Hypothesis

On the potential role of glutamate transport in mental fatigue

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Abstract

Mental fatigue, with decreased concentration capacity, is common in neuroinflammatory and neurodegenerative diseases, often appearing prior to other major mental or physical neurological symptoms. Mental fatigue also makes rehabilitation more difficult after a stroke, brain trauma, meningitis or encephalitis. As increased levels of proinflammatory cytokines are reported in these disorders, we wanted to explore whether or not proinflammatory cytokines could induce mental fatigue, and if so, by what mechanisms.

It is well known that proinflammatory cytokines are increased in major depression, "sickness behavior" and sleep deprivation, which are all disorders associated with mental fatigue. Furthermore, an influence by specific proinflammatory cytokines, such as interleukin (IL)-1, on learning and memory capacities has been observed in several experimental systems. As glutamate signaling is crucial for information intake and processing within the brain, and due to the pivotal role for glutamate in brain metabolism, dynamic alterations in glutamate transmission could be of pathophysiological importance in mental fatigue. Based on this literature and observations from our own laboratory and others on the role of astroglial cells in the fine-tuning of glutamate neurotransmission we present the hypothesis that the proinflammatory cytokines tumor necrosis factor-α, IL-1β and IL-6 could be involved in the pathophysiology of mental fatigue through their ability to attenuate the astroglial clearance of extracellular glutamate, their disintegration of the blood brain barrier, and effects on astroglial metabolism and metabolic supply for the neurons, thereby attenuating glutamate transmission. To test whether our hypothesis is valid or not, brain imaging techniques should be applied with the ability to register, over time and with increasing cognitive loading, the extracellular concentrations of glutamate and potassium (K⁺) in humans suffering from mental fatigue. At present, this is not possible for technical reasons. Therefore, more knowledge of neuronal-glial signaling in in vitro systems and animal experiments is important.

In summary, we provide a hypothetic explanation for a general neurobiological mechanism, at the cellular level, behind one of our most common symptoms during neuroinflammation and other long-term disorders of brain function. Understanding pathophysiological mechanisms of mental fatigue could result in better treatment.
Background
Mental fatigue with reduced capacity for attention, concentration, and learning, as well as subsequent disturbance of short-term memory, is a common symptom in diseases with general or patchy neuroinflammation, such as multiple sclerosis (MS) and neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases [1-6]. The mental fatigue often appears prior to other more prominent mental, cognitive, or physical symptoms from the nervous system in these diseases. Mental fatigue is also common during the rehabilitation after meningitis or encephalitis (postinfectious mental fatigue), stroke or brain trauma (posttraumatic mental fatigue), being especially troublesome when major neurological symptoms have disappeared and the patient is on his way back to work. According to the International Classification of Diseases, 10th revision (ICD-10), mental fatigue is covered by the diagnoses "mild cognitive disorder" or "neurasthenia" and according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [7], mental fatigue is included in the group of "mild neurocognitive disorders". According to the diagnostic classification by Lindqvist and Malmgren [8], mental fatigue is one of the symptoms of the "astheno-emotional syndrome".

Although mental fatigue is not exactly the same as depression, where the patient has a feeling of not being able to do anything, there are overlaps and both disorders have behavioral manifestations such as reduction in motivation that would appear similar in animal models, where affective state is either irrelevant or difficult to assess. Even the "sickness behavior" [9] contains a component of fatigue. Mental fatigue is also prominent after sleep deprivation. In addition to the fatigue itself, the patient with mental fatigue often suffers from loudness and light sensitivity, irritability, affect lability, stress intolerance, and headaches [8].

Mental fatigue appears as a decreased ability to intake and process information over time. Mental exhaustion becomes pronounced when cognitive tasks have to be performed for longer time periods with no breaks (cognitive loading). Often, the symptoms are absent or mild in a relaxed and stress-free environment. To explore the possible cellular neurobiology of mental fatigue, we start by looking at some components important for information intake and processing within the central nervous system, namely glutamate neurotransmission, and focus on the clearance of extracellular glutamate ([Glu]ec).

Glutamate neurotransmission is indispensable for information intake and processing within the central nervous system
Glutamate neurotransmission is crucial in information intake and information processing within the brain [see 10]. Glutamate transmission is also indispensable for long-term potential (LTP) formation, the cellular correlate to memory formation [see 11].

