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Novel Treatment Approach in Schizophrenia: Substitution of Glial Binding Proteins

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Abstract

In chronic schizophrenia, synaptic information processing is unbalanced, as shown in a model of glial-neuronal synaptic units, called tripartite synapses. The glial component of the synapse exerts a modifying function in neurotransmission since the astrocyte activated by neurotransmitters produces gliotransmitters that negatively feedback to the presynapse. It is hypothesized that in schizophrenia nonfunctional astrocytic receptors cannot be activated, thus losing their modulating function. This causes a generalization of information processing in the neuronal networks such that the brain is unable to distinguish between subjects and objects in the environment. Delusions, hallucinations and cognitive impairment occur on the behavioral level. In a model of a cholinergic tripartite synapse, it is shown that glial binding proteins modify neurotransmission by occupancy with cognate neurotransmitters temporarily turning off neurotransmission on the presynapse. Most recently, glial binding proteins have been engineered. It is proposed that the substitution of glial binding proteins may balance synaptic information processing in schizophrenia since these proteins exert a modulatory function comparable to functional astrocytic receptors. Rapid technical developments may enable this novel treatment approach in schizophrenia.

Keywords

Schizophrenia, Synaptic unbalance, Astrocytic Receptors, Glial Binding Protein, Treatment

1. Introduction

Schizophrenia is a worldwide neuropsychiatric disorder with about 1% incidence. The core symptoms are delusions, hallucinations and cognitive impairment. Although episodic courses of illness are described [1], the present paper refers to schizophrenia as a

chronic, therapy-resistant illness. Various brain models of schizophrenia such as the neurodegenerative model [2] with white matter abnormalities [3] are proposed. My brain model is based on impaired neuro-glial interactions. In normal brain function, glia is modifying information transmission [4], structuring neuronal networks in distinct time periods such that the brain is capable of distinguishing subjects and objects in the environment.

If information processing in glial-neuronal synaptic units, called tripartite synapses, is unbalanced, a generalization of information processing is generated in the brain [5] [6]. As experimentally indicated [7], an unconstrained flux of neurotransmission in synapses may cause a generalization of information processing in the brain, since oligodendrocyte-axonic information transfer is also affected [8]. Such severe impairment of brain functions makes the patient incapable of distinguishing between himself and the others. I speak of a loss of self-boundaries in schizophrenia [5] [9].

The hypothetical model presented here focuses on non-functional astrocytic receptors that cause a total unbalance of synaptic information processing, since the glial modifying function is lost. Importantly, since current antipsychotic drugs exert no significant effect on astrocytic receptor dysfunction, a substitution of engineered glial binding proteins could enable normal astrocytic receptors. Hence, I propose that engineered glial binding proteins may exert a balancing effect, modifying synaptic information processing and structuring cognitive operations in the neuronal networks.

2. Model of a Tripartite Synapse

The basic components of a tripartite synapse are composed of the presynaptic neuron, the postsynaptic neuron, and the astrocyte embodying the glial cell with a synaptic cleft in between. The glial-neuronal interactions in chemical tripartite synapses occur via neurotransmitters, gliotransmitters and other substances (neuromodulators, transporters, ions, etc.). Experimental neurophysiological research has demonstrated that the glial system exerts a modulatory function in its interactions with the neuronal system [10]. Astrocytes are interconnected by gap junctions building a glial network, called syncytium. Gap junctions consist of connexin proteins forming channels by hemichannels of different kinds [11]. Whereas astrocytes are interconnected with their neighbors via gap junctions, the interactions of astrocytes with neurons occur mainly in tripartite synapses [12] (The interactions of astrocytes with oligodendrocytes and microglia are for the sake of clarity not considered here).

