Neurotransmitters and signal transduction processes in bipolar affective disorders: a synopsis

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Abstract

New technologies have led to tremendous progress in understanding what today we call bipolar disorders, whose clinical diagnosis has been refined continuously since Kraepelin first described them. Molecular genetic studies have produced interesting findings, but to date have failed to identify specific genes that are so far responsible for the vulnerability to bipolar disorders. Biochemical studies in combination with pharmacotherapy give hints that the neurotransmitter function and the related signal transduction may be abnormally regulated. Since all the neurotransmitter circuits are interconnected, the dysregulation may occur on different levels and it is rather improbable that one single abnormality should account for the disorder. This paper reviews these promising developments. © 2001 Elsevier Science B.V. All rights reserved.

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The classical manic-depressive disorders, as first described by Kraepelin (1921) are today considered bipolar according to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (4th Edition). Their lifetime prevalence is estimated to be 0.4–1.6% (Weissman et al., 1996), but may even be much higher based on new epidemiological studies on hypomania by Angst (1995), as well as according to Akiskal's (1996) concept of the soft bipolar spectrum in clinical populations. Already Kraepelin described in his classic works manic depressive insanity and paranoia life charts of patients with a great variation of illness courses. Based on these studies, as well as new European work (Bourgeois et al., 1996), it becomes more and more evident that bipolar disorders are heterogeneous diseases with a high variation in symptomatology and course. Different categories like mixed states, rapid cycling and bipolar II disorders are described in the literature (Perugi et al., 1997, 1998). The frequency rate of episodes is also considerably varying. Cycle exacerbation with shortening of free intervals and increase of episodic severity up to ultradian cycling occur frequently. Although lithium, introduced 40 years ago as a specific treatment for bipolar disorders, has markedly improved treatment and prognosis, it is not effective in all patients (Post et al., 1993). This supports the idea that bipolar disorders are heterogeneous and may therefore have different causes or pathophysiologies. Furthermore, the boundaries of cyclothymia and hyperthymic temperament to full-blown bipolar disorders are unclear (Akiskal, 1996).

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In spite of the immense body of research work with methods of biological psychiatry and the current knowledge about the mechanisms of action of the anti-bipolar drugs, the ultimate aetiology of bipolar disorders is still far from being completely understood.

The various characteristics of bipolar disorders with high pleomorphism may be one of the reasons for this insufficient knowledge. In general, models of bipolar disorders, which focus on single neurotransmitters or neuromodulator systems, cannot sufficiently explain the various clinical pictures. A valid model has to consider opposite effects of neuronal activities, leading to manic and/or depressive episodes. Therefore, it must be a system which dampens oscillations in both directions. Such an abnormality can either be a brain circuit, or regulating cerebral activities, or a cellular abnormality which is involved in regulating transmitter release, or a regulatory protein which is interacting on the level of signal transduction with various signal systems.

Models based on the effects of psychotropic drugs that affect and stabilise mood, can only insufficiently explain the varying clinical picture of the disorder alternating between depressive and manic states. A general theory has to consider both. Therefore, either neurotransmitter systems with opposite effects on brain activity or the signal transduction system which puffers this activity may be involved. Common and distinct effects of mood stabilizers have to be considered. Case reports demonstrate that the available mood stabilizers lithium, valproinic acid, carbamazepine and Ca^{2+} antagonists are inadequately effective in many patients, indicating that they have different targets of action and that the individual patient should have a different abnormality responsible for his disorder. Therefore complex combination therapy is frequently used. The treatment of acute depressive symptoms with antidepressants, and of manic symptoms with typical and atypical antipsychotics is common clinical practise and makes sense. However, the combination of different mood stabilizers lacks scientific justification and expresses the insufficient knowledge of the pathophysiology of the bipolar disorder and therefore attempts to target many different neurobiological systems which may account for this disorder.

The present review tries to give a selective overview on new and existing theories and today's state of the art.

Biological research is actually focusing on molecular genetic studies, metabolism and molecular biology of neurotransmitters and on the mechanism of action of psychotropic drugs, antidepressants and antibipolar drugs such as mood stabilisers. The results with new neuroimaging techniques like positron emission tomography, nuclear magnetic resonance tomography and functional NMR finally give new insights in the function of the brain. Postmortem studies are appropriate to measure the amount of transmitters, their receptor binding and the gene expression of proteins relevant for neurotransmitter function and neurotransmitter abnormalities which are responsible for bipolar disorders.