In brain, the [Glu]ec has to be maintained at approximately 1–3 µM in order to assure a high precision (high signal-to-noise ratio) at normal glutamate neurotransmission [12] and also, to avoid excitotoxic actions of glutamate on neurons. The clearance of glutamate from the extracellular space is achieved by high-affinity, sodium (Na+)-dependent electrogenic uptake transporters. The glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1) are most abundantly located on astrocytes surrounding synapses of glutamate-bearing neurons [13]. In fact GLAST and GLT-1 have different expression patterns. GLAST is the major transporter for glutamate uptake during development while expression of GLT-1 increases with the maturation of the nervous system. Glutamate transporter 1 expression seems to follow the formation and maturation of synapses and especially synaptic activity [14]. Even more convincing for the role of astroglia in keeping the [Glu]ec low, it has been demonstrated with knockout techniques in rats that loss of GLT-1 or GLAST produces elevated [Glu]ec and neurodegeneration characteristic of excitotoxicity, while the loss of neuronal glutamate transporter does not elevate [Glu]ec [15].

Regulation of astroglial glutamate transporter capacity – role of proinflammatory cytokines
A large number of factors have been shown to affect the activity and expression of the glutamate transporters GLT-1 and GLAST. For example, GLT-1 is stimulated by phosphorylation by protein kinase C (PKC), while GLAST is inhibited by PKC at a non-PKC consensus site [16]. The synthesis of GLT-1 has been shown to be stimulated by factors acting via receptor tyrosine kinases and pathways dependent on phosphatidylinositol-3-kinase (PI3K) and the nuclear transcription factor NFκB. One mechanism of regulation of GLT-1 is related to formation of cysteine bridges. Glutamate transporter 1 contains cysteines that are sensitive to oxidative formation of cysteine bridges. Oxidative species such as hydrogen peroxide can readily oxidize the functional sulfhydryl groups of cysteines, to form disulfide bridges which exert an inhibitory effect towards glutamate transporters [17]. Examples of factors or altered conditions that impair astroglial glutamate transport are arachidonic acid, lactic acid, cytokines, nitric oxide (NO), β-amyloid protein, peroxyximate, and glucocorticoids. The altered conditions could be disturbed energy metabolism with lowering of adenosine triphosphate (ATP) levels or lowering of pH. Notable is the finding that many of these substances or conditions also decrease astroglial gap junction communication and even disintegrate the BBB, thus impairing the astroglial support of the glutamate neurotransmission [for references, see [18]].
Proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6 have since long been known to impair astroglial glutamate uptake even if the mechanisms are not fully understood. The inhibitory function of TNF-α was established as early as the 1990s, when TNF-α was shown to inhibit astroglial glutamate uptake [19]. Hu and coworkers [20] reported a dose-dependent inhibition of astrocyte glutamate uptake by a mechanism involving nitric oxide (NO). In a study from 2001, Liao and Chen [21] demonstrated that TNF-α potentiates glutamate-mediated oxidative stress, which results in a decrease in glutamate transporter activity. Recently, Wang and coworkers [22] showed a reduced expression of GLT-1 and GLAST, and also, an impaired glutamate transport in human primary astrocytes, by TNF-α. The nuclear factor NFκB has been suggested to be involved in this regulation [23]. Even IL-1β and IL-6 have been shown to impair astroglial glutamate uptake capacity by involvement of oxidative stress or NO [20,24,25].

Even dysregulation of the blood brain barrier (BBB) is seen early in neuroinflammation, and parallels the release of proinflammatory cytokines [26-28]. Mechanisms for disruption of the BBB in neuroinflammation are incompletely understood, but appear to involve direct effects of cytokines on endothelial regulation of BBB components. Exposure of endothelium to TNF-α interrupts the BBB by disorganizing cell-cell junctions. Furthermore, TNF-α has been shown to depress calcium (Ca2+) signaling between BBB endothelial cells by reducing gap junction coupling and inhibiting triggered ATP release [29].

