Possible Role of Glia in Cognitive Impairment in Schizophrenia

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Cognitive impairment is a core disorder of the schizophrenia syndrome. Based on glial-neuronal interactions, a pathophysiological model is proposed that could be explanatory for cognitive impairment in schizophrenia. The model consists of three main hypotheses concerning the pathophysiology in tripartite synapses, oligodendrocyte-axonic interactions, and in the glial networks (astrocytic syncytium). In tripartite synapses nonfunctional astrocytic receptors may cause an unconstrained synaptic information flux, since they cannot be occupied by neurotransmitters (NTs). Therefore, a generalization of information processing may occur in the brain causing hallucinations, delusions, and thought disorder. If the oligodendrocyte-axonic system decomposes, the brain is unable to process information in qualitative domains or categories. This may lead to severe incoherence phenomena such as thought disorder. Supposing that in the astrocytic syncytium gap junctions (g.js) normally form plaques functioning as memory devices, loss of function of g.j. may also cause cognitive impairment, since the syncytium decomposes and g.j. plaques cannot be generated. These hypotheses are experimentally testable. Finally, the problem of treatment of patients with schizophrenia is discussed, in case the presented model of schizophrenia might be verified.

Introduction

Cognitive impairment in schizophrenia essentially concerns disorders of thought, perception, and memory [1,2]. Since the term cognition (Latin: cognoscere = to know, recognize) refers to the capability of information processing of the brain, first we need a brain model of normal information processing from which cognitive impairments can be deduced. Although biological schizophrenia research is now proposing various hypotheses of the pathophysiology of schizophrenia, these mostly refer only to the neuronal system of the brain. However, voices become louder that the glial system may also be affected in schizophrenia [3,4]. The present article focuses on disorders of glial-neuronal interactions that may be responsible for cognitive impairment in schizophrenia.

Schizophrenia is a vastly heterogeneous disorder, most likely not caused by one etiological factor, but rather due to a complex network of different interacting pathogenic influences [5]. Therefore, one could speak

of a schizophrenia syndrome [4]. Disorders of the three main systems or compartments of glial-neuronal interactions may be responsible for cognitive impairment in schizophrenia. First, the synaptic information flux in tripartite synapses is unconstrained caused by nonfunctional astrocytic receptors. This may cause a compartmentless neuronal network leading to severe impairment of perception (delusions and hallucinations) and thought disorder. Second, the oligodendrocyte-axonic system is decomposed caused by a decrease or loss of oligodendrocytes (Oc) and their myelin sheaths. Supposing that axonal information processing is categorized by the processes of Oc, this function may be severely disturbed, or even lost in schizophrenia causing the symptoms of disorganization such as thought disorder. Third, the glial network or syncytium is severely affected. Glial gap junctions (g.js) may register the neuronal activations of glial-neuronal compartments by generating g.j. plaques dependent on the activation frequency embodying a memory structure. If the g.j. proteins lose this function, they cannot generate plaques so that their memory

Figure 1 Model of a tripartite synapse. This figure is very schematic, showing only the basic signalling pathways at a tripartite synapse. Neurotransmitters (NT) are released from the presynapse (prR) occupying postsynaptic receptors (poR). In parallel, NT occupies glRs on the astro-

cyte activating Ca^{2+} waves. The increase of Ca^{2+} in the astrocyte causes it to release gliotransmitters (GT). GT feed back negatively to cognate presynaptic receptors (prR), so that neurotransmission is temporarily turned off. (Modified after Araque, Parpura, Sanzgiri and Haydon, 1999).

generating function is severely impaired or lost, causing the memory impairment in schizophrenia.