Figure 1 outlines the function of a balanced tripartite synapse, since the number of astrocytic receptors and the amount of cognate neurotransmitters is appropriate. This situation also holds for the other receptor locations. Neurotransmitters (NT) released from the presynapse occupy the postsynaptic receptors (poR). In parallel, NT occupy the astrocytic receptors (acR) on the astrocyte (Ac) activating the production of gliotransmitters (GT) within the astrocyte and the gap junctions (g.j.) or hemichannels (HC) in the glial network via Ca^{2+} waves. The GT are released in the synaptic cleft occupying the presynaptic receptors (prR), exerting a negative feedback. Dependent on

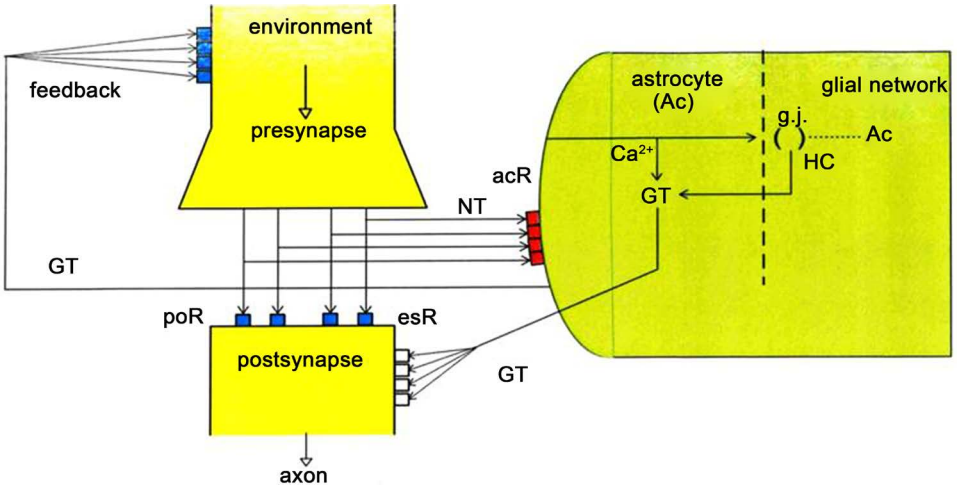

Figure 1. Model of a tripartite synapse.

the excitatory or inhibitory function of gliotransmitters, a positive or negative feedback mechanism determines the production of neurotransmitters in the presynapse. A comparable mechanism of GT in the extrasynaptic receptors (esR) of the postsynapse either depolarizes or hyperpolarizes neurotransmission. In addition, the occupancy of postsynaptic receptors directly depolarizes the neuron. Gliotransmitters temporarily turn off synaptic information processing and neurotransmission starts again. Here, I focus on the active role of astrocytic receptors and the negative feedback mechanism exerted by gliotransmitters. Receptors on astrocytes are meanwhile identified for the various neurotransmitter types. The same holds for the identification of transmitter substances by astrocytes, called gliotransmitters and the identification of cognate presynaptic receptors [13].

3. Logic of Balance

The formalism applied is the logic of balance introduced by the German-American philosopher Guenther [14]. It can serve as an explanatory basis for the various balancing mechanisms identified in the operation of synapses, as pointed out in earlier publications [6] [15]. Importantly, this formalism enables the computation of the amount of substituted glial binding proteins based on experimental findings. My formal request is this: the operations of tripartite synapses are balanced if the number of variables and values is 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). 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

Table 1. Logic of balance.

			Glial receptors (variables)					
	m	n	1	2	3	4	5	6
Neuro-Transmitters (values)	1		1	2	3	4	5	6
			1	1	1	1	1	1
	2		1	2	3	4	5	6
			2	2	2	2	2	2
	3		1	2	3	4	5	6
			3	3	3	3	3	3
	4		1	2	3	4	5	6
			4	4	4	4	4	4
	5		1	2	3	4	5	6
			5	5	5	5	5	5
	6		1	2	3	4	5	6
			6	6	6	6	6	6

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. In the case of a totally unbalanced tripartite synapse (as proposed in schizophrenia), no variables are available (nonfunctional astrocytic receptors). 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, presumably responsible for the pathophysiology of depression. Third, the neurotransmitters outnumber the astrocytic receptors. This synaptic system is overbalanced because of an excess of material for the activation of astrocytic receptors, presumably 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 hypothesized in schizophrenia.