**Could glutamate neurotransmission be dynamically regulated by extracellular glutamate levels?**

As stated above, already when the [Glu]ec exceeds some 3–5 μM, the efficiency of the glutamate signaling is considered to be reduced [12]. There is prolonged postsynaptic and adjacent glial receptor activation [30], with less precision (with a decreased signal-to-noise ratio) in the glutamatergic transmission. As a consequence, the information taken into the brain will be less distinct. In addition, activation of astroglial networks, with induction of Ca2+ oscillations, both within and between the gap junction-coupled astroglial syncytia [31-33], and with subsequent astroglial glutamate release [34] could increase the excitability level in neighboring neuronal circuits. The overall result may be that more, and larger, neuronal circuits would be activated over time [35,36]. This conclusion is further supported by studies demonstrating that inhibition of GLT-1 could facilitate hippocampal neurotransmission [37] and lead to increased neuronal excitability, as seen in for example hepatic encephalopathy [38].

Increased [Glu]ec would also lead to astrogial cell swelling, with a resulting decrease in the extracellular space volume, and locally further increased [Glu]ec [39-42]. The astrogial swelling would give rise to relative depolarization of the astrogial cell membrane, with a further decreased astrogial glutamate uptake capacity, and in addition, a decreased capacity of the astrocytes to remove [K+]ec [43,44]. Even moderately increased (up to 8–10 mM) [K+]ec levels have been shown in experimental systems to inhibit glutamate release [45].

Recent data indicate a dynamic and fine-tuning regulation of the glutamatergic transmission. One mechanism by which neurons regulate excitatory transmission is by altering the number and composition of glutamate receptors at the postsynaptic plasma membrane. This has been shown for the NMDA receptor in experimental systems and could have prominent importance for dynamic processes as learning and memory [46]. Of great importance in this context are also studies where stimulation of metabolic glutamate receptors (mGluR3 and mGluR5) have been shown to critically and differentially modulate the expression of glutamate transporters [47] thus creating a substrate for a fine-tuning of the glutamate neurotransmission. Even the proinflammatory cytokine IL-1β could act as a regulator of glutamate transmission, as it was shown recently that this cytokine inhibits glutamate release and reduces LTP as a consequence of the formation of reactive oxygen species [11].

Furthermore, in states of decreased astroglial glutamate uptake capacity, even astroglial glucose uptake, and consequently the supply of metabolic substrates to the neurons, has been reported to decrease [48-50] and there may be relative energy insufficiency at the cellular level in neuronal circuits. In addition, glutamate release from the presynaptic terminals could decrease due to factors such as a decreased glutamine supply of the neurons.

Experimental investigations in the rat and monkey have demonstrated a feedback loop from the left basal frontal cortex, with an inhibitory influence on the locus coeruleus in the brain stem [51]. If this loop also exists in humans, a slight increase in the neuronal firing due to slightly elevated [Glu]ec in the basal frontal cortex could lead to a decrease in the noradrenaline and serotonin (5-HT) release in the cerebral cortex, which would also decrease glucogenolysis [52,53] and, furthermore, impair metabolic substrates for cortical neurons.

Thus, it might be that glutamate neurotransmission could be regulated by changing astroglial glutamate transporter capacity, and thus, increases in [Glu]ec levels could be one factor to impair glutamate transmission.
Proinflammatory cytokines and neuroinflammatory and degenerative diseases, major depression, sickness behavior, and sleep deprivation

There is an extensive literature on inflammatory response with microglial activation and the production of proinflammatory cytokines (TNF-α, IL-1β and IL-6) in neuroinflammatory/infectious and neurodegenerative diseases as well as in stroke and trauma [5,54]. The inflammatory activation starts early in some neurodegenerative disease such as Alzheimer’s and Parkinson’s diseases, being prominent for long time in these diseases and also in neuroinflammatory diseases, in meningitis, encephalitis and in trauma or stroke [see [58]].

Several groups have also described enhanced production of proinflammatory cytokines in major depression [see [55]] and sickness behavior [9,56,57]. This is interesting as there are overlaps between mental fatigue and these disorders. Furthermore, proinflammatory cytokines are activated in sleep deprivation [58], a state where mental fatigue is often prominent.

In states of anxiety and stress, often experienced as secondary to mental fatigue, increased glucocorticoid levels have been demonstrated. Interestingly, long-term increases in glucocorticoids have been demonstrated to result in the production of both TNF-α and IL-1β [59].

Could mental fatigue be the consequence of a dysfunction in a specific brain region?

