Downregulation and Upregulation of Glial Connexins May Cause Synaptic Imbalances Responsible for the Pathophysiology of Bipolar Disorder

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Astrocytic syncytium; Bipolar disorder; Cognitive impairment; Dysregulations; Imbalances; Tripartite synapses.

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SUMMARY

The model of the pathophysiology of bipolar disorder proposed is based on imbalances in tripartite synapses caused by dysregulations of connexin expression in the astrocytic syncytium. If the expression of connexins is downregulated, a compensatory upregulation of astrocytic receptors may occur and be responsible for the pathophysiology of depression. Conversely, if the expression of connexins is upregulated, the expression of the astrocytic receptors may be downregulated and be responsible for the pathophysiology of mania. In depression, a relative lack of neurotransmitters exerts a protracted synaptic information processing, whereas in mania a relative increase of neurotransmitters may accelerate synaptic information processing. In addition, the modulatory role of gliotransmitters may be affected in bipolar disorder. Since the dysregulations of connexins impair the astrocytic syncytium, these disorders could be explanatory for cognitive impairment both in depression and in mania. Finally, the testability of this model is discussed.

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Bipolar affective disorder is a severe psychiatric disorder with a strong genetic component but unknown pathophysiology [1]. Mood disorders encompass a large group of psychiatric disorders in which pathological mood and related vegetative and psychomotor disturbances dominate the clinical picture. Bipolar disorder represents a special syndrome consisting of at least one agitated (manic or hypomanic) episode and one or more depressive episodes. Numerous recurrences are possible. Mixed states, comprising depressive and manic symptoms simultaneously, can also occur.

Contemporary explanatory models of bipolar disorder focus on biological, psychological, and sociological approaches. But there is broad consensus that bipolar disorder is multifactorially determined, caused by a stress–diathesis interaction, as described in the final common pathway model of Akiskal and McKinney [2]. Importantly, as far as the pathophysiology of bipolar disorder is concerned, there is growing evidence that not only the neuronal system but also the glial system is af-

ected [3–5]. In various imaging studies glial decreases have been reported in the prefrontal cortex [6,7]. Brauch et al. [8] found that the percentage of glial space was substantially lower in bipolar subjects, suggesting that glia may be smaller in bipolar subjects. This size reduction may be reflective of glial dysfunction. However, a decreased neuron somal size in the lateral amygdalar nucleus of patients with bipolar disorder has also been identified [9]. Recently, the role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders has been reviewed [10].

In 2004, I proposed a model of imbalances in tripartite synapses responsible for the pathophysiology of bipolar disorder [11]. The pathophysiological mechanism proposed focused on glial binding proteins [12]. Because these proteins have not been found in vertebrate or human brains, I elaborated a comparable mechanism based on the decisive function of receptors on astrocytes determined by the astrocytic network, called syncytium.

My hypothesis is that in tripartite synapses the overproduction of astrocytic receptors (acR) may lead to a relative lack of neurotransmitters (NTs) responsible for the pathophysiology of depression, and conversely, an underexpression of acR may cause a relative excess of NTs responsible for the pathophysiology of mania. These synaptic imbalances may be determined by a downregulation or upregulation of connexins in the astrocytic syncytium. If connexin expression is downregulated, an upregulation of the expression of acR may occur, representing a compensatory genetic mechanism. Inversely, in the case of an upregulation of the expression of connexins, a downregulation of the expression of the acR may be the consequence. Based on these imbalances, synaptic information processing is protracted in depression and accelerated in mania. Since the disordered expression of connexins in the astrocytic syncytium also affects the communication between astrocytes via gap junctions, some typical cognitive impairments of patients with bipolar disorder can be deduced [13].

Outline of an Astrocytic Syncytium

Since the model of the pathophysiology of bipolar disorder proposed basically concerns dysregulations of connexins in the astrocytic syncytium, this glial network must be described at first. A typical feature of macroglial cells, in particular the astrocyte, is that they establish cell–cell communication *in vitro* and *in situ*, through intercellular channels forming specialized membrane areas defined as gap junctions [14]. Different connexins allow communication between diverse cell populations or segregation of cells into isolated compartments according to their pattern of connexin expression [15]. Gap junctions are composed of hemichannels (connexons) that dock to each other via their extracytoplasmic extremities. Each hemichannel is an oligomer of six connexin proteins (Cx). In the central nervous system, cell-specific and developmentally regulated expression of eight connexins has been demonstrated.