4. Model of an Unbalanced Tripartite Synapse Responsible for Schizophrenia

As in Figure 2 depicted, glial receptors (glR) on the astrocyte are non-functional (crosses) and cannot be occupied by neurotransmitters (NT), and thus, the activation of gliotransmitters is impossible. Hence, they cannot negatively feedback to the receptors on the presynapse (prR) and are unable to depolarize the postsynaptic neuron. As a consequence, the glia lose their inhibitory or boundary-setting function [16] and the neural transmitter flux is unconstrained, corresponding to the flux of thought on the phenomenological level.

The loss of glial boundary-setting function and generalization of neuronal information processing is shown in Figure 3. In the glial-neuronal compartments (x, y) the as-

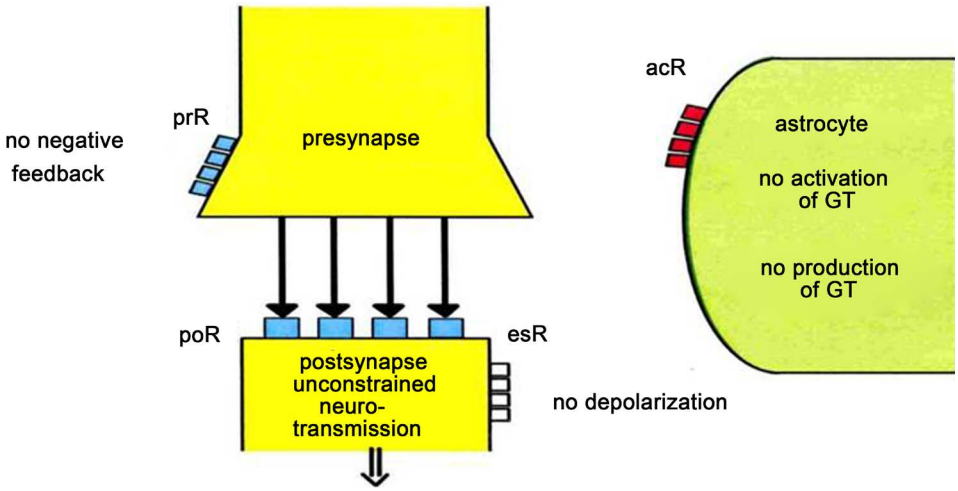

Figure 2. Unconstrained neurotransmission may cause schizophrenia.

