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Imbalances of Tripartite Synapses Responsible for the Pathophysiology of Mental Disorders and Epilepsy

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ABSTRACT

A model of imbalances in tripartite synapses responsible for the pathophysiology of mental disorders and epilepsy is reviewed. A tripartite synapse consists of the presynapse and the postsynapse as the neuronal component and the astrocyte as the glial component. Based on a formalism of system-balancing it is hypothesized that the expression of astroglial receptors determines imbalances of neurotransmission. In depression, tripartite synapses are imbalanced since neurotransmitters cannot activate the overexpressed astroglial receptors in the time leading to a prolonged neurotransmission. Inversely, in mania the imbalance of tripartite synapses is caused by a surplus of neurotransmitters overactivating underexpressed astroglial receptors causing a shortened neurotransmission. If astroglial receptors are non-functional, they cannot be activated by neurotransmitters leading to an unconstrained neurotransmission responsible for schizophrenia. In epilepsy, astroglial receptors are overexpressed, but glutamatergic synapses are hyperactivated and GABAergic synapses are hypoactivated causing an imbalance between excitatory and inhibitory tripartite synapses responsible for epileptogenesis. It is suggested that common imbalances of astroglia-synapse interactions may be responsible for mental disorders and epilepsy.

Introduction

Synaptic dysregulations or imbalances are commonly found in neuropsychiatric disorders and epilepsy. Recently, it is becoming increasingly clear that dysregulations and structural changes of astroglia play a central role in the pathophysiology of these disorders[1-3]. Here, I will focus on imbalances in tripartite synapses mainly determined by the expression of astroglial receptors. A tripartite synapse consists of the presynapse and the postsynapse as the neuronal component and the astrocyte as the glial component[4].

The structure and basic functions of tripartite synapses is well established[5-7]. Elementary mechanisms of balancing have been identified in both the neuronal synapses and tripartite synapses where astrocyte coordinate synaptic networks generating a balanced excitation and inhibition[8,9]. This review outlines my models of imbalanced tripartite synapses that may be responsible for the pathophysiology of depression, mania, schizophrenia and, epilepsy.

Logic of System-Balancing

The operations between astroglial receptors (acr) and neurotransmitters (NT) can be described by a formalism of system-balancing[10,11,12,13]. Figure 1 shows four elementary system states in tripartite synapses deduced from the formalism applied. If the concentration of NT, formally interpreted as values, is appropriate for the occupancy of acr, interpreted as variables, the synaptic state is in