Because of the heterogeneity of bipolar disorders, it cannot be assumed that a single cause or aetiology is valid for all patients. The various aspects, as presented in the following, may be responsible for the aetiology and pathophysiology of subgroups of bipolar patients.

Such subgroups can be defined by biological parameters, specific behavioural traits and/or response to treatment.

1. Genetics of bipolar disorders

The genetic contributions to the etiopathogencity of bipolar disorders are well documented through family, adoption and twin studies.

Historically, early reports referring to bipolar linkage disorders have shown three chromosomes, Xq28, 11, p. 15 and 18. Already in 1969, a linkage of bipolar disorders with the phenotypic marker of colour-blindness and with glucose-6-phosphate dehydrogenase deficiency was reported in Israeli families (Reich and Clayton, 1969), which was confirmed later by a positive LOD Score on Xq28 (Baron et al., 1987). Newer studies, using molecular genetic techniques (Straub et al., 1994; NIMH initiative, 1997), have shown a weak positive finding in this region. Another positive finding of a linkage of bipolar disorders on chromosome 11P15 among the old Amish families could not be confirmed in independent sets of families. The same group of researchers (Egeland et al., 1987) even had to correct their first

report because the LOD scores changed dramatically by further evaluation of newly associated individuals in the original pedigrees. Therefore, it seemed to be too naive to expect a major gene effect for such a complex disorder, after these first results. In the mean time, several other positive reports on chromosomes 4, 5, 6, 10, 13, 18, 21, 22 and Xq have been published, but again most of them could not be replicated.

Considering these problems with false-positive or -negative findings, exclusion studies indicating the percentage of patients with an association to a certain chromosome, will be more informative. Such analyses have been attempted in molecular genetic studies of a huge European consortium, organized by the European Science Foundation, showing that only a small percentage of bipolar patients may be associated with the chromosomal loci (Sandkuijl, personal communication).

Because of these difficulties with linkage studies, recent research has switched to the candidate gene approach.

These feasible candidate genes are related to the catecholamine and serotonin hypothesis of bipolar disorders and the mechanism of action of mood stabilisers, of antipsychotics and of antidepressants. Therefore, genes for proteins being responsible for the regulation of neurotransmitter metabolism, release, transport and receptors of biogenic amines, are frequently investigated. Among them, a gene, located on chromosome 18, is of high interest for bipolar disorders, because this gene for the α subunit of the G-protein has been localised on the 18P11.2 region (Overhauser et al., 1993), which may be involved in the pathophysiology of bipolar disorders. Linkage as well as association studies have produced interesting positive findings on this chromosome (Berrettini et al., 1997).The G-protein-coupled receptors are the starting points of a cascade of intracellular events. Activation of these G-proteins lead to an activation of the adenylcyclase (AC) and the phosphoinositol system (PIS), and to an increase in intracellular Ca^{2+} concentrations. Lithium decreases the binding of the G-protein α-subunit to guanosine triphosphate (GTP), a requirement for G-protein activation. However, some promising findings could not be replicated in other independent samples (Ram et al., 1997), nor was the response to lithium-treatment

related to the genetic markers of chromosome 18 (Turecki et al., 1996). In an interesting article Risch and Botstein (1996) discussed the problems of genetic studies in complex disorders, e.g., bipolar disorder or schizophrenia. It is common opinion that a single major locus accounting for the majority of bipolar illnesses can be rejected by now. The lack of consistent replications of any of the observed linkages reinforces the notion that bipolar illness has a genetically complex aetiology and that further to genetic risks, environmental factors are interfering variables. Assuming that bipolar disorders are heterogeneous, it seems to be justified that, in individual families, some of the proposed candidate genes are indeed involved in the pathophysiology of bipolar disorders. Functional polymorphisms of tyrosine hydroxylase, G-proteins, serotonin transporter, dopamine transporter, dopamine receptors and additional genetic and environmental factors may be responsible for the outbreak of this disorder under certain conditions.

However, the clinical complexity of BPD and the uncertainty of an acceptable model impair the search of feasible candidate genes.

The observation of anticipation in families with BPD, stimulated the research for trinucleotide repeats. Anticipation results clinically in an earlier age of onset and in a higher severity in offspring generations of families with BPD. Such trinucleotide repeats have been seen in monogenic disorders such as fragile X syndrome, and Huntington disease. A few positive results were published, but anticipations with related abnormal trinucleotide repeats seem to occur rather seldom among BP patients (McInnis et al., 1993; Nylander et al., 1994; Lipp et al., 1995).