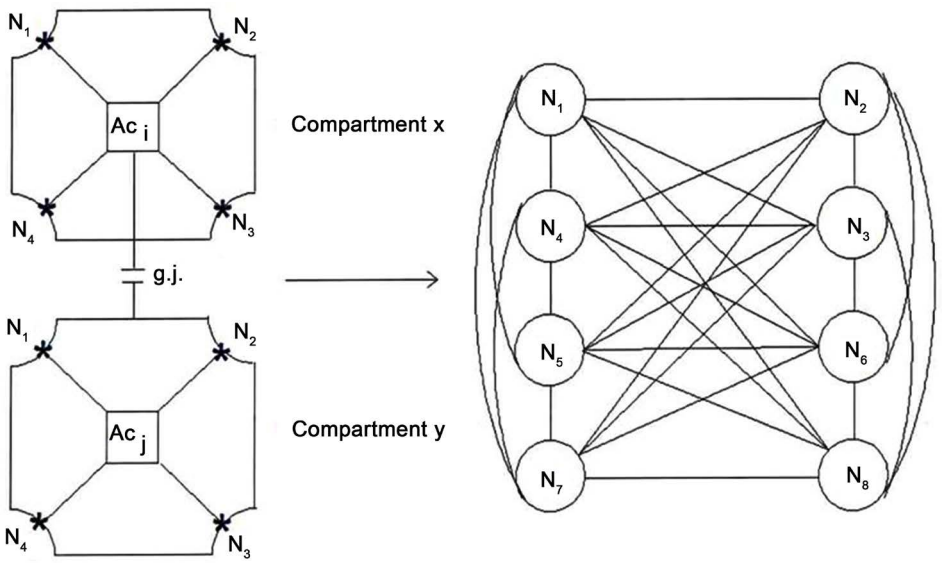

Figure 3. Loss of glial boundary-setting function and generalization of neuronal information processing.

trocytes (Aci, Acj) are unable to inactivate (negative feedback) any of the neurons (Ni…Nj). Therefore, they cannot influence the neurotransmission in the synapses (asterisks). This loss of glial boundary setting results in a compartmentless neuronal network where all neurons are interconnected [9]. Such a brain is unable to structure the environmental information. Importantly, in the American Psychiatric Textbook of Psychiatry [17] the psychotic symptoms of hallucinations and delusions are characterized as a loss of ego boundaries and the patient is unable to distinguish between his or her own thoughts/perceptions and those referring to the outer world. According to my pathophysiological model [5], the main systems of schizophrenia (thought disorder, delusions, hallucinations, catatonic symptoms, affective flattening) can be deduced from this conception.

5. Glial Binding Proteins in a Cholinergic Tripartite Synapse

The model of a tripartite synapse proposed by Smit and coworkers [18] is prototypic for my approach to a protein-substitution treatment of schizophrenia. In **Figure 4** a neurotransmitter (NT) is released from the presynaptic terminal, ready for occupancy of glial binding protein (BP) and postsynaptic receptors. In parallel, glial receptors are occupied by NT, which increases the production and secretion of soluble glial BP into the synapse. The increased levels of soluble BP in the synapse reduces that amount of free NT that can bind to postsynaptic receptors, and neurotransmission is inactivated by this form of negative feedback. Once the NT levels have returned to baseline, the BP levels will drop because the glial cells are no longer being stimulated to produce BP. The synapse will return to its initial state and synaptic information processing can start again.

Since glial BP has not been found in human brains, I have elaborated a model of a tripartite synapse where receptors on astrocytes exert the same function as glial BP in synaptic information processing [6] [15]. I propose that in schizophrenia astrocyte receptors do not function since their protein structure is impaired. Supposing that genes responsible for the expression of astrocytic receptors are spontaneously or exogenously (stress, etc.) mutated causing a non-functional astrocytic receptor structure, astrocytic receptors are flooded by NT. If it would be possible to supply proteins embodying the protein structure of astrocytic receptors in brains with unbalanced tripartite synapses, in accordance with the pathophysiological mechanism described, NT could activate these proteins such that the amount of NT produced in the presynapse is reduced and the postsynaptic neurotransmission is balanced. If such a therapeutic intervention works, balanced synaptic information processing may be capable to structure the brain functions for normal perception and cognition in pertinent brain locations.