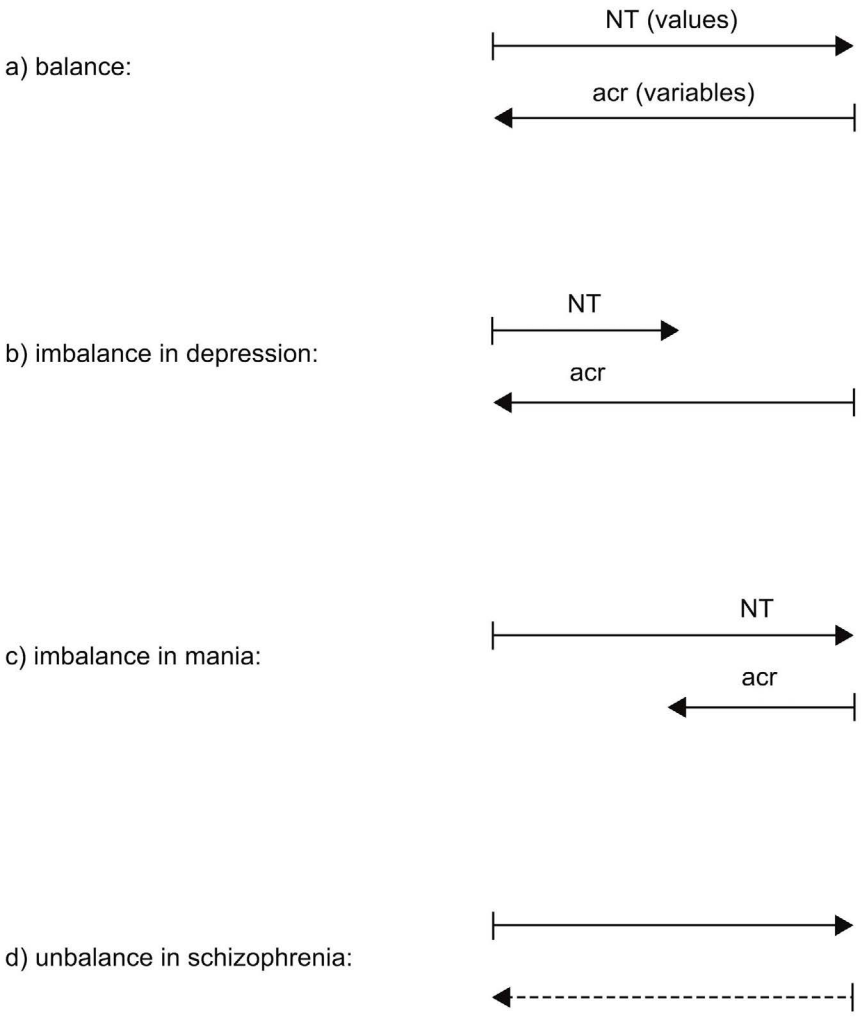

Figure 1: System-balancing in tripartite synapses
Neurotransmitter (NT) represent values, astroglial receptors (acr) variables signified by two inverse parallel lines. If NT (values) correspond to acr (variables), the synaptic system is in balance (a). If acr dominate NT (shorter upper line), the synaptic system is imbalanced causing depression (b). If acr are underexpressed (shorter lower line) in relation to the concentration of NT, the synaptic system is imbalanced causing mania (c). If acr are non-functional (dashed line), the system is totally unbalanced responsible for schizophrenia (d). (modified[11])

balance (a). In the case of an overexpression of acr, the amount of NT is not sufficient for the complete occupancy of the acr leading to an imbalanced synaptic system. This system state operates in depression (b). If acr are underexpressed, a surplus of NT arises. This system state is imbalanced operating in mania (c). In the case of non-functional acr they cannot be activated by NT representing a totally unbalanced synaptic system state responsible for the pathophysiology of schizophrenia (d).

Imbalanced Tripartite Synapses in Depression

Figure 2 outlines a model of an underbalanced tripartite synapse responsible for the pathophysiology of depression[14,15]. The upregulation of gap junctions (GJ, red) exerts an overexpression of acr that cannot be activated by NT in real time leading to a diminished Ca^{2+} concentration (↓) and an underproduction of gliotransmitters (GT) (↓). Consequently,the negative feedback on presynaptic receptors (psr) is protracted. Since acr outnumber the available NT, a relative lack of NT arises and neurotransmission is prolonged. This may explain the main symptoms of depression such as psychomotor retardation, feelings of insufficiency and disturbed circadian rhythms.

There is some evidence that acr are upregulated in depression. Adenosine A2A receptors are overexpressed in animal models of chronic stress and polymorphisms of A2A receptors are associated with emotional disturbances or depression[16]. Moreover, overexpressed acr have been identified in Parkinson's disease[17], Alzheimer's disease[18], and temporal lobe epilepsy[3].