Unconstrained Information Flux in Tripartite Synapses may Cause Delusions and Hallucinations

Model of a Tripartite Synapse

Glia, especially astrocytes, are intimately involved in the active control of neuronal activity and synaptic information transmission. Already in 1999, Haydon et al. [6] showed that glia respond to neuronal activity with an elevation of their internal Ca^{2+} concentration which triggers the release of chemical transmitters from glia themselves and, in turn, causes feedback regulation of neuronal activity and synaptic strength. Accordingly, the signalling pathway at a tripartite synapse can be described as follows:

During synaptic neurotransmission, neurons release neurotransmitters (NTs) from synaptic nerve terminals into the synaptic cleft to communicate with other neurons. The transmitter released from the synapse (or other coreleased NT) can—under certain circumstances—spill

over from the synaptic cleft and reach NT receptors in adjacent glial cells (astrocytes or perisynaptic Schwann cells), eliciting intracellular increases in Ca^{2+} concentration in the glial cells (astrocytes). The increase in the astrocyte Ca^{2+} concentration causes it to release a chemical transmitter from the astrocyte (“gliotransmitter”) that feeds back to the presynaptic nerve terminal to modulate synaptic neurotransmission (Fig. 1). Meanwhile, various models of a tripartite synapse are proposed [7].

Synaptic Model of the Pathophysiology of Schizophrenia

As in Fig. 2 depicted, the glial receptors (glRs) are non-functional (crosses) and cannot be occupied by NTs, so that the activation of the gliotransmitters (GTs) is impossible. Hence, they cannot negatively feedback to the receptors on the presynapse (prR). As a consequence, the glia lose their inhibitory or boundary-setting function, and the neural transmitter flux is unconstrained, as the flux of thought on the phenomenological level.

The glial system in its interaction with the neuronal system generates glial-neuronal compartments in the sense of specific functional units or operational domains

Figure 2 Unconstrained neurotransmission in tripartite synapses may cause cognitive impairment in schizophrenia. Nonfunctional glRs, depicted by crosses, cannot be occupied by neurotransmitters (NT). Since the activation and production of gliotransmitters (GT) is not possible, glia do not negatively feed back to the presynaptic receptors (prR). This severe synaptic disturbance leads to an unconstrained neurotransmission (fat arrows) [11].

[8–10]. The interactional structure of an astrocyte with n-neurons can be defined as an elementary compartment of nerve cells. By simultaneously activating and deactivating neurotransmission in all of the synapses enveloped by an astrocyte [11], the astrocyte calcium wave may coordinate synapses into synchronously firing groups, interpretable as harmonization [12].

A loss of the glial boundary-setting function is depicted in Fig. 3 [10]. The astrocytes (Ac_i ; Ac_j) of compartment x and compartment y have nonfunctional glial receptors (asterisks), so that glia cannot influence neuronal information processing. This genetically determined disturbance results in a compartmentless neuronal network displayed as a group of eight neurons with 28 connecting lines (according to the formula $[n^2 - n]/2$). Such a brain is unable to structure the environmental information. One may argue that a glial determination of neuronal networks into functional units is not necessary because the neuronal system is compartmentalized *per se* [13]. However, there is a qualitative difference between the purely neuronal compartments and the glia-determined compartments. Neuronal compartments may be merely functional for information processing, whereas glial-neuronal compartments may, in

addition, have an information-structuring potency that we need for recognizing the qualitative differences between objects and individuals in our environment. That capacity may be lost in schizophrenic patients. Therefore, one can also speak of a loss of conceptual boundaries in schizophrenia. This disorder can affect cognitive processes such as thinking. If a schizophrenic patient is unable to delimit conceptual boundaries among words, thoughts, or ideas with different meanings, then meaningless word constructs (neologisms), or disorganized speech are the typical phenomenological manifestations, called “thought disorder”.

From an ontological point of view, delusions are the consequence of the loss of boundaries between the self and the others (nonselves). Here, the self is defined as a living system capable of self-observation. One could also say that our brain embodies a distinct ontological locus of self-observation. Everything taking place in the brains of schizophrenic patients is reality because they cannot differentiate between their inner world and the outer world. Therefore, they cannot see ontological differences between the selves and the nonselves. This loss of ontological boundaries may lead to a delusional misinterpretation of reality.

