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Balancing and imbalancing effects of astrocytic receptors in tripartite synapses. Common pathophysiological model of mental disorders and epilepsy

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ABSTRACT

Based on a logic of balance mechanisms influencing information processing in tripartite synapses are proposed. It is hypothesized that the number of expressed astrocytic receptors determines balanced and imbalanced synaptic states. Synaptic information processing in mental disorders is underbalanced in depression, overbalanced in mania, and completely unbalanced in schizophrenia. The synaptic pathophysiology of the epileptic syndrome may also be based on comparable imbalances. In addition, this model of synaptic balancing enables a deduction in explaining the therapeutic effect of ECT in therapy resistant depression. Together, the model proposed may represent a contribution to the search for common synaptic mechanisms in normal brains and its various disorders.

Introduction

There is currently growing experimental evidence for some changes occurring in astrocytic signaling in the epileptic tissue of the brain, also described as dysregulations of molecules and pathways in various brain disorders [1]. However, these experimental findings concern mainly the neuronal system. Therefore, the experimental exploration of glial–neuronal interactions in brain disorders like epilepsy or mental disorders are still in its infancy [2]. Here, the hypothesis by Robertson [3] is promising, since it postulates a central role of astrocytes in glial–neuronal interactions. Importantly, this hypothesis is receiving growing experimental support [4].

Since astrocytic receptors, expressed for the occupancy by the known activating substances, may basically determine imbalances in tripartite synapses, I propose pathophysiological mechanisms focusing on the balancing function of astrocyte receptors [5]. Searching for a common synaptic mechanism from which synaptic imbalances can be deduced, mental disorders and the epileptic syndrome might serve as a preliminary model. These common synaptic mechanisms can also explore why electroconvulsive treatment (ECT) in therapy resistant depression may exert an improvement of this severe suffering.

Hypothesis

Basically, synaptic imbalances can be found in various brain disorders. With concern to the glial system I hypothesize that astrocytic receptors, ready for occupancy by various activating substances, cannot exert their normal balancing effect in tripartite synapses. In undisturbed synaptic information processing astrocytes also produce transmitter substances, called gliotransmitters, released in the synaptic cleft and which occupy appropriate presynaptic receptors. Dependent on the function of the activating substances, either a positive feedback (excitation) or a negative feedback (inhibition) is generated.

Based on a formalism of balancing it can be shown if a system is balanced, underbalanced, overbalanced, or completely unbalanced. Accordingly, if a synaptic system is underbalanced (astrocytic receptors > the amount of activating substances), the symptoms of depression may develop. In the case of an overbalanced synaptic system (astrocyte receptors < activating substances), manic symptoms may occur. In the case of schizophrenia non-functional astrocytic receptors may be responsible for a complete synaptic imbalance and the corresponding symptomatology.

Moreover, these pathophysiological mechanisms may basically not only cause these mental disorders, but may also play a central role in the epileptic syndrome. Contrary to the pathophysiology of depression, in epilepsy an unconstrained overproduction of excitatory transmitter substances, especially glutamate, cannot be interrupted since a relative lack of astrocytic receptors affects their modulating and inhibitory functions. The principle of this

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balancing effect, co-determined by astrocytic receptors, can be shown for all transmitter substances, independent of their excitatory or inhibitory functions.

It may not be surprising that an appropriate application of ECT in patients with a therapy resistant depression may "augment" the amount of lacking transmitter substances and exert a balancing effect via occupancy and activating astrocytic receptors which were overexpressed and not activated in the state of depression. The model proposed is experimentally testable. Presently, "optogenetics" experiments are promising.

Logic of balance

The formalism applied is the logic of balance introduced by the German–American philosopher Guenther [6]. It can serve as an explanatory basis for the various balancing mechanisms identified in the operations of synapses. My formal request is this: the operations of tripartite synapses are balanced if the number of variables and values are equal. Biologically, astrocytic receptors function as variables, substances activating them can be interpreted as values.

Accordingly, there are principally four system states in tripartite synapses (Table 1). First, the number of astrocytic receptors (variables) and the number of neurotransmitters (values) is equal. Second, the astrocytic receptors outnumber the neurotransmitters. This system is underbalanced since not enough activating substances are available. Third, the neurotransmitters outnumber the astrocytic receptors. This synaptic system is overbalanced because of an excess of material for the occupancy of astrocytic receptors, causing the pathophysiology of mania and other brain disorders, such as epilepsy. Fourth, in tripartite synapses a total lack of functional astrocytic receptors generates unbalanced synaptic mechanisms as is the case in the schizophrenic syndrome.

Balance of information processing in tripartite synapses

The concept of a synapse has originally been introduced by Sherrington [7]. Since then many experiments on information transmission in purely neuronal synapses are available. Moreover, Araque and coworkers [8] have proposed an interpretation of neuronal–glial units, termed tripartite synapses. Pertinent experiments are opening a window for a new vista of brain research [9,10].