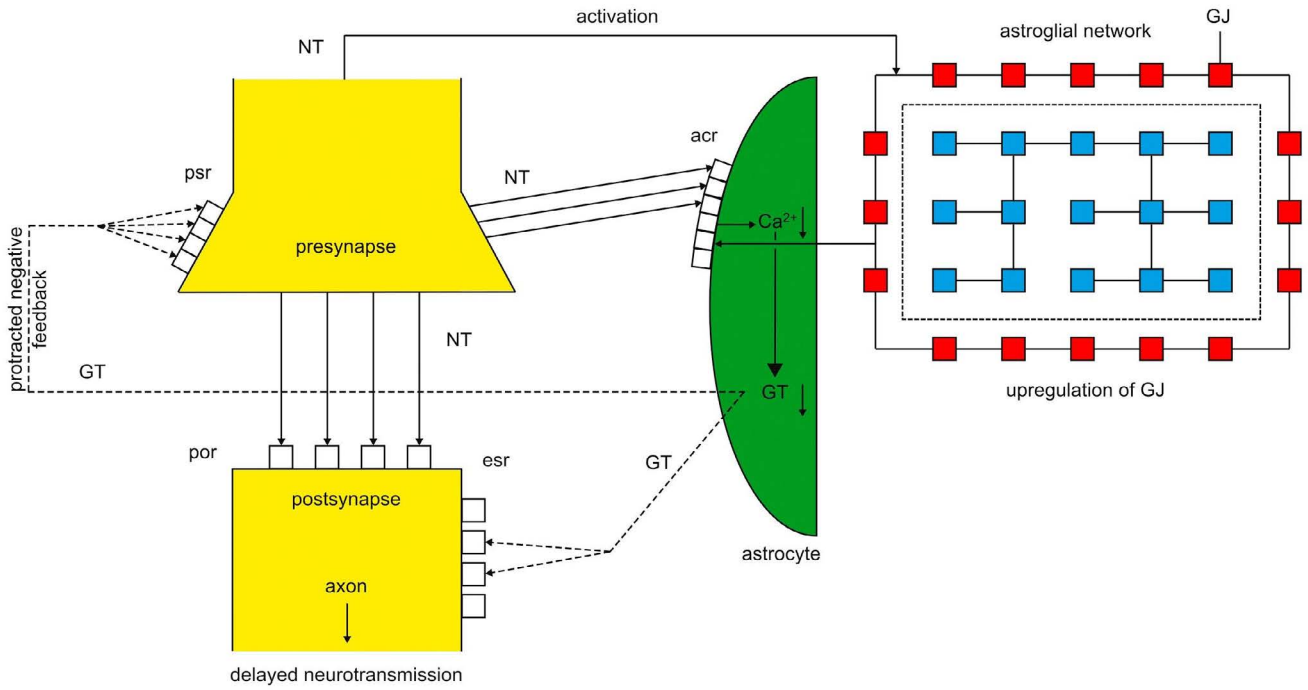

Figure 2: Imbalanced tripartite synapse in depression
Neurotransmitters (NT) released from the presynapse activate postsynaptic receptors (por) and astroglial receptors (acr). Overexpressed gap junctions (GJ, red) upregulate the expression of acr. Overexpressed acr cannot be completely activated by NT causing diminished Ca^{2+} concentration (↓) and production of gliotransmitters (GT, ↓). This leads to a protracted activation of por, extrasynaptic receptors (esr) and a protracted negative feedback on presynaptic receptors (psr) delaying neurotransmission. (dashed lines)[15]

Imbalanced Tripartite Synapses in Mania

The imbalance of astroglia-synapse interactions in mania occurs, if gap junctions in the astroglial network and acr are underexpressed. This leads to a surplus of NT relative to the underexpressed acr causing a flooding of acr with NT. As shown in figure 3 the overactivation of acr increases the Ca^{2+} concentration and GT production that exert a shortened feedback on the psr accelerating neurotransmission. This may explain the main symptoms of mania as manic distractibility, the flight of ideas, overactivity and circadian-biorhythmic disturbances such as insomnia[19,20].

Although excessive neurotransmission caused by the underexpression of acr is as yet not identified, relevant studies indicate excessive dopaminergic activity in brains with mania or bipolar disorder[21].

Unbalanced Tripartite Synapses in Schizophrenia

The model of schizophrenia is based on unbalanced astroglia-synapse interactions caused by non-functional acr leading to an unconstrained synaptic flux so that astroglia loses their modulatory function in tripartite synapses[22,23]. As shown in figure 4 non-functional acr (crosses) cannot be activated by NT. Hence the production of GT is not possible and GT cannot exert a negative feedback on cognate psr leading to an unconstrained neurotransmission. Given that patients with schizophrenia are unable to distinguish between the self and the others, the model proposed is explanatory. Since the flux of neurotransmission cannot be modulated by astroglia, a gap between the sensory information processing of the neuronal system and the "inner" astroglial network exists resulting in incoherent thoughts, delusions, and affective flattening[23].

Recent experimental findings indicate that alterations in excitatory signaling, particularly involving hypofunction of N-methyl-D-aspartate receptors (NMDR) play a key role in the schizophrenia disease process[24]. Theoretically, a model of the pathophysiology of schizophrenia focusing on non-functional gliotransmission in tripartite synapse has been mathematically described[25].

Imbalanced Tripartite Synapses in Epilepsy

In addition to the various recognized findings in the neuronal system, there is growing evidence that dysfunctional astrocytes are crucial players in epilepsy[3,26,27]. Here, I outline a model of imbalanced tripartite synapses responsible for the pathophysiology of epilepsy based on the imbalance between hyperactivated glutamatergic and hypoactivated GABAergic tripartite synapses.