Figure 3 Loss of glial boundary-setting function. Generalization of neuronal information processing. In the glial-neuronal compartments (x, y) the astrocytes ($A_{i,j}$) are unable to activate any of the neurons ($N_1 \dots N_4$). 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 [11].

Hallucinations may be caused by the same disorder. However, the perception systems are phenomenologically affected. A schizophrenic, who hears the voice of a person in his head, is absolutely convinced that this person is really speaking to him. The loss of ontological boundaries or inner/outer confusion shows its phenomenological manifestation in the auditory system. Such a disorder can also occur in other sensory systems. The loss of the glial boundary-setting function may also be responsible for motoric and emotional symptoms in schizophrenia as catatonia and affective flattening. Importantly, Kondziella et al. [3] argued that astrocytes are important in controlling glutamate homeostasis, and it is therefore, necessary to assign a significant role to glial-neuronal interactions in the pathophysiology of schizophrenia. Moreover, there is extensive evidence suggesting glial impairment in the cerebral cortex of patients with schizophrenia [14,15].

The Incoherence Hypothesis of Schizophrenia: Based on Decomposed Oligodendrocyte-Axonic Relations

The processes of Oc that envelop axons via myelin sheaths tie axons together in groups according to a combinational rule [16]. Axons conduct information of various properties. These axonal properties are classified into

categories by the processes of Oc. By means of this mechanism the undisturbed brain is capable to compose informational qualities and can construct meaning from the many details of information. In the case of a decrease or loss of Oc and their myelin sheaths (demyelination), the oligodendrocyte-axonic system decomposes so that it is incapable of generating categories of information. This incoherence may be responsible for symptoms of disorganization in schizophrenia such as thought disorder, inappropriate affect, and incommunicable motor behavior.

Combinational Analysis of Axonal Properties via the Processes of Oligodendrocytes

Generally speaking, the oligodendrocyte-axonic system embodies a structure. The elements of this structure are n-axons interconnected with m-processes of Oc that envelop axons by their myelin sheaths. Supposing that each axon conducts information of a special property, the processes of Oc may categorize a set of axonic properties. A property is defined as an essential quality common to all members of a class. The logical definition of a category is any of the various basic concepts into which all knowledge can be classified. The structure of the oligodendrocyte-axonic system can be analyzed on three levels of complexity [17]:

Table 1 Qualitative counting in categories ($n = 4$) shown on an oligodendrocyte-axonic system. On the left from the vertical line the numbers of the processes of Oc (1...4) are enumerated. On the right from that line the categories of all possible oligodendrocyte-axonic structures are counted

Number of the oligodendrocytic (Oc) processes								
1	[1]	[2]						
2	[11]	[12]						
3	[111]	[112]	[121]	[122]	[123]			
4	[1111]	[1112]	[1121]	[1122]	[1123]	[1211]	[1212]	
	[1213]	[1221]	[1222]	[1223]	[1231]	[1232]	[1233]	[1234]

- 1) Protoanalysis: How many different properties are there? This corresponds to cardinality,
- 2) Deuteroanalysis: How are the properties distributed? This corresponds to distribution,
- 3) Tritoanalysis: Where are the individual properties located? This corresponds to the position.