In the search for pathophysiological correlates to fatigue in MS, Roelcke and co-workers [60] demonstrated reduced glucose metabolism in the frontal cortex and basal ganglia in MS patients with fatigue. A hypotheses by Chaudhuri and Behan [6] also focused on basal ganglia as one part of the brain crucial for mental fatigue to appear. Using patients with chronic fatigue syndrome, which is not however exactly the same as mental fatigue, studies have revealed prefrontal and temporal cortices, anterior cingulate and cerebellum as regions possibly involved in fatigue [61]. Interestingly these later studies also pointed at a possible connection between glutamate transmission and fatigue. Even if the mental fatigue is not the central problem in attention deficit hyperactivity disorder (ADHD), some of the symptoms in this disorder is similar to the symptom complex associated with mental fatigue, and there is some support for glutamate being involved in the disorder and its treatment [62] and also, at least hypothetically, a deficient astroglial metabolism due to decreased noradrenaline and serotonin levels [63]. Until now there is no evidence for a specific brain region being affected in mental fatigue. On the contrary, it seems that mental fatigue could appear from disturbances of different neuronal systems. We will therefore present a hypothesis (figure 1) where the functional disturbance of mental fatigue at the cellular level is coupled to the fine-tuning of the glutamate neurotransmission.

Mental fatigue – a stereotypical reaction upon brain function disturbance – a hypothesis focusing on impaired glutamate neurotransmission (figure 1)

It may be that mental fatigue is a stereotypical reaction to disturbance of “higher” brain functions. The brain, with its billions of specialized neurons and supporting glial cells, works as a “whole” organ. Every disturbance of brain homeostasis, no matter where the anatomical localization is, would therefore attenuate brain capacity for information processing and, as a consequence, information intake. One way to diminish information intake and processing at the cellular level would be to impair glutamate neurotransmission by attenuating the glial support and especially diminishing the astroglial capacity to clear [Glu]ec. The initial consequence would be slightly increased [Glu]ec, with less precision in glutamate transmission. This would disintegrate the “filter”, which normally selects information and prevents it from reaching the cerebral cortex. We can take the sound from a low-frequency fan as an example. This sound is normally sorted out after hearing it for a while. If this sound is handled with less precision by auditory recognition systems, it will continually be recognized by brain centers as “new” information and be processed in the cerebral cortex as long as the sound is on. The “filter” that normally restrains already recognized information from reaching higher brain centers, has been “opened”. From a physiological point of view, it seems appropriate that the individual, and not the brain at the synaptic level, should determine which information should reach, and be processed by, the cerebral cortex. The decreased attention, increased loudness and light sensitivity, and irritability could be physiological ways of avoiding overstimulation of higher cortical centers. In case the individuals cannot protect themselves from too much sensory stimulation, the filter’s opening leads to overstimulation of the cerebral cortex. Here, the final shutdown of the glutamate transmission could be one mechanism underlying mental exhaustion (figure 1).

In line with these theoretical proposals, increased [Glu]ec, has in fact been demonstrated in MS, meningitis, and encephalitis, Alzheimer’s disease, ischemia and traumatic brain injury [64-69]. Furthermore, it has been shown in experimental studies that even extracellular K+ is involved in the post-traumatic hyperexcitability, and a recent study has proposed that the larger extracellular K+ increase evoked by neuronal activity is a consequence rather than the primary mechanism underlying post-traumatic hyperexcitability [70].
Figure 1

