunotherapy
HPA axis activity, depression, fatigue and MS patients [22]	Patients with MS, also patients with MS and major depressive disorder showed hyperactivity of the HPA axis (normal morning cortisol but elevated evening levels; $p = 0.04$). This study supports a role for HPA axis hyperactive in patients with MS, more specifically patients with depression and MS, and the hypothesis that there is an inflammatory and neuroendocrine factor
Sexual hormones, HPA axis and patients with MS [23]	The mean basal values of LH, FSH and testosterone were lower in the MS patients in comparison to healthy control subjects ($p = 0.01$). Findings in the MS patients related to the responses to the GnRH test where interesting: the injection of GnRHa did not yield a significant increase in FSH and LH levels in patients with MS compared to controls ($p = 0.001$). These manifestations were strongly statistical related to EDSS positive scores and the progression of the disease

the table I, we summarized the main findings and directions of the related investigations that have been done since 10 years ago until now.

Following with the imaging description above, there are studies that have reported structural changes of the CNS *in vivo* (using T_1-relaxed and DTI, for instance), and more specifically they reported a structural hypothalamic abnormalities in MS [11, 12,24,25]. Mostly this pattern is observed in Caucasians patients with MS [12].

One study have also reported that the hypothalamus is prone to suffer demyelinating lesions in patients with MS [26]. This study, however, have found that the active lesion (in comparison to the chronic inactive lesion) was correlated negatively with the disease duration [26]. Another from those findings was that active hypothalamic lesions act on the CRH neurons, and can influence on the course and manifestations of the disease self [26]. These obtained information, regarding the hypothalamic lesions, agree with another study in which they conclude that MS patients with hypothalamic lesions are prone to have an impaired activation of the CRH system, because there a diminishing expression of CRH mRNA and a low number of CRH/VP-immunoreactive neurons was observed [27].

What role does glutamate play in this disturbance?

Glutamate is one of the principal excitatory neurotransmitters in the CNS [28]. Neurons and glial cells (oligodendrocytes, astrocytes, microglia) use it to communicate between each other [28]. Under normal conditions, the presynaptic vesicles release Glutamate into the synaptic cleft [28]. Because of its toxicity, it must be cleared away quickly before it accumulates [28]. In the glutamate-glutamine cycle, a metabolic cycle, the main enzymes involved are glutaminase and glutamine-synthetase [28]. Oligodendrocytes have glutamine synthetase activity as well, and they produce glutamate dehydrogenase [28]. Microglia, the main source of extracellular glutamate uses glutaminase to produce it from glutamine [28].

Table II. We organized the information obtained in this table reviewing the articles mentioned by Azevedo et al [30].

	Sample size	Glutamate involved in MS
Werner et al [31]	*n* = 6 (post-mortem study, neurological tissue)	Abnormal elevation of levels of phosphate-activated glutaminase, the principal enzyme for the production of glutamate, in macrophages and microglial cells over a damaged white matter and dystrophic axons
Pitt et al [32]	*n* = 6 (post-mortem tissues) and comparison with fetal tissue	Deficient expression of glutamate transporters on the surface of oligodendrocytes responsible for glutamate reuptake in MS white matter.
Geurts et al [33]	*n* = 12 (tissues from MS patients)	Overexpression of metabotropic glutamate receptors on injured axons in MS
Sarchielli et al [34], Stover et al [35]	*n* = 80, *n* = 110	Elevation of glutamate concentrations in the cerebrospinal fluid of MS patients experiencing relapses and progressive disability worsening
Baranzini et al [36]	*n* = 7500 (gene samples)	Association of glutamate receptor genes with MS susceptibility

As we have reviewed before, MS is a multifactorial disease that her stronger component is the inflammatory pathologic mechanism [7]. This last mechanism is in charge of destroying and disrupting the physiological function of the neuron as well as its structure [10]. Most of the inflammatory cells (monocytes, macrophages, microglia and dendritic cells) are the ones who are responsible to segregate glutamate to most of the neuronal cells, because there is an overexpression of an enzyme (glutaminase) in those cells and glutamate is free in every direction [10,29]. Additionally there is a reduced expression of the glial transporter of glutamate, EAAT2, and the detoxifying glial enzyme, glutamine-synthetase and glutamine-dehydrogenase, in a way that the extracellular glutamate cannot be taken again and consequently metabolized [29]. As a consequence, there is an accumulation of extracellular glutamate and destruction of the myelin in the neurons by facilitating excytotoxic death in oligodendrocites [10,29]. In addition, the glutamate released from inflammatory cells activate glutamate receptors on the endothelial cells to facilitate their infiltration into the CNS [10,29].