If the oligodendrocyte-axonic system uses four processes, we must qualitatively count to four in order to achieve all combinational possibilities. Table 1 shows the qualitative counting from one to four [18]. On the left from the vertical line the numbers of the processes of Oc (1...4) are enumerated. On the right from that line the categories of all possible oligodendrocyte-axonic structures are counted. In the first case, only one process of an oligodendrocyte is available. This can merely connect one axon with property one (1) or another with property two (2). Oc with two processes are able to connect two axons with the same (11) or with different (12) properties. In the case of three processes, the position of the processes becomes relevant. In order to refer to all possible positions of the axonic properties, already five categories are generated. Applying this rule to four processes, we must count to fifteen (1111...1234). Each number designates a specific category (brackets) with increasing complexity. Such qualitative counting or categorization follows the sequence of the Bell numbers. Bell numbers $B(n)$ are generated according to the formula

$$B(n) = \sum_{i=1}^n S(n, i)$$

($S(n, i)$ are the Stirling numbers of the second kind). Table 2 shows the first ten Bell numbers that rapidly increase. Taken this integer sequence, Oc with ten processes generate a combinational structure with 115975 categories. Here one is seduced to speculate if this high potential of the brain to categorize information could be an inexhaustible source of creativity.

Fig. 4 gives an example how Oc with one to four processes connect ten axonic lines with four different

Table 2 The Bell number $B(n)$ indicates how many categories n processes of Oc can generate. The rapid increase of the first ten Bell numbers is shown. Taken this integer sequence, Oc with ten processes generate a combinational structure with 115975 categories

n: number of processes	1	2	3	4	5	6	7	8	9	10
$B(n)$: number of categories	1	2	5	15	52	203	877	4,140	21,147	115,975

properties (1...4). Each Oc is characterized with the category that its processes generate. From the left to the right examples of one to four processes (according to Table 1) are given. Together, the capacity of the oligodendrocyte-axonic system to generate categories may lead to a coherent information processing. Coherence in cognition means that we are able to abstract, generalize and extract meaning from different properties of information. This capacity can be severely disturbed in schizophrenia.

It may be controversial to assign information processing and topical properties to axons, especially if the brain is placed into conceptual framework of nonlinear dynamics [19]. However, in considering the myriads of various receptors within the brain and on the sensory receptor sheaths, structural specificity and topical precision may be very relevant for information processing. Take, for example, the identified specific molecular quality of olfactory receptors [20,21]. Another argument is visual perception where the concept of retinotopy supports a topological organization of information processing [22]. Furthermore, there are various types of neurons in the brain that exert specific function in the sense of special purpose computers as example identified in the visual cortex [23]. If a neuron or sensory receptor transfers their information via axons to other systems in the brain, then these axons may not only conduct currents, but also specific properties of information.

Figure 4 Example of an oligodendrocyte-axonic structure according to the rule of categorization (Table 1). Oligodendrocytes (Oc) and myelin sheaths (Ms) are represented in red colour. Ten axons (black) with different or equal properties of information processing (1...4) are shown.

Each Oc is characterized with the category that its processes generate. From the left to the right examples of one to four processes (according to Table 1) are given. Blue coloured processes connect axonic property 1, green property 2, yellow property 3 and brown property 4 [19].

Schizophrenic Symptoms Presumably Caused by Incoherence in the Oligodendrocyte-Axonic System

The research criteria for alternative dimensional descriptors for schizophrenia [24] differentiate between a psychotic (hallucinations, delusions) dimension, a disorganized dimension and a negative (deficit) dimension of schizophrenia. The disorganized dimension describes the degree to which disorganized speech, disorganized behavior or inappropriate affect have been present. This kind of schizophrenic symptomatology can be deduced from the incoherence of brain functions that may be caused by decomposed oligodendrocyte-axonic relations.