With concern to synaptic balancing equalizing excitation–inhibition ratios across visual cortical neurons have recently been identified [11]. However, this elementary synaptic principle has also been shown in tripartite synapses, where astrocytes coordinate synaptic networks leading to a balanced excitation and inhibition [12]. Importantly, every model of synaptic balancing should differentiate between the general principles of "wiring" and "value" transmission [13–16]. Hence, we must also refer to extrasynaptic receptors and to the extrasynaptic space in a model of tripartite synapses.

In the synaptic model proposed here I focus on the balancing function of astrocytic receptors which is somewhat neglected in pertinent brain research. Basically, all types of receptors for known neurotransmitter substances have been found in astrocytes embodying both metabotropic and ionotropic receptors [13,17].

Fig. 1 shows schematic diagrams of balanced tripartite synapses focusing on the decisive effects of astrocytic receptors. Referring to the various activating substances of astrocytic receptors only glutamate (GLU, a) and gamma-amino-butaric-acid (GABA, b) are

Table 1
Logical balance, overbalance and underbalance in tripartite synapses. This matrix shows six glial receptors (variables, $n = 6$) and six neurotransmitters (values, $n = 6$). In each number pair the upper number designates glial receptors, the number below neurotransmitters. According to the logic of balance, the system is balanced if the number of variables (glial receptors) and the number of values (neurotransmitters) is equal. The number pairs (in squares) in the diagonal of the matrix (1…6) represent balanced tripartite synapses. The number pairs above the diagonal designate underbalanced synaptic systems, since the glial receptors outnumber the neurotransmitters. In contrast, the number pairs below the diagonal represent overbalanced tripartite synapses, because the neurotransmitters outnumber the glial receptors.

Glial receptors (variables)

neurotransmitters (values) m \ n	1	2	3	4	5	6
1	[1 1]	2 1	3 1	4 1	5 1	6 1
2	1 2	[2 2]	3 2	4 2	5 2	6 2
3	1 3	2 3	[3 3]	4 3	5 3	6 3
4	1 4	2 4	3 4	[4 4]	5 4	6 4
5	1 5	2 5	3 5	4 5	[5 5]	6 5
6	1 6	2 6	3 6	4 6	5 6	[6 6]

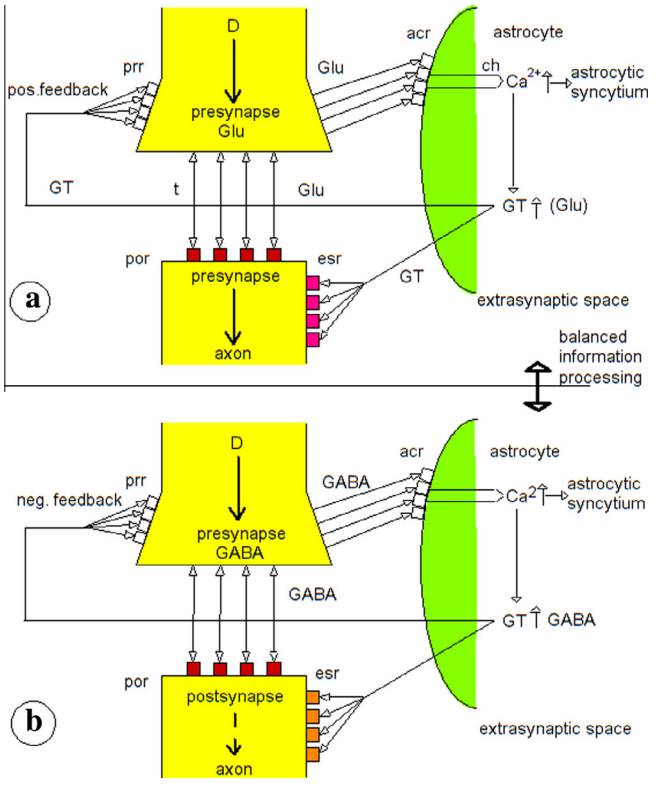

Fig. 1. Schematic diagrams of a balanced, an excitatory (a) and an inhibitory (b) tripartite synapse. A dendrite (D) activates the excitatory neurotransmitter glutamate (GLU) in the presynapse. GLU occupies postsynaptic receptors (por), reuptaken (↔) via transporters (t). In parallel, receptors on the astrocyte (acr) are occupied by an appropriate amount of GLU (→). This activates channels (ch), the production of Ca^{2+}-waves and gliotransmitters (GT) with the structure of GLU. GT occupy presynaptic receptors (prr) and extrasynaptic receptors (esr) on the postsynapse. The excitatory effect of GLU corresponds with a positive feedback mechanism on the presynapse and the depolarization by the occupancies of postsynaptic and extrasynaptic receptors. These mechanisms depict the excitatory effect of GLU in tripartite synapses. (b) In an inhibitory synapse GABA exerts inverse mechanisms. The synaptic effects of (a) and (b) enable a balanced information processing (↕).