My model focuses on gap junctions between astrocytes, the main glial cell type besides oligodendrocytes and microglia. Gap junctions are considered to provide a structural link by which single cells are coupled to build a functional syncytium with a communication behavior that cannot be exerted by individual cells. Gap junctions of an astrocytic syncytium consist of the four identified connexins Cx43, Cx32, Cx26, and Cx45, forming homotypic (i.e., gap junction channels formed by hemichannels of the same kind) and heterotypic gap junction channels (i.e., formed by hemichannels of dif-

ferent kinds). Whereas astrocytes are interconnected with their neighbors via gap junctions, the interactions of astrocytes with neurons occur mainly in synapses called tripartite synapses [16].

Figure 1 shows a diagrammatic scheme depicting an astrocytic syncytium. Six astrocytes ($Ac_1 \dots Ac_6$) are completely interconnected via 15 g.j. according to the formula $n:2 (n-1)$. Each astrocyte contacts a neuronal synapse, building a tripartite synapse in the sense of a glial-neuronal unit. Admittedly, this simple diagram refers only to the elementary components and their connections in an astrocytic syncytium.

Because in the brain each macroscopic gap junction is an aggregate of many, often hundreds of tightly packed gap junction channels are observed [17]. The number and composition of gap junctions can be regulated dynamically at the level of the endoplasmic reticulum by either upregulating connexin biosynthesis or decreasing the rate of connexin degradation, and at the cell surface by enhancing gap junction assembly or reducing connexin degradation. Most importantly, a downregulation of the expression of connexins can also occur that may exert a compensatory upregulation of acR causing a protracted synaptic neurotransmission, responsible for the main symptoms of depression.

Generation of Gap Junction Plaques, Intentional Programming, and Memory

If gap junctions between astrocytes are coupled frequently within a time scale of seconds, minutes, or hours, they form plaques. Whereas rarely coupled or noncoupled gap junctions are endocytosed and destroyed [18], it is hypothesized that protoplasmatic astrocytes bind attended sensory information into consciousness and store encoded memories in gap junction plaques [19]. Gap junction plaques may also operate as an intentional program [20] deciding which and where acR in astrocytic-neuronal compartments must be activated for occupancy with cognate NTs in the sense of a readiness pattern. Because gap junctions are composed of either the 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 gap junction-based mechanism for the registration or recognition of qualitative identities and differences in the sense of an elementary cognitive capability of the brain.

In Figure 2 a schematic diagram of dynamic compartmentalization is depicted. In undisturbed dynamic compartmentalization frequently activated gap junction channels (indicated by arrows) generate a gap junction

Figure 1 Outline of an astrocytic syncytium. Six astrocytes ($Ac_1 \dots Ac_6$) are interconnected via 15 gap junctions (g.j.) building a complete syncytium. Each astrocyte contacts a neuronal synapse representing a tripartite synapse (for the sake of clarity only one synaptic contact [Sy] is shown).

Figure 2 Schematic diagram of gap junction plaque formation. An astrocytic syncytium composed of four astrocytic compartments ($Ac_1 \dots Ac_4$) is shown. In undisturbed dynamic compartmentalization frequently activated gap junctions (indicated by arrows) generate a gap junction plaque that positively feeds back to the syncytium. This mechanism changes the structure of the astrocytic syncytium in the sense of a dynamic compartmentalization.

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 [21]. 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.

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+) [22]. The authors conclude that the elimination of Cx30 can alter the reactivity to novel environments, pointing to the importance of gap junctional signaling in behavioral or cognitive processes.

Another study utilizes the ground-breaking development of a method to genetically inactivate connexin 43 (Cx43) only in astrocytes [23]. 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.

In addition, I propose that these experimental results on Cx30 and Cx43 also may support my hypothetical model of the generation of intentional programs in glial syncytia [20]. In this model, a glial syncytium is formally described as a multirelational structure. Gap junction function within this structure as exchange operators of different valuedness. Valuedness means that the type of a gap junction determines which kind of exchange relation is generated in the multirelational structure of the glial syncytium (for formal details see [20]). Therefore, dependent on the type of gap junction activated, various syncytial pathways or cycles are generated. Each pathway is interpreted as a multirelational program. Such an intentional program is transferred to the neuronal network via tripartite synapses. In that manner, a glial intentional program determines a specific relational structure in the neuronal network for testing its feasibility in the environment via sense organs and motion.