Thought disorder is the main symptom of cognitive disorganization. This appears in incoherent words, termed neologisms, and in incoherent sentences (word salad) [25]. These symptoms of incoherence may be caused by decomposed oligodendrocyte-axonic relations, if the cognitive systems are affected. However, one may argue that multiple sclerosis is also based on a demyelinating disorder of the brain where oligodendroglia is decreased or lost, comparable to the mechanism that is hypothesized for symptoms of incoherence in schizophrenia. In addition, patients with multiple sclerosis show not only the typical motoric symptoms, but can also suffer from cognitive impairments, affective disorders, and even psychotic

symptoms [26,27]. First of all, although the pathophysiology of schizophrenia is as yet unknown, there is a consensus that the core symptoms (delusions and hallucinations) of schizophrenia may be basically caused by a disorder in the synaptic information processing, so that the astrocyte-neuronal interaction in tripartite synapses must primarily be disordered, which is not the case in multiple sclerosis. In line with this argumentation, all macroglial cells (astrocytes and oligodendrocytes) with their syncytia must be considered in their interaction with the neuronal system with regard to research of the pathophysiology of schizophrenia. Therefore, abnormalities of white matter in brains with schizophrenia may be mainly responsible for symptoms of incoherence and not for the whole schizophrenic syndrome.

Structural magnetic resonance imaging research suggests that schizophrenia is associated with grey matter reductions in a network of frontal, temporal, limbic, thalamic, and striatal areas [28]. In addition, abnormalities of cerebral white matter, Oc and myelin have been observed in schizophrenia with in-vivo imaging and postmortem biochemistry [29,30]. White matter abnormalities are also frequently associated with cognitive impairment, in both healthy and diseased individuals, and cognitive dysfunction is an important component of schizophrenia [31–33].

Although the neurobiological origins of the abnormalities in white matter of brains with schizophrenia are unclear, gene studies involved in the maintenance of white matter structures may be particularly fruitful in schizophrenia. Recently, data gathered in a number of model systems indicated that axonal RNAs are synthesized in the surrounding glial cells. Experiments on the perfused squid giant axon have definitely proven that axoplasmic RNAs are transcribed on periaxonal glia. Their delivery to the axon occurs by a modulatory mechanism based on the release of NT from the stimulated axon and on their binding to glial receptors [34].

Loss of Function of Glial Gap Junctions may Cause Severe Cognitive Impairment in Schizophrenia

Gap junctions provide intercellular pathways that allow the direct exchange of ions for the propagation of currents and small metabolites, including second messengers [35]. Gap junctions are composed of hemichannels (connexons) that dock to each other via their extracytoplasmic extremities. Each hemichannel is an oligomer of six proteins (connexins, Cx). In the central nervous system, cell-specific and developmentally regulated expression of eight connexins has been demonstrated [36]. The cellular profile of connexin expression indicates that a given connexin can be expressed by more than one cell type and a given cell type can coexpress a variety of different proteins [37]. Glial g.j. may register the neuronal activations of glial-neuronal compartments by generating g.j. plaques dependent on the activation frequency embodying a memory structure. The various proteins (connexins) of g.js may be able to differentiate between the operation qualities of the cognate synapses defined by the NT types. Therefore, the brain is able to distinguish between different cognitive domains or qualities. If the function of glial g.j. proteins is lost, the brain is incapable of distinguishing between same and different qualities of synaptic information processing. Dependent on the brain regions affected, this disorder may be responsible for severe cognitive impairment in schizophrenia [38].

Astrocytic-neuronal Compartments

Different connexins allow communication between diverse cell populations or segregation of cells into isolated compartments according to their pattern of connexin expression [39,40]. Gap junctions between astrocytes are considered to provide a structural link by which single cells are coupled to build a functional syncytium with a communicative behavior that cannot be exerted by indi-

Figure 5 Diagrammatic schema of an astrocytic syncytium. Two astrocytes (A_{c1} , A_{c2}) are interconnected via gap junctions (g.js). Each astrocyte contacts four synapses (S_y) with four different qualities (a, b, c, d) building two astrocytic-neuronal compartments. Since these two compartments are interconnected via g.js, a network is generated, called syncytium [41].

vidual cells. Whereas astrocytes are interconnected with their neighbours via g.js, the interactions of astrocytes with neurons occur mainly in synapses. Thus, one can also speak of astrocytic-neuronal compartments.