This action affects the transmission of information by altering the voltage-gated sodium channels (VGSC) on the axon terminals, modulating also the presynaptic release of glutamate [10]. The concentrations of sodium become higher in patients with chronic lesions, depolarizing the axon terminal, leading to presynaptic or axomyelinic release of glutamate and subsequent toxic effects [10].

Table II shows evidence that glutamate is involved in MS pathophysiology [30].

The first one to describe a relationship between glutamate levels and MS were Kim and Holzmüller [37]. They reported a diminished level of glutamate in the cerebrospinal fluid (CSF) in 15 patients with MS [37]. Discrepancies with this study where reported by Stover, who reported an elevated glutamate level in CSF of MS patients [28]. Years later, it was described that high glutamate levels where dangerous and damage axons of the neurons [28]. Mostly because it was showed that there was an axonal damage and demyelination, as well as oligodendrocite loss, in patients with MS [28].

At the same time, there where studies that demonstrate that there is a strong positive statistical correlation between the levels of glutamate and with the MSSS (Multiple Sclerosis Severity Scale), that correlates probably with a neuroaxonal loss [11]. This same study has demonstrated a correlation between glutamate levels and a high value of fatigue scores (Simple Numerical Fatigue Scores, SNFS) [11].

This glutamate levels are very related to hypothalamic damage in MS, generating the metabolic problems described above, resulting in fatigue and emotional disorders [11].

Conclusions, future ideas and directions

There is described in the literature the theory that mood disorders (specially unipolar depressive disorders) and fatigue are related with the abnormal functioning of the HPA axis [22]. Also there are many descriptions that those types of psychiatric disorders are mostly related to MS. As we have postulated and reviewed, we know that MS is strongly related to an abnormal function of the HPA axis. Making a relationship between both variables we come to the question that: is it possible that mood disorders and fatigue in MS are strongly related to an abnormal function of the HPA axis, that is caused by a CNS inflammation, specifically to a hypothalamic inflammation? [14].

As far we know, the HPA axis and the immune system interact constantly [15]. Cascades or series of pro-inflammatory cytokines can activate the HPA axis [15,38]. The existence of such an immune-regulatory cytokine that influence HPA axis circuit plays an important role in the central control of systemic inflammation [38]. In this circuit, glucocorticoids work as inhibitor substances to the production of pro-inflammatory cytokines, acting on the nuclear transcription factor kappa B, as well as

the unbalance of Th1/Th2 in MS patients and the phospholipase A2 function in MS [39-41].

As an inflammatory disorder, in MS is speculated that there is a dysfunctional response of the HPA axis in the MS (either hyper- or hyporesponse) [13-16]. Additionally, patients fail to produce the right cortisol levels in response to the inflammatory component of MS, and this might be at particular high risk for neurological decline [14].

This inflammatory pathophysiological mechanism increases the susceptibility of normal appearing white matter (NAWM) to develop lesions, which will take to an inflammatory demyelination and neurodegeneration. Demyelination process and cytokines may alter the HPT axis and hormonal functions, resulting in altered serum hormones levels [23].

When this 'vicious circle' becomes chronic and last longer, it is described that it would generate a fast disease progression [14]. There is a proposal that the evaluation of axis responsiveness to inflammation might help for the prognostic for the disease [14].

Current data from research allows us to speculate about the implications of these findings, specially what is related to the pathophysiological mechanism and theoretically promoted disinhibition of inflammatory processes, thereby potentially contributing to disease progression [20].

And, the other question is: What does glutamate have to do with all this thoughts and lucubration? As a hypothesis, we want to demonstrate if there is a structural damage caused by glutamate in the hypothalamic neurons that lead a disturbance in the HPA axis.

We all know that the HPA axis regulates the secretion of the suprarenal hormones. When we are in a transitory state of stress, we tend to raise our levels of internal corticoids, for generating a 'steady state', a sympathetic state. When we are in constant and chronic secretion of stress hormones, we tend to produce depression or fatigue.

In this case, due to the no regulation of glutamatergic pathways caused by the destruction from inflammatory cells and the structural damage of HPA axis, we have a chronic exposition to corticoids that take to a chronic exposure and finally to fatigue [18].

This idea may be plausible, because there are different studies that show that there is an elevation of glutamate levels, and there is an association of high glutamate levels with tissue damage, more specifically with HPA tissue axis damage [11,30].