Schematic drawing of cellular regulation of extracellular glutamate concentrations ([Glu]ec) in normal brain function (left), and in the presence of the proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 (right). Possible pathophysiology underlying mental fatigue at the cellular level is outlined below. To the left: Two neuronal cell bodies with processes (white) make contact with each other through a synapse (center). Astrocytic (pink) processes encapsulate the synapse and cover also the abluminal side of the blood vessel wall (right). The endothelial cells covering the luminal (blood) side of the vessel wall and the astrocytic processes make up the blood brain barrier (BBB). An oligodendroglial cell (bluish), with its myelin encapsulating the axon, and a microglial cell (yellow) are seen. The astrocytes, with their high-affinity glutamate transporters, are the main site for keeping [Glu]ec low. Even neurons express glutamate transporters, as do oligodendroglial cells, and endothelial cells at their abluminal side. To the right: TNF-α, IL-1β and IL-6 attenuate astroglial glutamate uptake transport and disintegrate the BBB, allowing glutamate from the blood to enter the brain. The overall result is slightly increased [Glu]ec. Tumor necrosis factor-alfa also decreases oligodendroglial cell glutamate uptake [78], while microglial glutamate uptake has been demonstrated to increase (Persson, M., Hansson, E., and Rönnbäck, L, to be published), though not to levels to compensate for the decreased astroglial glutamate uptake capacity. Due to increased [Glu]ec, astroglial swelling is shown. Below: Hypothetic cellular events underlying mental fatigue. Slightly increased [Glu]ec could make the glutamate neurotransmission less distinct (decrease the signal-to-noise ratio). At the cellular level, there would be astroglial swelling, which in turn would decrease the local extracellular (ec) volume and, as a consequence, lead to further increased [Glu]ec. Astroglial swelling also depolarizes the astroglial cell membrane, which further attenuates the electrogenic glutamate uptake and, in addition, the astroglial K+ uptake capacity. As a consequence, even [K+]ec may rise. The increased [K+]ec, together with decreased glutamine production and reduced glucose uptake concomitant with the decreased glutamate uptake, could lead to decreased presynaptic glutamate release and thereby decreased glutamate transmission, which, according to our hypothesis, is one cellular correlate to mental fatigue/exhaustion. Increased extracellular glutamate levels in the prefrontal region could lead to inhibition of the brain stem nuclei locus coeruleus (LC) and raphe nuclei and thereby inhibit noradrenaline (NA) and serotonin (5-HT) release in the cerebral cortex resulting in decreased astroglial metabolism and neuronal metabolic supply. Increased neuronal excitability may be part of the loudness and light sensitivity often accompanying the mental fatigue. In addition, the decrease in noradrenaline and serotonin release might be part of decreased attention and the appearance of depression often accompanying the mental fatigue.
The theory also involves the possibility of a disturbed noradrenaline/serotonin turnover in the cerebral cortex due to a slight hyperexcitability in the frontal cortex. Interestingly, increased $[\text{Glu}]_{ec}$ in the prefrontal cortex has been reported by Bossuet and coworkers [67] in asymptomatic simian immunodeficiency virus (SIV)mac251-infected macaques without major brain involvement, being consistent with our theory at least in this set of animal experiments. If valid even in humans, a disturbed noradrenaline/serotonin turnover in the cerebral cortex could be coupled to the disturbed attention and depression often occurring in addition to the mental fatigue [see [71-73]].

Testing of the hypothesis

It is not possible at present to ultimately prove whether or not the altered neuronal-glial interactions in glutamatergic transmission induced by proinflammatory cytokines could serve as a model to explain cellular mechanisms underlying mental fatigue. Brain imaging techniques able to determine and follow $[\text{Glu}]_{ec}$ and $[\text{K}^+]_{ec}$ over time would be important to use in humans suffering from mental fatigue. Today, this is not possible for technical reasons. Instead, we must use experimental systems to learn about glial cell biology and neuron-glia-neuron signaling and interactions, and thus test specific parts of the hypothesis. Neuroactive substances produced by, or altered conditions related to, the production of proinflammatory cytokines could be evaluated with regard to their effects on astroglial support of glutamate transmission, and especially glutamate transport capacity. The role of the intact astroglial network in higher brain functions (cognition and behavior) could be studied in animal models. Effects of astroglial dysfunction with regard to glutamate transport capacity would be of special interest. Even clinical studies with different treatment strategies could be important in casting some light on the accuracy of the hypothesis. Of utmost importance in all such studies would be test batteries making it possible to objectify and even quantify the degree of mental fatigue.

Why do the symptoms persist in some patients?

Normally, mental fatigue and the associated symptoms disappear when the brain dysfunction is over. In some patients, the symptoms persist. We have at present no explanation for this, but if our hypothesis is correct, there could be a genetic failure preventing astroglial glutamate transporters from upregulating. Another explanation for why the symptoms persist could be that the pathological stimulation by brain plasticity creates new neuronal networks [18,36].