Fig. 5 shows a diagrammatic schema depicting an astrocytic syncytium composed of two astrocytes (A_{c1} , A_{c2}) interconnected via g.js. Each astrocyte contacts four synapses (S_y) with four different qualities (a, b, c, d) building an astrocytic-neuronal compartment. A quality is defined as the specific NT type that mainly operates in synaptic neurotransmission, say glutamate (a), acetylcholine (b), serotonin(c), and dopamine (d). The g.j.consist of the four identified astrocytic connexins Cx43, Cx30, Cx26, and Cx45, forming g.j channels (for the sake of clarity not shown in the figure).

The two astrocytes (A_{c1} , A_{c2}) with four processes each of which contacts four synapses with the qualities a, b, c, and d are interconnected via sixteen g.js. Table 3 presents the combinations of the comparison of identities and differences of the qualitative information processing, if all synapses are activated.

Table 3 Combinations of four synaptic qualities (a, b, c, d) interconnected via sixteen g.js. Two astrocytes (A_{c1} , A_{c2}) interconnected via g.js contacting four synapses with four different qualities (a, b, c, d) as shown in Figure 5. Here, only the combinations and qualitative identities (e.g. a1, a2) and differences (e.g. a1, b2) are listed

A_{c1}	A_{c2}	A_{c1}	A_{c2}	A_{c1}	A_{c2}	A_{c1}	A_{c2}
$a_1 - - a_2$	$b_1 - - a_2$	$c_1 - - a_2$	$d_1 - - a_2$				
$a_1 - - b_2$	$b_1 - - b_2$	$c_1 - - b_2$	$d_1 - - b_2$				
$a_1 - - c_2$	$b_1 - - c_2$	$c_1 - - c_2$	$d_1 - - c_2$				
$a_1 - - d_2$	$b_1 - - d_2$	$c_1 - - d_2$	$d_1 - - d_2$				

Generation of Gap Junction Plaques and Their Influence on Qualitative Synaptic Information Processing

If g.j. between astrocytes are frequently coupled within a time scale of seconds, minutes or hours, they form plaques. Whereas rarely coupled or noncoupled g.j. are endocytosed and destroyed [41], it is hypothesized that a plaque embodies a memory structure [42] that may also operate as an intentional program [43] deciding which and where astrocytic receptors in astrocytic-neuronal compartments must be activated for occupancy with cognate NT in the sense of a readiness pattern. Since g.j. are either composed of same or different connexins, they may function as biological devices for the distinction between identity and difference of the NT qualities in synaptic information processing. This may represent a g.j.-based mechanism for the registration or recognition of qualitative identities and differences in the sense of an elementary cognitive capability of the brain.

Table 4 offers an example of plaque formation based on Table 3. The frequently activated g.j. channels are indicated with rectangles. Thus, the plaque generated is composed of these g.j. registering qualitative identities and differences in synaptic information processing as follows: $|a_1a_2|a_1b_2|b_1a_2|a_1c_2|c_1a_2|$. Most importantly, the g.j. channels a_1b_2 and b_1a_2 or a_1c_2 and c_1a_2 do register the same synaptic qualities, but on different locations in the astrocytic syncytium (indicated by the numerals 1, 2). Here, the topology is significant, since the g.j. of a plaque reinforce exactly those synapses which already have operated successfully in the inner and outer environment. Together, g.j. plaques may embody three elementary functions underlying cognitive processes:

Table 4 Example of a gap junction (g.j.) plaque formation based on Table 1. The frequently activated g.j. channels are indicated by rectangles. Thus, the plaque generated is composed of these g.j.s registering qualitative identities and differences in synaptic information processing. The generated g.j. plaque is composed of these g.j.s: $a_1a_2|a_1b_2|b_1a_2|a_1c_2|c_1a_2|$. The numerals 1, 2 designate the location of the synaptic qualities compared by a g.j. in the astrocytic syncytium