Structurally many studies have demonstrated the relationship between the disruption of the hypothalamus, the dysfunction of the HPA axis and MS.

Table III. Information taken from Hanken et al [42], in which a summary is made in order to describe the main results of the DTI-study of the hypothalamus and corpus callosum.

Group effect	Main hypothalamic fibers	Main results
$F = 4.047$; $p = 0.023$	Posterior hypothalamic fibers	The fibers between the posterior hypothalamus and mesencephalon, cognitive fatigued patients showed significantly lower axial ($p = 0.025$), and radial ($p = 0.033$) diffusivity values averaged over both hemispheres than cognitively non-fatigued patients
$F = 5.882$; $p = 0.021$ $F = 8.744$; $p = 0.008$	Anterior hypothalamic fibers	The effects of the psychological Beck Depression Inventory component were found for fibers between the anterior hypothalamus and the two brainstem regions, and also for the fibers between the anterior hypothalamus and the frontal cortex
$F = 9.904$; $p < 0.001$	Fibers of the corpus callosum	The fibers of the corpus callosum revealed a significant interaction, that showed in health subjects significantly lower means of axial and radial diffusivity than cognitively fatigued and cognitively non fatigued MS patients

In one post-mortem study there was shown that patients with MS contained hypothalamic lesions, and the active ones were demyelinated and contained lipid-laden foamy HLA-positive and CD68-positive macrophages [26,27]. The active and reactive MS lesions were mostly founded in the internal capsule and the anterior commissure [26,27]. Within there is an association with the number of CRH-VP immunoreactive neurons and the lesions founded in the hypothalamus ($p = 0.005$) [26,27].

Other study have shown that the frequency of hypothalamic lesions was higher in MS patients with active disease [12].

In other study, there is shown that deep gray matter (DGM) demyelination was most extensive in the caudate nucleus and hypothalamus, followed by the thalamus, putamen and pallidum ($p < 0.001$) [25]. These lesions in MS patients were also in early MS stages present and this study pointed out that they contributed to the clinical deficits [25]. Finally this study showed that patients with active DGM lesions showed significantly more perivascular cuffs in comparison with patients without those lesions ($p = 0.007$) [25].

Based on the DTI study of Hanken et al, in which the hypothalamic fibers are analyzed, we have organized a table (Table III) with the most important information showing and supporting our main hypothesis described above [42].

Finally with all the information gathered and summarized, we conclude and confirm that there is an relationship between HPA axis dysfunction and MS. Due to the inflammatory process of the disease,

there is also a relationship between glutamate levels and MS. What us concerns with this review is to create an hypothesis that could join both relationships, in order to demonstrate that there exist a higher level of glutamate that disrupts the HPA axis and generates the classic fatigue symptoms in patients with MS. Future studies should concentrate on this area of research, mainly on the functional magnetic resonance imaging (fMRI) of this hypothalamic areas, and integrate that information with the immunological and endocrinological function in MS patients. After showing a dysfunctional neuronal activity with the fMRI of the hypothalamic neurons in the HPA due to the abnormal glutamate levels and abnormal corticosteroid levels, the next step is to build models of psychogenic diseases (i.e. depression or chronic fatigue disorder) taking into consideration the extrapolation of our described model supported by our future dissertations and research.

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Importancia del glutamato en las funciones neuroendocrinológicas en la esclerosis múltiple relacionadas con la fatiga

Resumen. La esclerosis múltiple es una enfermedad inflamatoria que hasta el día de hoy afecta a la población del hemisferio norte, generando una gran carga socioeconómica. Uno de los síntomas menos favorables en este fenómeno patológico crónico es la fatiga. En esta revisión, sustentamos y favorecemos una alteración principal en el complejo del eje hipotálamo-hipófiso-adrenal y sus consecuencias fisiopatológicas, relacionadas mayormente con el glutamato y los niveles de cortisol. Trataremos de sustentar nuestra hipótesis en lo que se ha notificado hasta el momento, corroborando que las células inflamatorias liberan mayormente glutamato, una sustancia neurotóxica que conlleva un efecto desmielinizante y como resultado principal fatiga como síntoma. Cuando esta hipótesis se demuestre, podríamos trazar dianas terapéuticas para detener la liberación de glutamato en estas células inmunológicas, de manera que podamos evitar la fatiga en la esclerosis múltiple.

Palabras clave. EAAT2. Esclerosis múltiple. Fatiga. Glutamato. Hipotálamo. Resonancia magnética.