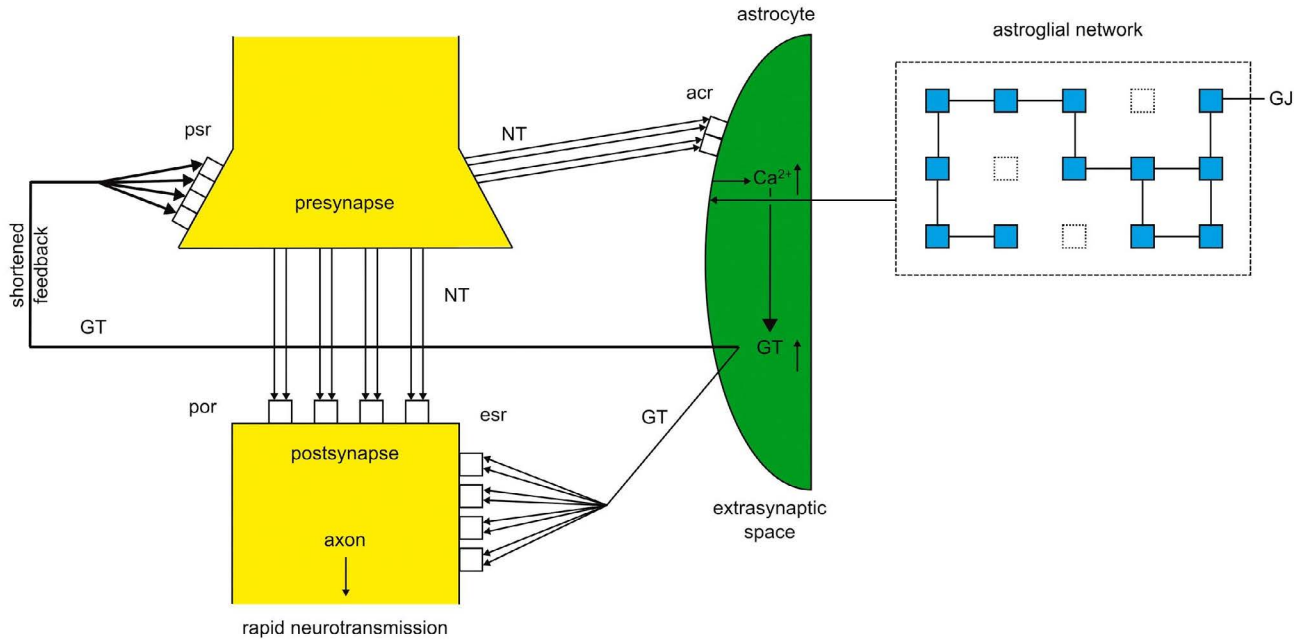

Figure 3: Imbalanced tripartite synapse in mania
Underexpression of gap junctions (dashed squares) downregulates the expression of acr. Underexpressed acr are flooded (bold lines) by NT increasing Ca^{2+} concentration (↑) and the production of GT(↑) leading to a shortened feedback on psr (bold line). por and esr are also hyperactivated causing a rapid neurotransmission. (modified[13])