A_{c1}	A_{c2}	A_{c1}	A_{c2}	A_{c1}	A_{c2}	A_{c1}	A_{c2}
$a_1 a_2$	$a_1 b_2$	$b_1 a_2$	$b_1 b_2$	$c_1 a_2$	$c_1 b_2$	$d_1 a_2$	$d_1 b_2$
$a_1 b_2$	$a_1 c_2$	$b_1 a_2$	$b_1 c_2$	$c_1 a_2$	$c_1 c_2$	$d_1 a_2$	$d_1 c_2$
$a_1 b_2$	$a_1 d_2$	$b_1 a_2$	$b_1 d_2$	$c_1 a_2$	$c_1 d_2$	$d_1 a_2$	$d_1 d_2$
↓							
Gap junction plaque							
a_1a_2	a_1b_2	b_1a_2	a_1c_2	c_1a_2			

- 1) a memory structure [44] with regard to successful astrocyte-neuronal interactions,
- 2) an intentional program [45] determining which and where astrocytic receptors in astrocytic-neuronal compartments must be activated for occupancy with cognate NT in the sense of a readiness pattern, and
- 3) registration and qualitative comparison of identical and different synaptic operations characterized by the NT types.

Experimental Evidence for the Role of Astrocytic Gap Junctions in Cognition and Behavior

Geneticists and psychological physiologists have collaborated to develop mice that have connexin 30 (Cx30) deleted from their genome in homozygous (Cx30-I-) and heterozygous (Cx30-I+) phenotypes and compared the behavioral and neurochemical changes with normal "wild" mice (Cx30-I+) [46]. The authors conclude that the elimination of connexin 30 can alter the reactivity to novel environments, pointing to the importance of gap junctional signalling in behavioral or cognitive processes.

Another study utilizes the ground-breaking development of a method to genetically inactivate connexin 43 (Cx43) only in astrocytes [47]. These animals show opposite behavioral changes to those in Cx30-I- mice. They exhibit increased locomotion and exploratory activity in novel environments with an "anxiolytic-like effect". The authors stress that the results of both Cx30 and Cx43 studies imply that the astrocyte gap junctional network (syncytium) seems to control behavior in concert with the neuronal matrix, affecting different behavioral categories with different intensity.

Supposing that astrocyte g.j.s are the site of memory formation [44] and intentional programming [45], their functions must be essential for cognition and higher information processing. Therefore, a loss of this gap junctional function may cause severe cognitive impairment, as is the case in schizophrenia.

Loss of Astrocyte Gap Junctional Functions may Cause Cognitive Impairment in Schizophrenia

Cognitive impairments may be caused by the incapability of schizophrenia patients to differentiate between cognitive domains (categories) or qualities, because of a loss of function of astrocytic g.j. in special brain regions, especially in the prefrontal cortex. The underlying systemic model is as follows:

In Fig. 6 a schematic diagram of dynamic compartmentalization is depicted [41]. In undisturbed dynamic

Figure 6 Dynamic compartmentalization and decomposed astrocytic compartments caused by the loss of gap junctional functions, responsible for cognitive impairment in schizophrenia. An astrocytic syncytium composed of four astrocytic compartments (A_{c1} , A_{c2} , A_{c3} , A_{c4}) is shown. In undisturbed dynamic compartmentalization frequently activated g.j.s (indicated by arrows) generate a g.j. plaque that positively feeds back to the pertinent synapses. This mechanism changes the structure of the as-

trocytic syncytium in the sense of a dynamic compartmentalization (a). If g.j.s have lost their function (indicated by crosses), g.j. plaques cannot be generated so that the interactions of astrocyte-neuronal compartments cannot be registered and qualitatively compared. This leads to a decomposition of the astrocytic syncytium that may be responsible for cognitive impairment in schizophrenia (b) [41].

compartmentalization frequently activated g.j. channels (indicated by arrows) generate a g.j. plaque that positively feeds back to the pertinent synapses and in this manner changes the structure of the astrocytic syncytium in the sense of a dynamic compartmentalization (a). Here we deal with an elementary mechanism of registration or recognition of the various qualitative identities and differences of our perception of the inner and outer environment, a basic condition for appropriate behavior.