What the formation of memory in the astrocytic syncytium concerns, Banachlocha [24] proposes similar to the Astrocentric Hypothesis [19] 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 [25].

Model of a Glutamatergic Tripartite Synapse

The close morphological relations between astrocytes and synapses as well as the functional expression of relevant receptors in the astroglial cells prompted the appearance of a new concept known as the tripartite synapse. In 1999, Haydon and coworkers [26] 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 [16]. Although a true understanding of how the astrocyte interacts with neurons is still missing, several models have been published. Here, I focus on a modified model proposed by Newman [27]. Figure 3 represents the interaction of the main components of synaptic information processing as follows: sensori-motoric networks compute an environmental information activating the presynapse (1). The activated presynapse releases glutamate (GLU) from vesicles (v) that occupy both postsynaptic receptors (poR) and receptors on the astrocyte (acR) (2) (For the sake of clarity, only one receptor is shown). Moreover, GLU may also activate gap junctions in the astrocytic syncytium leading to an enhanced spreading of Ca^{2+} waves (3). In parallel, the occupancy of the acR by GLU also activates Ca^{2+} within the astrocyte (4). This mechanism exerts the production of GLU (5) and adenosine triphosphate (ATP) (6) within the astrocyte, now functioning as gliotransmitters (GT). Whereas the occupancy of extrasynaptic pre- and poR by GLU is excitatory (7), the occupancy of these receptors by ATP is inhibitory (8). In addition, neurotransmission is also inactivated by the reuptake of GLU in the membrane of the presynapse mediated by transporter molecules (t) (9). Most importantly, ATP inhibits the presynaptic terminal via occupancy of cognate receptors [26] temporarily turning off synaptic neurotransmission in the sense of a negative feedback (10). Finally, synaptic information processing is transmitted to neuronal networks that can activate the synapse again (11).

In spite of evidence that astrocytes release GLU by a Ca^{2+} -dependent vesicle mechanism that resembles release from neurons, important differences between glial and neuronal release exist. GLU release from astrocytes occurs at a much slower rate than does release from neurons, and is probably triggered by smaller increases of cytoplasmic Ca^{2+} [28]. Importantly, we apparently deal with different time scales of presynaptic and astrocytic GLU release. Hence, the astrocytic modulatory function of synaptic neurotransmission may occur within seconds or minutes [29]. Here, I hypothesize that the duration from presynaptic activation to the inhibition of synaptic neurotransmission may also be dependent on the amount

Figure 3 Schematic diagram of possible glial–neuronal interactions at the glutamatergic tripartite synapse (modified after Newman 2005). Sensor-motor networks compute environmental information activating the presynapse (1). The activated presynapse releases glutamate (GLU) from vesicles (v) occupying both postsynaptic receptors (poR) and receptors on the astrocyte (acR) (2). GLU also activates gap junctions (g.j.) in the astrocytic syncytium, enhancing the spreading of Ca²⁺ waves (3). In parallel, the occupancy of acR by GLU also activates Ca²⁺ within the astrocyte (4). This mechanism exerts the production of GLU (5) and adenosinetriphosphate

(ATP) (6) within the astrocyte, now functioning as gliotransmitters whereas the occupancy of the extrasynaptic pre- and postsynaptic receptors by GLU is excitatory (7), the occupancy of these receptors by ATP is inhibitory (8). In addition, neurotransmission is also inactivated by the reuptake of GLU in the membrane of the presynapse mediated by transporter molecules (t) (9). ATP inhibits the presynaptic terminal via occupancy of cognate receptors (prR) temporarily turning off synaptic neurotransmission in the sense of a negative feedback (10). Synaptic information processing is transmitted to neuronal networks activating the synapse again (11).

of acR that must be occupied by GLU. This mechanism may be based on the occupancy probability of acR by GLU releases from the presynaptic terminal. In addition, the release of ATP from astrocytes may also be dependent on a comparable mechanism [30]. Accordingly, in tripartite synapses glia may have a temporal boundary-setting function in temporarily turning off synaptic information transmission [31,32].

Because my model of synaptic imbalances that may cause bipolar disorder is essentially based on the overexpression of acR in depression and the underexpression in mania, the glial–neuronal interaction described for a glutamatergic tripartite synapse should hold for all (NT) types. At least in the culture disk astrocytes

express almost all receptors for important NT systems [33].