Aspects of treatment

Providing information about mental fatigue, its cause and the prognosis, is of utmost importance for breaking the vicious circle, which comes with the risk for secondary anxiety and depression. Furthermore, it is important for the patient to imagine and learn how much sensory stimulation they can tolerate prior to feeling too exhausted. Due to recent results on changes in cell signaling and neuronal plasticity [18,36], it may be important to identify the symptoms and treat them as early as possible to avoid formation of new and functionally disturbing neuronal circuits due to overstimulation of neuronal-glial units. If our hypothesis is correct, it may be possible to further improve the symptoms by suppressing the production of proinflammatory cytokines and, thereby, restoring the normal astroglial glutamate uptake. In this context, xanthine derivatives may be of use [74]. Another substance, worth considering, may be minocycline, a synthetic tetracycline derivative that has been shown to attenuate microglial activation and, consequently, the production of proinflammatory cytokines [75]. During recent years substances, which enhances glutamate uptake have been identified. Nicergoline [76], different growth factors including pituitary adenylate cyclase-activating polypeptide (PACAP) [77], some low molecular weight factors [23] as well as metabotropic glutamate agonists [47] have all been able to stimulate glutamate transport in experimental systems and could be of interest in the pharmacotherapy of mental fatigue. Interestingly, even AMPA receptor modulators have been demonstrated as cognitive enhancers [10].

List of abbreviations used

ADHD attention deficit hyperactivity disorder

AMPA alpha-amino-3-hydroxy-5-methyl-4-isoxazolepro- pionate

ATP adenosine triphosphate

BBB blood brain barrier

$\text{Ca}^{2+}$ calcium

$\text{Ec}$ extracellular

GLAST glutamate aspartate transporter

GLT-1 glutamate transporter-1

$[\text{Glu}]_{ec}$ extracellular glutamate concentration

5-HT 5-hydroxytryptamine

ICD-10 International Classification of Diseases, 10th revision

IL-1/-6 interleukin-1/-6
K⁺ potassium
[\text{K}_e^{+}]_\text{e}^{+}, \text{extracellular potassium concentration}
LC locus coeruleus
LTP long term potential
MS multiple sclerosis
Na⁺ sodium
NA noradrenaline
NFκB nuclear transcription factor kappaB
NM2A N-methyl-D-aspartate
NO nitric oxide
PACAP pituitary adenylate cyclase-activating polypeptide
PI3K phosphatidylinositol-3-kinase
PKC protein kinase C
Siv mac simian immunodeficiency virus macaques
TNF-α tumor necrosis factor alpha