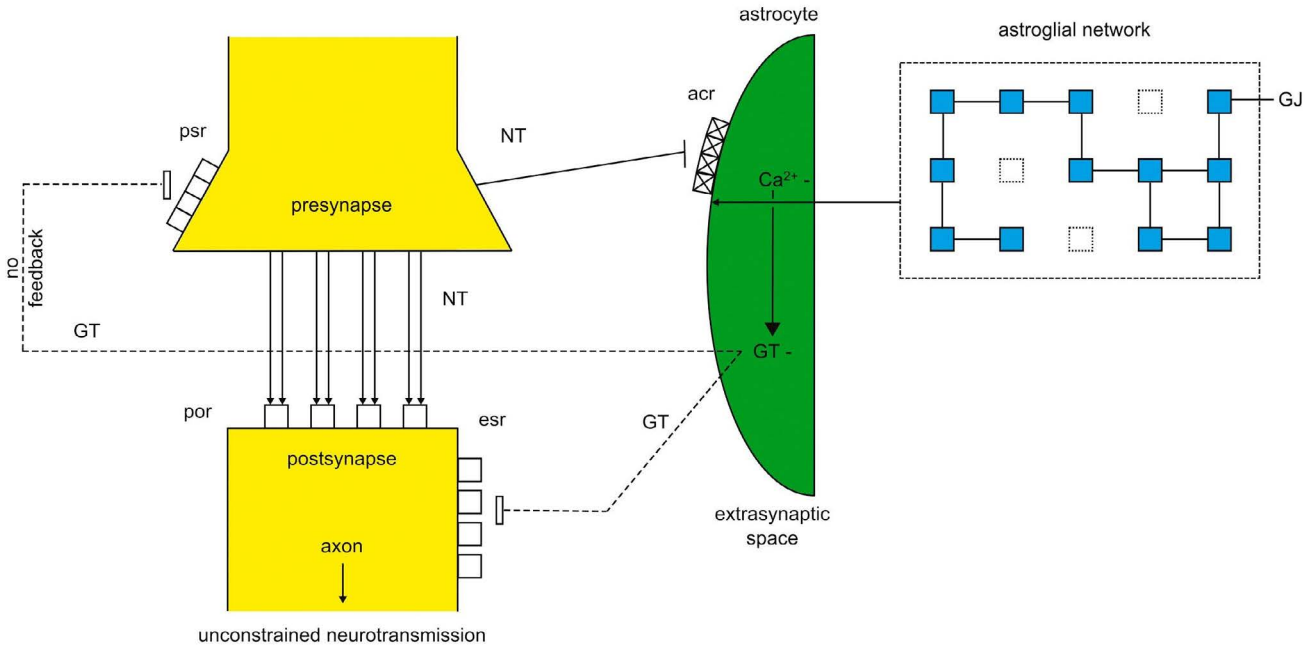

Figure 4: Unbalanced tripartite synapses in schizophrenia
acr are non-functional (crosses) and cannot be activated by NT. Ca^{2+} and GT production is not activated by NT leading to an unconstrained neurotransmission (bold arrows), since no negative feedback is exerted by NT on psr (dashed line).

Figure 5a depicts a hyperactivated glutamatergic tripartite synapse. Glutamate (GLU) is excessively released from the hyperactivated presynapse flooding both postsynaptic receptors (por) and acr. As identified in temporal lobe epilepsy metabotropic GLU receptors (mGluR) in astrocytes are overexpressed and become