Downregulation of Glial Connexins May Cause an Upregulation of acR Responsible for the Pathophysiology of Depression

The core symptoms of depression are depressed mood, diminished interest or pleasure, disturbance of circadian rhythms, psychomotor disturbances (retardation or agitation), feelings of insufficiency [34], and cognitive impairment [35]. Figure 4 shows the main effects on synaptic information transmission if the expression of connexins in the astrocytic syncytium is downregulated.

Figure 4 Downregulation of glial connexins may cause an upregulation of astrocytic receptors responsible for the pathophysiology of depression. Neurotransmitters (NT) are released from the presynapse occupying both the postsynaptic receptors (poR) (1) and astrocytic receptors (acR) (2). In parallel, the downregulation of connexins (3) forms an incomplete "leaky" astrocytic syncytium (red crosses) consisting of gap junctions (g.j.) leading to an upregulation of acR (5). The enhanced amount of acR causes a relative lack of NT so that synaptic information processing is imbalanced. In an

incomplete syncytium the activation of Ca^{2+} is diminished (6) causing an underproduction of gliotransmitters (GT) (7). The overproduction of acR leads to a prolonged production of GT (dashed line) so that the negative feedback mechanism on presynaptic receptors (prR) is protracted (8). The same prolongation occurs on the postsynaptic neuron (9). In addition, the relative lack of NT leads to a protracted activation of g.j. (10). In this tripartite synapse, neurotransmission is significantly delayed (11).

(For the sake of clarity the function of the various substances like ions, second messengers, is omitted.) It is generalized for all NT types as GLU, GABA, serotonin, noradrenaline, dopamine, and acetylcholine. NTs are released from the presynapse occupying both the poR (1) and acR (2). In parallel, the downregulation of connexins (3) forms an incomplete "leaky" astrocytic syncytium (4) that may lead to an upregulation of acR (5). If these receptors are increased, a relative lack of NTs arises so that synaptic information transmission is imbalanced. Because the syncytium is incomplete, the activation of Ca^{2+} waves may be diminished (6) which causes an underproduction of GT (7). In addition, the overproduction of acR also may lead to a prolonged production of GT (dotted line), and, therefore, the negative feedback mechanism on presynaptic receptors (prR) is protracted (8). The same holds for the depolarization of the postsynaptic neuron (9). Because of the relative lack of NTs the activation of gap junctions may also be protracted (10). In such a tripartite synapse neurotransmission is significantly delayed

(11). This could explain symptoms of depressive retardation of thinking, concentration, and motor behavior. Agitation would then occur as a reaction of impatience.

Considering the delayed and imperfect information processing in these imbalanced tripartite synapses, feelings of insufficiency may arise on the behavioral level. Furthermore, the synaptic imbalance could be responsible for the disturbance of circadian rhythms, a core symptom of depression [36]. From a psychological point of view, patients with depression have high aspirations [37], but these are unfeasible. One can also say that these patients are hyperintentional [11,38]. As already suggested, the glial functions in tripartite synapses operate not only modulatory, but could also be intentional [20]. Therefore, the excess of glial receptors may represent an explanatory model for both the high aspirations and their unfeasibility, since this system state has not enough NTs available. Thus, the mood is depressed.

The individual and manifold symptomatology of depression may depend upon the types of NTs or brain

regions involved. Because most of the effective treatments of mood disorders were discovered by empiricism, the effectiveness of somatic treatment has propelled NT theories rather than vice versa [39]. My approach is contrary to this trend by deducing the pathophysiology of so-called mental disorders from a theoretical model. Supposing that not only the excess of glial receptors but also the relative lack of NTs in the synaptic cleft is responsible for depressive mood, it is conceivable that a treatment with reuptake inhibitory substances could be successful. Most importantly, according to my model of depression, the increased concentration of NTs in the synaptic cleft may lead to a balance of synaptic information processing via a sufficient occupation of glial receptors. Interestingly, as early as 1960, Hydén showed that antidepressant drugs cause profound changes in glial RNA [40].

The biogenic amine hypotheses of depression postulate a deficiency of biogenic amines in synapses [41–44]. In this context, it should be mentioned that brain diseases, such as Parkinson's disease, also show a lack of transmitters in pertinent synapses, but this is not necessarily accompanied by a depressive mood [45]. Hence, depression may arise only if the glial system is also affected in the sense of an imbalanced tripartite synaptic system.