**Competing interests**
The author(s) declare that they have no competing interests.

**Authors’ contributions**
Equal contributions by both authors.

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**References**
1. Colosimo C, Millefioreni E, Grasso MG, Vinci F, Fiorelli M, Koudriavtseva T, Pozzilli C: Fatigue in MS is associated with specific clinical features. Acta Neurol Scand 1995, 92:353-355.
2. Krupp LB, Pollina DA: Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 1996, 9:456-460.
3. Ford H, Triggel P, Johnson M: The nature of fatigue in multiple sclerosis. J Psychosom Res 1998, 45:33-38.
4. Schreurs KM, de Ridder DT, Bensing JMJ: Fatigue in multiple sclerosis: reciprocal relationships with physical disabilities and depression. J Psychosom Res 2002, 53:775-781.
5. Flachenecker P, Bihler I, Weber F, Gottschalk M, Toya KV, Rieckmann P: Cytokine mRNA expression in patients with multiple sclerosis and fatigue. Mult Scler 2004, 10:165-169.
6. Chaudhuri A, Behan PO: Fatigue and basal ganglia. J Neurol Sci 2000, 179:34-42.
7. American Psychiatric Association: Diagnostic and statistical manual of mental disorders. 4th edition. Washington DC: American Psychiatric Association; 1994.
8. Lindqvist G, Malmgren H: Organic mental disorders as hypothetical pathogenetic processes. Acta Psychiatr Scand Suppl 1993, 88(Suppl 373):5-17.
9. Kelley KW, Bluteke RM, Danszter R, Zhou JH, Shen WH, Johnson RW, Broussard SR: Cytokine-induced sickness behavior. Brain Behav Immun 2003, 17(Suppl 1):S112-S118.
10. Lynch G: AMPA receptor modulators as cognitive enhancers. Curr Opin Pharmacol 2004, 4:4-11.
11. Vereker E, O’Donnell E, Lynch MA: The inhibitory effect of interleukin-β on long-term potentiation is coupled with increased activity of stress-activated protein kinases. J Neurosci 2000, 20:6811-6819.
12. Yudkoff M, Nissim I, Daikhin Y, Lin Z-P, Nelson D, Pleasure D, Erecinska M: Brain glutamate metabolism: neuronal-astroglial relationships. Dev Neurosci 1993, 15:343-350.
13. Huang YH, Bergles DE: Glutamate transporters bring competition to the synapse. Curr Opin Neurobiol 2004, 14:346-352.
14. Perego C, Vani C, Bossi M, Massari S, Basudev H, Longhi R, Pietrini G: The GLT-1 and GLAST glutamate transporter are expressed morphologically distinct astrocytes and regulated by neuronal activity in primary hippocampal cultures. J Neurochem 2000, 75:1076-1084.
15. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl R, Kanai Y, Hediger MA, Wang Y, Schelke JP, Weiley DF: Knockout of glutamate transporters reveals a major role of astroglial transport in excitotoxicity and clearance of glutamate. Neuro 1996, 16:675-686.
16. Danbolt NC: Glutamate uptake. Prog Neurobiol 2001, 65:1-105.
17. Anderson CM, Swanson RA: Astrocyte glutamate transport: review of properties, regulation, and physiological functions. Glu 2000, 32:1-14.
18. Hansson E, Rönnbäck L: Altered neuronal-glial signaling in glutamatergic transmission as a unifying mechanism in chronic pain and mental fatigue. Neurochem Res 2004, 29:989-996.
19. Fine SM, Angel RA, Perry SW, Epstein LG, Rothstein JD, Dewhurst S, Gelbard HA: Tumor necrosis factor alpha inhibits glutamate uptake by primary human astrocytes. Implications for pathogenesis of HIV-1 dementia. J Biol Chem 1996, 271:15303-15306.
20. Hu S, Sheng WS, Ehrlich LC, Peterson PK, Chao CC: Cytokine effects on glutamate uptake by human astrocytes. Neurommunodulation 2000, 7:153-159.
21. Liao SL, Chen CJ: Differential effects of cytokines and redox potential on glutamate uptake in rat cortical glial cultures. Neurosci Lett 2001, 299:13-116.
22. Wang Z, Pekarskaya O, Bencheikh M, Chao W, Gelbard HA, Ghorpade A, Rothstein JD, Volsky DJ: Reduced expression of glutamate transporter EAAT2 and impaired glutamate transport in human primary astrocytes exposed to HIV-1 gp120. Virology 2003, 312:60-73.
23. Su Z-z, Leszczyniecka M, Kang D-c, Sarkar D, Chao W, Volsky DJ, Fisher PB: Insights into glutamate transport regulation in human astrocytes: Cloning of the promoter for excitatory amino acid transporter 2 (EAAT2). Proc Natl Acad Sci 2003, 100:1955-1960.
24. Ye ZC, Sontheimer H: Cytokine modulation of glial glutamate uptake: a possible involvement of nitric oxide. Neuroreport 1996, 7:2181-2185.
25. Chao CC, Hu S, Ehrlich L, Peterson PK: Interleukin-1 and tumor necrosis factor-alpha synergistically mediate neurotoxicity: involvement of nitric oxide and N-methyl-D-aspartate receptors. Brain Behav Immun 1995, 9:355-365.
26. Minager A, Alexander JS: Blood-brain barrier disruption in multiple sclerosis. Mult Scler 2003, 9:540-549.
27. Lynch NJ, Willis CL, Nolan CC, Roscher S, Fowler MJ, Welie E, Ray DE, Swabbel WJ: Microglial activation and increased synthase.
soll of component C1q precedes blood-brain barrier dysfunction in rats. Mol Immunol 2004, 40:709-716.

28. Hwang HY, Choi AM, Bernadac A, Laurenzi S, Bouthy S, Muller RN, Styles P, Anthony DC: MRI detection of early endothelial activation in brain inflammation. Magn Reson Med 2004, 51:248-252.

29. Vandamme W, Braet K, Cabooter L, Leybaert L: Tumour necrosis factor alpha inhibits purinergic calcium signaling in blood-brain barrier endothelial cells. J Neurochem 2004, 88:411-421.

30. Hansson E, Rönnbäck L: Astrocytic receptors and second messenger systems. Adv Molec Cell Biol 2004, 31:475-501.

31. Cotrina ML, Lin JH, Alves-Rodrigues A, Liu S, Li J, Azmi-Ghadimi H, Kang J, Naus CC, Nedergaard M: Connexins regulate calcium signaling by controlling ATP release. Proc Natl Acad Sci USA 1998, 95:15735-15740.

32. Blomström F, Khatibi S, Muyderman H, Hansson E, Olsson T, Ronnback L: S-5-Hydroxtryptamine and glutamate modulate velocity and extent of intercellular calcium signalling in hippocampal astroglial cells in primary cultures. Neuroscience 1999, 88:1241-1253.