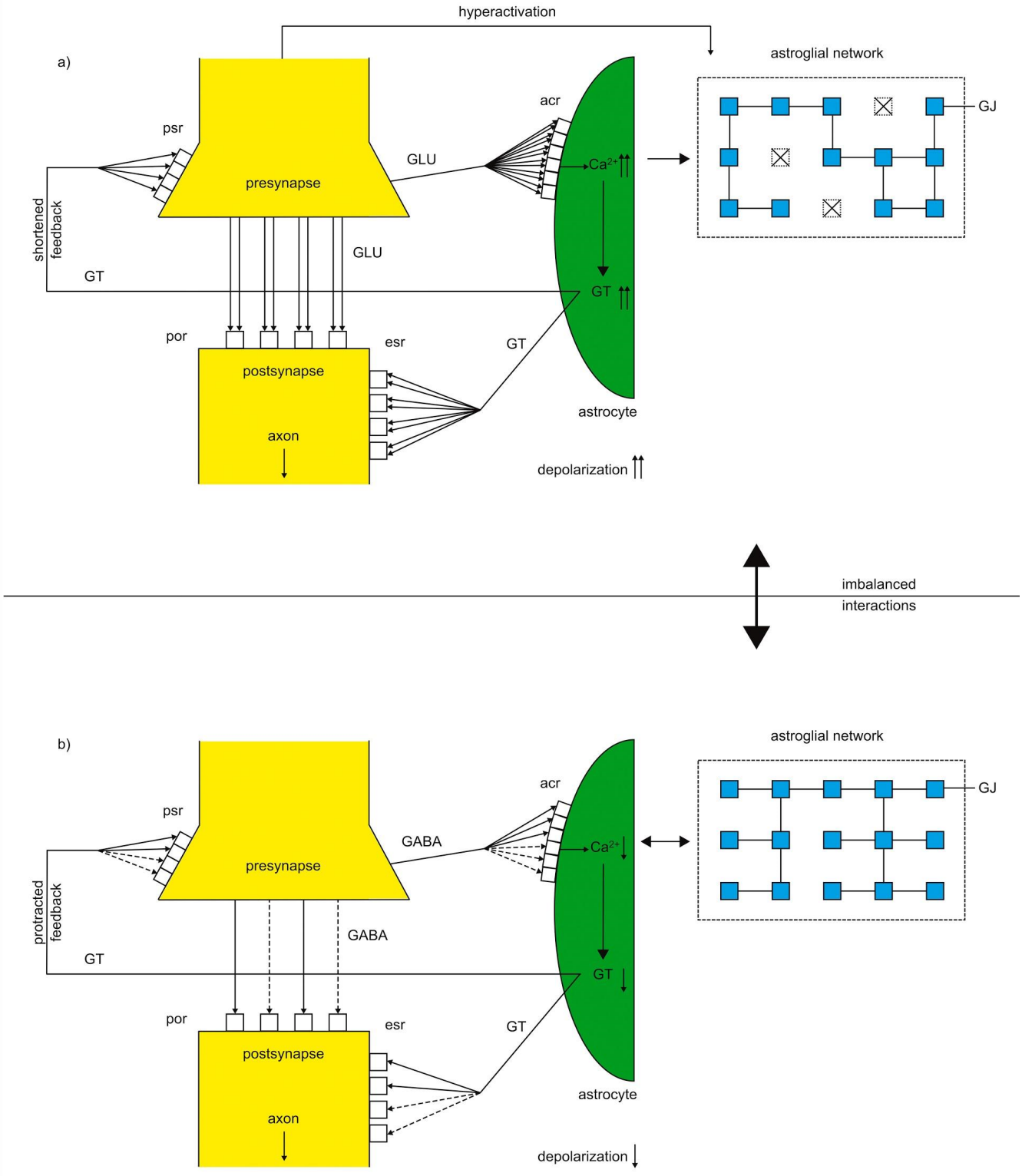

Figure 5: Imbalance between glutamatergic and GABAergic tripartite synapses in epilepsy

a.) Glutamate (GLU) hyperactivates por and acr (bold lines). The Ca^{2+} concentration and GT production is excessively increased (↑↑) leading to a shortened feedback on psr and the hyperactivation of esr (bold lines) excessively depolarizes the postsynapse.

b.) Decreased GABA release (dashed lines) from the presynapse hypoactivates por and acr. Ca^{2+} and GT production is diminished (↓) causing a protracted feedback on psr and a protracted depolarization of the postsynapse, since esr are hypoactivated by GT (dashed lines). The interactions between the glutamatergic and GABAergic tripartite synapses are imbalanced (bold double-headed arrow).(modified[13])

overactivated by GLU. This hyperactivation of mGluR causes excessive Ca^{2+} concentrations and GT production in the astrocyte. GTs hyperactivate psr and esr exerting a shortened feedback and an excessive depolarization of the postsynapse. Note, overexpressed mGluR are not balanced by GLU, but hyperactivated because of the flooding with GLU. The hyperactivated astrocyte may exert excitotoxic effects leading to a decoupling of gap junctions in the astroglial network[3].

In parallel, inverse mechanisms may operate in hypoactivated GABAergic tripartite synapses shown in figure 5b. Here, acr are also overexpressed, but the production of GABA is decreased and unable to completely activate acr. Consequently, Ca^{2+} concentration in astroglia is too low and the underproduction of GT exerts a protracted negative feedback on psr. Therefore, GABAergic tripartite synapses cannot put into action their inhibitory effect in time causing an imbalance (bold,double-headed arrow) between hyperactivated and hypoactivated tripartite synapses. This imbalance may play a key role in epileptogenesis[28].

Concluding Remarks

In the perspective of common pathophysiological mechanisms operating in mental disorders and epilepsy, the determining function of acr is comparable in these disorders. Considering epilepsy, on the one hand, acr are overexpressed in glutamatergic tripartite synapses and flooded by GLU comparable to imbalanced synapses in mania. On the other hand, acr are also overexpressed in GABAergic tripartite synapses but hypoactivated by GABA comparable to imbalanced synapses in depression. The model here proposed is mainly theoretical and must be clinically and biologically tested. Concerning depression, we could show in a computer simulation that prolonged synaptic information processing may be responsible for retarded depressive behavior[29]. This result is clinically supported by a sample of patients with major depressive disorder[30]. In addition, comprehensive case studies on depression and schizophrenia indicate that the model of synaptic imbalance based on astroglia-synapse interactions may be explanatory for the main symptoms of these disorders[14,31].

Admittedly, the testing of the abnormal expression of acr in animal models and in patients with neuropsychiatric disorders with imaging techniques has not yet been conducted, but should be done in the near future.

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