Experimental Evidence for Downregulation of Connexins and Upregulation of acR

Cx43 is the most abundant gap junction protein in the brain, where it is found primarily between astrocytes. Experimental data indicate a surprisingly high degree of impact of deletion of Cx43 on other astrocyte genes, implying that gap junction gene expression alters numerous processes in addition to intercellular communication. Generally, mutations in connexin genes or altered expression of wild-type gap junction proteins may play important roles in the pathogenesis of various diseases not only of the central nervous system, but also of other organs, such as the heart (for review see [46]).

Here I will focus on altered expression of the astrocytic Cx43 protein. A growing number of studies suggest that connexin proteins may play functional roles supplemental to their unique mediation of direct intercellular communication. In addition to effects on growth rate [47] and apoptosis [48], purinergic receptor expression is altered in Cx43-null astrocytes from brain and spinal cord [49].

Generally, purinergic receptors are divided into adenosine receptors and ATP (P2) receptors of the ionotropic (P2X) and metabotropic (P2Y) subtypes. Most importantly, under certain pathological conditions the mode of calcium wave propagation between astrocytes can switch from gap junction-dependent to a gap junction-independent mechanism due to downregulation of the

gap junction protein Cx43 and upregulation of the metabotropic P2Y2 receptor mRNA [50]. Although the loss of expression of Cx43 mRNA can upregulate the expression of the ionotropic P2 receptor P2X7R and downregulation of Cx43 also leads to decreased expression of levels of the metabotropic P2Y1 receptor [49], the overexpression of metabotropic receptors may be decisive for the proposed synaptic model of depression. As verified experimentally, NTs occupy their cognate receptors on astrocytes activating the various glial substances (transmitter, ion, transporters, etc.) for modulating neurotransmission in tripartite synapses [27]. Furthermore, since receptors for all NT have been found on astrocytes, the downregulation of astrocytic connexin may exert an upregulation not only of purinergic receptors, but this effect may hold for the receptors of all transmitter types.

In addition, brain macrophages inhibit gap junctional communication and downregulate Cx43 expression in cultured astrocytes. Because astrocyte interactions with brain macrophages and dying neurons both result in the downregulation of Cx43 expression and in the inhibition of gap junctional communication, a critical consequence on astrocyte phenotype in those situations could be the inhibition of gap junctions [51]. Some experimental evidence suggests that apoptosis of neurons is accelerated in several brain regions in depression [52]. Because of its considerable consequences for the connectivity of the neuronal networks, increased neuronal loss may be responsible for memory impairment in depression [53]. However, current depression research does not refer to the possible role of pathophysiological mechanisms in the astrocytic syncytium and their effects on synaptic information transmission responsible for the main symptoms of depression.

Downregulation of the Expression of Astrocytic Connexins May Cause Memory Impairment in Depression

Most patients with a major depressive episode are suffering from memory impairment. Recently, significant correlations between depression severity and cognitive performance were found especially in the domains of memory [54]. Moreover, memory impairment in depression can be deduced from the model of an astrocytic syncytium (Figure 1).

As already described, a downregulation of astrocytic connexins may affect the completeness of the astrocytic network in the sense of an incomplete "leaky" syncytium. Supposing that gap junctions embody memory structures, such incomplete structures may be responsible for memory impairment in depression. In parallel, the delay of synaptic information processing negatively influences the

retrieval of memory. Because gap junctions are normally activated by the neuronal system (e.g., GLU) within a millisecond time scale, in the case of delayed synaptic information processing the neuronal system is incapable of retrieving memories to compare them with an actual perception pattern in real time. Therefore, the working memory may be particularly impaired in depression. In addition, there is some evidence for plasticity at the tripartite synapses implying a function of astrocytes in learning and memory [55] so that synaptic imbalances may also affect memory.

Upregulation of Glial Connexins May Cause a Downregulation of acR Responsible for the Pathophysiology of Mania

The core symptoms of mania are elevated mood, irritability, flight of ideas, grandiosity, and insomnia [34]. These

clinical features of mania are generally the opposite of those in depression. Figure 5 shows schematically an imbalanced tripartite synapse which may cause mania. The upregulation of connexins (1) forms an overcompensated astrocytic syncytium (2) that may lead to a downregulation of the acR (3). NTs released from the presynapse occupy both the poR (4) and the acR (5). Since the overcompensation of the astrocytic syncytium may exert an enhanced generation of Ca^{2+} waves, an increase of the production of GT may also arise (6). The decreased number of acR causes a relative excess of NTs in the synaptic cleft. In parallel, the fastened production of GT exerts a rapid occupancy of cognate prR in the sense of a shortened negative feedback on the presynapse (7) and a rapid glial depolarization of the postsynaptic neuron (8). The increased amount of NTs may cause an enhanced activation of gap junctions in the astrocytic syncytium (9), additionally raising the production of Ca^{2+} waves in the syncytium. This system state of a tripartite synapse leads