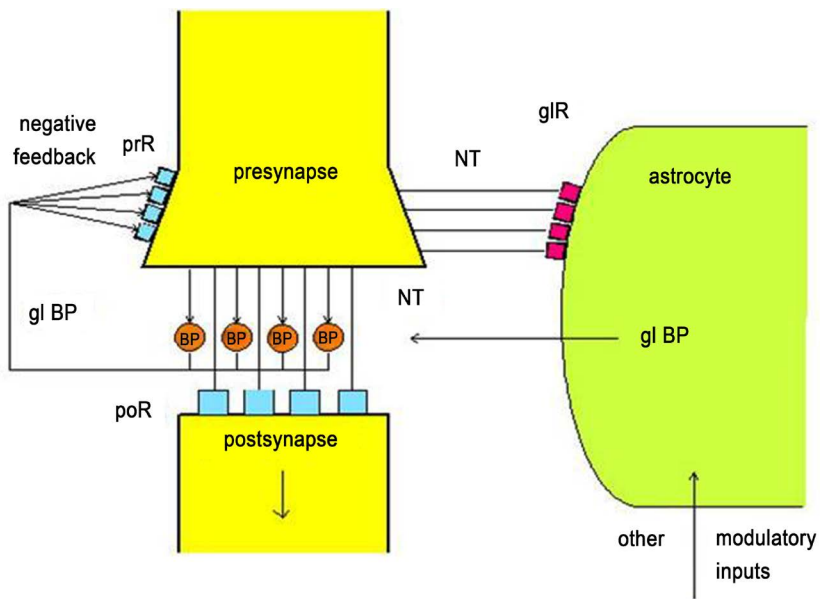

Figure 4. Model of a cholinergic tripartite synapse. Neurotransmission via glial binding proteins.

6. Treatment of Schizophrenia by Glial Binding Proteins

Engineering of Proteins

The ability to design proteins that self-assemble into precisely specified, highly ordered icosahedral structures open the door to a new generation of proteins [19]. Recently, a new method for producing and isolating human glial progenitor cells has been developed enabling a cell-based therapy for neurological and neuropsychiatric disorders [20]. The engrafted human progenitor cells proceed to generate parenchymal astrocytes, and when faced with a hypomyelinated environment, oligodendrocytes as well within the muring host. These brains provide us with a fundamentally new tool to assess the species-specific attributes of glia in modulating human cognition and information processing. The mechanism of pairing the construction of human glial chimeras with the production of patient-specific human glial progenitor cells derived from pluripotent stem cells produces mice in which a substantial proportion of resident glia are both human and disease-derived.

For my treatment model of schizophrenia it is decisive that Otvos and coworkers [21] have managed to engineer binding proteins. Recently, a binding protein was engineered which contains the ligand recognition properties of the 5-Hydroxytryptamine 3 receptor (5-HT3R). This ligand-binding pocket of the 5-HT3R was engineered by mutation in the original scaffold of the Aplysia california acetylcholine-binding protein (AchBP). Sophisticated technical methods enable the engineering of binding proteins. Basically, online microfluidic screening of several snake venoms demonstrates the identification of new peptides binding to the 5-hydroxytryptamine binding protein. Most importantly, in the future these screening assays can be used for screening campaigns to identify novel bioactive compounds from complex mixtures [21].

7. Treatment Model

Engineered glial binding proteins could be applied on unbalanced tripartite synapses caused by non-functional receptors. It is principally possible to engineer glial binding proteins for all astrocytic receptor types or neurotransmitter substances. **Figure 5** depicts an unbalanced tripartite synapse in which non-functional astrocytic receptors (crosses) are substituted by a corresponding amount of glial binding protein (BP). Here the BPs are activated by neurotransmitters (NT). In parallel, NT occupies postsynaptic receptors (poR). BPs activate presynaptic receptors (prR), temporarily turning off neurotransmission in the sense of a feedback mechanism. This mechanism is normally exerted by gliotransmitters (GT).

There is experimental evidence that Ca2+ waves activate hemichannels (HC) in the glial network leading to the release of gliotransmitters that negatively feedback to prR turning off synaptic neurotransmission. In the extrasynaptic space GT may exert the same function. Although the exact mechanism of gliotransmission is unclear [22], there is growing evidence that increased intracellular free Ca2+ concentration allows the release of gliotransmitters into the synaptic cleft via vesicles and hemichannels [13].