In contrast, if g.j.s do not function due to a genetic or (and) exogenous disorder, g.j. plaques cannot be generated, so that the interactions of astrocyte-neuronal compartments cannot be registered and qualitatively compared. This leads to a decomposition of the astrocytic syncytium (b). In addition, since the synaptic information processing is not modified by a positive feedback mechanism from the g.j. plaques, such a brain may operate without a memory-based intentional program-

ming. Therefore, patients with schizophrenia are dysintentional, since they do not only suffer from cognitive impairment but also from their incapability to generate realizable intentional programs to cope successfully with the environment [11].

What the formation of memory in the astrocytic syncytium concerns, Banachlocha [48] proposes similar to the Astrocentric Hypothesis [44] that memories are stored in the astrocytic syncytium. Codification of specific items of information is manifested by changes in the resting electromagnetic status of astrocytes that are induced by simultaneous changes in adjacent neuronal associated magnetic fields during synaptic activity. Consolidation of specific memories occurs with repetition of similar firing patterns. This induces long-term potentiation in the magnetic response of both neuronal and astrocytic components. A lack of repetition leads to forgetfulness. These models of memory formation have been theoretically

supported by Caudle [49]. However, these authors do not refer to memory impairment in schizophrenia.

Future Prospects

The model proposed is experimentally testable. In tripartite synapses the already identified receptors on astrocytes for the various neurotransmitter types in normal post-mortem brains should be compared with postmortem brains with schizophrenia. Functional astrocytic receptors should not be identified in specific areas of brains with schizophrenia. Although the role of the oligodendrocyte-axonic system in information processing is not yet sufficiently understood and the pertinent interpretation of a possible pathophysiology responsible for schizophrenia is rather speculative, this hypothesis concerning the molecular biological basis may in fact also be testable. The rapid improvements of neuroimaging techniques may allow further identification of the detailed structure of oligodendrocyte-axonic relations and their decomposition in schizophrenia. In addition, neuropsychological tests must be applied for an exact examination of the schizophrenic symptoms caused by the biological mechanism of incoherence as proposed. Such investigation procedures allow the computation of correlates between brain areas affected and the types of symptoms of incoherence so that the extent of decrease of oligodendroglia might correlate with the severity of cognitive impairment. Considering the formalism upon which the possible capacity of Oc for the categorization of axonic properties is based, there is already a formal model for a computer simulation available. Since there are several methods (antibodies, immunocytochemistry, freeze-fracture replica immunogold labelling, electrophysiology) for the identification of g.js in brain tissue available, this investigation should also be possible in tissue with post-mortem brains with schizophrenia. What impairment of memory concerns, g.j. plaques should be significantly decreased or even not generated at all in schizophrenic brains. It would be a great break-through if it were possible to visualize glial g.js or plaques in the human brain in vivo, so that a biological parameter for the diagnosis of cognitive impairment especially of memory in schizophrenia would be available.

Typical and modern atypical antipsychotic drugs have efficiently controlled the dramatic psychotic symptoms (delusions and hallucinations) of schizophrenia, but their impact on negative and cognitive symptoms is negligible [3]. Therefore, there is much room for more efficient compounds [50]. Why? Supposing that astrocytic receptors in tripartite synapses are nonfunctional, antipsychotic drugs cannot occupy them at all, so that the

synaptic information flux cannot be turned off. It may only be decreased via the occupancy of receptors in the neuronal synapse by these substances. However, this effect may at least improve the ability for psychosocial adaptation of the patients, since delusions or hallucinations do not dominate the everyday life.

Conflict of Interest

The authors have no conflict of interest.

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