Figure 5 Upregulation of glial connexins may cause a downregulation of astrocytic receptors responsible for the pathophysiology of mania. The upregulation of connexins (1) forms an overcompensated astrocytic syncytium (2) that leads to a downregulation of the expression of astrocytic receptors (acR) (3). Neurotransmitters (NT) released from the presynapse occupy both the postsynaptic receptors (poR) (4) and the acR (5). The overcompensation of the astrocytic syncytium exerts an enhanced generation of Ca^{2+} causing an increased production of gliotransmitters (GT) (6). The decreased amount of acR causes a relative excess of NT in the synaptic

cleft. In parallel, the fastened production of GT exerts an accelerated occupancy of cognate presynaptic receptors (prR) such that the feedback mechanism on the presynapse (7) and the depolarization of the postsynaptic neuron (8) is shortened. The increased amount of NT causes an increased activation of gap junctions (g.j.) in the astrocytic syncytium (9) additionally raising the production of Ca^{2+} . In such a synaptic system neurotransmission is significantly accelerated (10) in the sense of shortened cycles of synaptic information processing.

to an accelerated neurotransmission (10) in the sense of shortened cycles of synaptic information processing.

From a psychological point of view, patients with mania are absolutely convinced that every thought or idea is immediately feasible. In other words, they have no problems to realize any intention, so these patients are actually hypointentional. There is no striving or testing since all seems to be possible and appropriate [11]. Dependent on the transmitter systems or brain areas affected, the synaptic imbalance could cause the typical manic symptoms of euphoria and feelings of omnipotence. In addition, the rapid synaptic cycles could be explanatory of the manic distractibility, flight of ideas, hyperactivity, and circadian disturbances, especially insomnia. Because the ideas of grandiosity are not feasible, I speak of pseudoomnipotence [56].

Møllerup and Kristensen [57] hypothesize that mania may be caused by a dysfunction of reentry. According to Edelman and Tononi [58], reentry is a process of ongoing parallel and recursive signaling between separate neuronal groups along parallel reciprocal fibers that link these groups anatomically. Reentry alters the activity of the target areas it interconnects until a synchronous activity across these areas is created, which may be the direct biological mechanism of consciousness. Reentry may be faster in mania, specifically what the repetitive recursive signaling concerns, hereby allowing reentry to produce a conscious state faster than usual [57].

Remarks on Memory Impairment in Mania

What cognitive impairment concerns, manic patients exhibit impaired verbal learning and memory, particularly following longstanding illness [59]. Supposing that the astrocytic syncytium embodies a memory structure, one would expect that an overexpression of connexins could enhance the storing capacity of information in manic episodes. In performing many complex tasks, it is necessary to hold information in temporary storage to complete the task. The system used for this is referred to as working memory [60]. Considering the pathophysiological model of mania proposed (Figure 5), not only synaptic information processing but also the activation of the astrocytic syncytium is significantly accelerated. Such fastened neuroglial interaction cycles may reduce the time intervals necessary for information storage in the astrocytic syncytium. Neural correlates of cognitive dysfunction in bipolar disorder have been identified in various brain regions including reduction of glial cells. However, the functional significance of glial cell pathology remains to be established [61].

Experimental Evidence for Upregulation of Connexins and Antibipolar Drug Mechanisms

Disease-causing mutations can potentially occur anywhere in connexin genes. They may cause disease through a variety of mechanisms, most of which alter intercellular communication. Connexin mutations can also lead to increased formation and opening of functional hemichannels or formation of gap junction channels that have altered gating permeability [62]. The number and composition of gap junctions can be dynamically regulated at the level of the endoplasmic reticulum by either upregulating connexin biosynthesis or decreasing the rate of connexin degradation [63].

Wei and coworkers found that the overexpression of gap junction proteins in glioma cells and the intercellular communication between tumor and nontumor glial cells may play important roles in the facilitation of glioma cell invasion [64]. Recently, increased Cx43 expression and enhanced gap junction communication contributing to neuroprotection after neurotoxic insults has been reported [65]. These experimental findings support the assumption that connexins in the astrocytic syncytium can be overexpressed accompanied by an enhanced intercellular communication, as may be the case in mania as well.