33. Carmignoto G: Reciprocal communication systems between astrocytes and neurons. Prog Neurobiol 2000, 62:561-581.

34. Muyderman H, Ångehagen M, Sandberg M, Björklund U, Olsson T, Hansson E, Nilsson M: α1-adrenergic modulation of metabotropic glutamate receptor-induced calcium oscillations and glutamate release. J Biol Chem 2001, 276:46045-4614.

35. Hansson E, Olsson T, Ronnback L, eds: On astrocytes and glial microenvironment. Landes Bioscience Company, Austin, Texas, USA, Springer Verlag, Heidelberg, Germany; 1997.

36. Hansson E, Ronnback L: Glial neuronal signaling in the central nervous system. FASEB J 2003, 17:341-348.

37. Tozaki H, Kanno T, Nomura T, Kondoh T, Kodama N, Saito N, Akhara H, Nagata T, Matsumoto S, Nogi K, Yajima Y, Nishizaki T: Role of glial glutamate transporters in facilitatory action of FK960 on hippocampal neurotransmission. Brain Res Mol Brain Res 2001, 97:7-12.

38. Butterworth RF: Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. Metab Brain Dis 2001, 16:55-65.

39. Kempski O, Staub F, Jansen M, Baethmann A: Molecular mechanisms of glial swelling in acidosis. Adv Neurol 1990, 52:33-45.

40. Stover JF, Pleines UE, Morganti-Kossmann MC, Kossmann T, Lowitt J, Fronckiewicz L: Brain regions involved in fatigue sensation: reduced acetylcarbinic uptake into the brain. NeuroImage 2002, 17:1256-1265.

41. Carrey N, MacMaster FP, Fogel J, Sparks S, Waschbusch D, Sullivan S, Schmidt M: Metabolic changes resulting from treatment in children with ADHD: A 1-HRS study. Clin Pharmacol 2003, 26:218-221.

42. Todd RD, Botteron KN: Is attention-deficit/hyperactivity disorder an energy deficiency syndrome? Biol Psychiatry 2001, 49:151-158.

43. Porreca VF, Young RS, Aguila WJ, During MJ: Effect of experimental Escherichia coli meningitis on concentrations of excitatory and inhibitory amino acids in the rabbit brain: in vivo microdialysis study. Pediatr Res 1993, 33:510-513.

44. Perry BL, Young RS, Aguila WJ, During MJ: Effects of experimental Escherichia coli meningitis on concentrations of excitatory and inhibitory amino acids in the rabbit brain: in vivo microdialysis study. Pediatr Res 1993, 33:510-513.

45. Kratochvil CJ, Vaughan BS, Harrington MJ, Burke WJ: Atomoxetine: a selective noradrenaline reuptake inhibitor for the treatment of attention-deficit/hyperactivity disorder. Expert Opin Pharmacother 2003, 4:165-174.

46. Abrams JK, Johnson PL, Hollis JH, Lowry CA: Anatomical and functional topography of the dorsal raphe nucleus. Ann N Y Acad Sci 2004, 1018:46-57.

47. Marlon MR, Colpaert FC, Rosenquist AC: Noradrenergic mechanisms in neurodegenerative diseases: a theory. Brain Res Rev 2004, 45:38-78.

48. Schubert P, Rudolphi K: Interfering with the pathologic activation of microglial cells and astrocytes in dementia. Alzheimer Dis Assoc Disord 1998, 12(suppl 2):S51-2.
75. Tikka T, Fiebich BL, Goldsteins G, Keinanen R, Koistinaho J: Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. J Neurosci 2001, 21:2580-2588.

76. Nishida A, Iwata H, Kudo Y, Kobayashi T, Matsuoka Y, Kanai Y, Endou H: Nicergoline enhances glutamate uptake via glutamate transporters in rat cortical synaptosomes. Biol Pharm Bull 2004, 27:817-820.

77. Fjigiel M, Maucher T, Rozycka J, Bayatti N, Engele J: Regulation of glial glutamate transporter expression by growth factors. Exp Neurol 2003, 183:124-135.

78. Pitt D, Nagelmeier IE, Wilson HC, Raine CS: Glutamate uptake by oligodendrocytes: Implications for excitotoxicity in multiple sclerosis. Neurology 2003, 61:1113-1120.