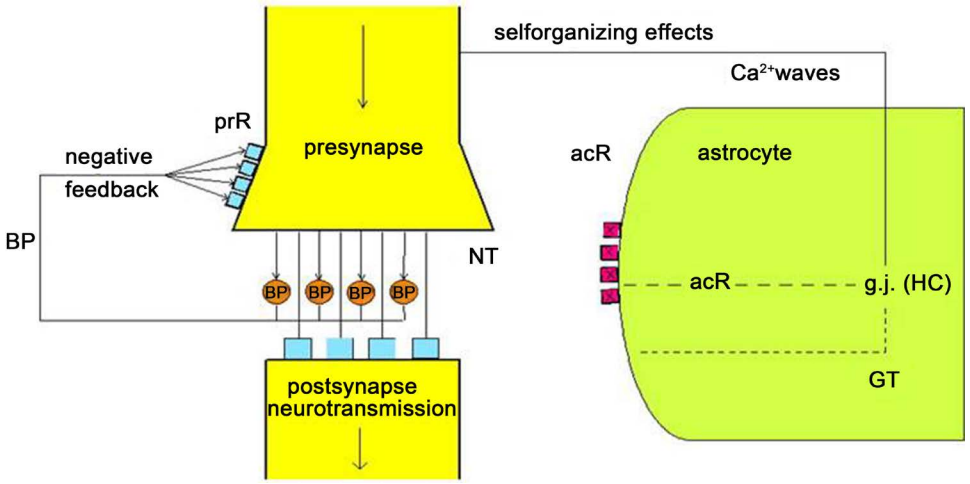

Figure 5. Substitution of glial binding proteins balancing neurotransmission in an unbalanced tripartite synapse.

The extraordinary capacity of astrocytes [23] to adapt to their surrounding environment by changing the expression of a vast number of proteins is evident in fast changes in the expression of synaptic receptors for neuro- and gliotransmitters [24]. Decisively, in the model of a cholinergic tripartite synapse shown by Smit and coworkers [18], the structure of glial binding proteins is appropriate for the occupancy of cognate neurotransmitters. Therefore, glial binding proteins put the same function into action as gliotransmitters balancing and timingly structuring synaptic information processing. In addition, the balancing effect of glial binding proteins in tripartite synapses may also work in the glial network, such that the expression of functional astrocytic receptors might be activated again. Such an initiation of a self-organizing process in tripartite synapses and their network as a long-term balancing effect of the substitution of glial binding proteins is not inconceivable.

8. Discussion and Prospects

Basically, protein engineering may provide significant progress in the treatment of neurological and neuropsychiatric disorders. Hereby, synthetic receptor molecules may play a central role [25]. In neuropsychiatric disorders (affective disorder, schizophrenia), various transmitter-receptor types may be affected. Current psychopharmacological drugs are only partly able to cope with this issue. Most excitingly, since glial-binding proteins can principally be engineered for all receptor qualities, a comprehensive treatment approach of schizophrenia is possible. One may argue that my model of schizophrenia is hypothetical and lacking experimental evidence. However, from a theoretical point of view, this model may provide a model system from which not only the main symptoms of schizophrenia are deducible, but it is also possible to develop a new treatment approach in schizophrenia based on the substitution of glial binding proteins balancing tripartite synapses.

The possible modeling of disease using human glial chimeric cells or proteins [20]

may provide opportunities for studying the human-specific contributions of glia to human psychopathology. Given the high complexity of glial-neuronal interactions and the impossibility to fully explore them, glial-binding proteins could exert a fundamental mechanism of balancing synaptic information processing in brains with schizophrenia. Evidently, this novel treatment approach of schizophrenia must stand tests in animal experiments, but could even be stepwise applied in human brains with new techniques [26].

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Abbreviations

Ac: astrocyte.
AChBP: acetylcholine-binding protein.
acR: astrocyte receptor.
BP: binding protein.
$Ca2^{+}$: calcium ions.
esR: extrasynaptic receptor.
GT: gliotransmitter.
g.j.: gap junction.
HC: hemichannel.
5-HT3R: 5-Hydroxytryptamine 3 receptor.
N: neuron.
NT: neurotransmitter.
poR: postsynaptic receptor.
prR: presynaptic receptor.