Most importantly, astrocytes have been identified as a target for antibipolar drugs. Both up- and downregulation of Ca^{2+} -dependent phospholipase A_2 (cPLA₂) gene expression are involved in the mechanisms of action of antibipolar drugs (lithium, valproic acid, carbamazepine) [66]. cPLA₂ is amply expressed in astrocytes and its upregulation has been shown to occur in a number of neurodegenerative diseases, including stroke and Alzheimer's disease [67]. Although experimental findings concerning an upregulation of glial connexins and a downregulation of acR and vice versa in bipolar disorder are as yet not available, the action of antibipolar drugs may be based on a comparable mechanism what the expression of the cPLA₂ gene concerns.

Current biological treatment of mania focuses on a reduction of the excess of NTs in the synaptic cleft. This seemingly leads to a normalization of information processing, because the occupancy of the glial receptors appears to be balanced. However, the underexpression of glial receptors may not be influenced by this treatment, so that after clinical remission of a manic episode hidden symptoms such as loss of motivation, loss of interests, and anhedonia still may persist. This state is often misinterpreted as a depressive reaction to the manic behavior. Hence, a real remission may occur only if the genetically determined imbalance of the glial-neuronal interaction in tripartite synapses is resolved.

Future Prospects

This article represents a further elaboration of my pathophysiological model of bipolar disorder [11,56]. The model focuses on the downregulation and upregulation of glial connexins and the possible effects on the expression of acR in tripartite synapses. Astrocytic receptors exert an activating function on the production of GT that temporarily turn off synaptic information processing via the occupancy of cognate receptors on the presynaptic terminal. This mechanism may be significantly disordered in bipolar disorder in the sense of synaptic imbalances. However, it is also conceivable that the production of GT *per se* is affected, leading to the same imbalances in tripartite synapses as suggested in this article.

The model of the pathophysiology of bipolar disorder proposed is experimentally testable. Recently, there has been a significant increase in studies involving astrocytic gap junctions [15]. These have demonstrated astrocytic networks (syncytia) in the juvenile brain and a gap junction-mediated astrocytic network in the mouse barrel cortex [68,69]. These studies are reminiscent of the study of neuronal tracts and pathways almost a century ago. Although it is presently not possible to visualize all of the plaques and constituent connexins of gap junctions in the entire brain simultaneously *in vivo*, the only way currently is to visualize individual plaques that are infinitely small representations of the total number of plaques.

However, the investigation of the expression of connexins in tissue of postmortem brains with bipolar disorder should be possible using freeze etched ultrastructure of plaques that immunolabel various connexins [70]. Moreover, the expression of connexin proteins must be analyzed with the common methods (Northern blot analyses, etc. [47]). If downregulation or upregulation of astrocytic connexins can be identified in brains with bipolar disorder, one can speak of syncytiopathy [13]. In addition, the various receptor types for NTs on astrocytes should be counted and quantitatively compared with the acR in normal brains, for instance with atomic force microscopy.

What the genetic mechanism responsible for a dysregulation of astrocytic connexin concerns, one should be cautious to look for specific “genes” [71]. A highly complex transcriptomic network may regulate genes encoding connexin proteins with synergistic or antagonistic functions [50]. Importantly, variability in the human genome has far exceeded expectations. Recent studies reveal that structural variants, including copy-number variants, are important contributors to disease risk. Hence, new approaches are needed to understand the contribution of structural variants to disease [72]. In sum, despite these genetic complexities the identification of syncy-

tiopathy proposed in bipolar disorder accompanied with a synaptic imbalance caused by an excess or decrease of acR may represent a new approach to bipolar disorder research and treatment.

Although experimental results concerning psychopharmacological treatments of bipolar disorder are promising [10], their explanatory value of symptoms on the behavioral level is rather scarce. Therefore, psychiatric research urgently needs comprehensive hypotheses or even theories that are explanatory for the main symptoms of bipolar disorder. Moreover, since white matter may play an important role in learning, cognition, and psychiatric disorders [73,74], a comprehensive model of bipolar disorder and other so-called mental disorders must also refer to the functions of oligodendrocytes, myelination, and the networks between astrocytes and oligodendrocytes, called panglial syncytium.

Conflict of Interest

The author declares no conflict of interests.

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