2. Neurotransmitters

Theories about neurotransmitter abnormalities in bipolar disorders are related to the effects of pharmacological treatments. For instance, the anti-hypertensive drug reserpine, which depletes noradrenaline, serotonin and dopamine from synaptic vesicles, frequently induces depressive symptoms in hypertensive patients. On the other hand, treatment of depressive symptoms with antidepressants increases the availability of these transmitters and the neuronal

activity by inhibiting the uptake of noradrenaline, serotonin and dopamine or the catabolism of this biogenic amines. In animal models of depression, antidepressants improve this so-called depressive behaviour of the animals. The reserpine sedation and catalepsy can be reversed and even a motoric hyperactivity results from treatment with tricyclic anti-depressants and L-dopa (Ackenheil, 1990).

There are clinical observations that tricyclic anti-depressants and MAO inhibitors can provoke a switch into manic states in depressive bipolar patients (Bottlender et al., 1998); amphetamine, which is generally not an effective anti-depression agent, can produce manic symptoms as well; cocaine, a powerful stimulant in normals and a potent inhibitor of the dopamine uptake at the synapse, precipitates manic symptoms, too; L-dopa, the precursor of dopamine which is mainly used for the treatment of Parkinson patients, is not considered as an anti-depressant and can induce manic episodes in some patients (Murphy et al., 1971). Thus, one of the most consistent pharmacological findings in manic depressive illness is the fact that direct and indirect dopamine agonists stimulate episodes of mania or hypomania in patients with underlying bipolar disorders or predisposition for it.

Extrapolating the old reserpine model of depression to human beings, it can be hypothesised that depression and mania result from a diminished transmitter transport into the presynaptic neurone and/or the synaptic vesicles. The synaptic vesicles, serving as a puffer system, cannot fulfill their function and a deficit as well as an overflow of the respective transmitter cannot be counterbalanced. A resulting higher fluctuation of transmitter in the synaptic cleft may be responsible for the fluctuation of mood as well. Which one of the three biogenic amines, noradrenaline, serotonin or dopamine, is mainly involved, needs further clarification. For manic symptoms direct and indirect signs point to the dopamine transmitter especially in the mesolimbic system, whereas for depressive states and anxiety primarily a noradrenaline deficit is discussed. The serotonin system modulates any kind of behaviour especially symptoms of impulse control like aggression and suicidality (Manji and Potter, 1997).

An abnormality of the dopamine turnover could so far not be demonstrated directly in man. Measuring dopamine or its major metabolite homovanillic acid in cerebrospinal fluid, in urine and in blood did not show any conclusive results so far. There is a tendency that in depressive states the dopamine turnover is lower and in manic states higher, but the results are not consistent. As the metabolism alone does not determine the neuronal activity, it is rather due to the interaction between metabolism, release, sensitivity of the different dopamine receptors and the balance with the other neuronal transmitters. This high complexity is the reason for the lack of consistent findings.

Furthermore, an abnormal function of the dopamine transporter leads to greater fluctuations of dopamine in the synaptic cleft, which has recently been shown in transgenic mice lacking the dopamine transporter (Spielewoy et al., 1998). Chronic treatment with classical tricyclic antidepressants like desmethylimipramine induces a higher messenger RNA D3 and D1 receptor expression in mesolimbic brain structures (Lammers et al., 1995). The additive dopamine reuptake inhibition of tricyclic antidepressants may be responsible for a switch to hypomanic or manic states. Other empirical results show that dopaminergic drugs like amineptine (Mendis et al., 1989; Rampello et al., 1991), nomifensine (Kinney, 1985), as well as bromocriptine, a D3 and D2 receptor agonist, also induce hypomanic states (Wells and Marken, 1989). The well-known effect of cocaine which induces hypomanic states and which leads after chronic treatment to sensitisation phenomena in animals, gives a further support of this hypothesis. Additionally, the beneficial effect of antipsychotics for acute manic patients (Sernyak and Woods, 1993) underlines once more the importance of the dopamine and the noradrenaline system for mania. Altogether there is a compelling evidence for the role of the dopaminergic system in manic states. A higher dopaminergic activity either induced by high release of dopamine, or a reduced puffer capacity of the synaptic vesicles, or a higher sensitivity of dopamine receptors, will cause manic symptoms, whereas a decrease of dopaminergic activity results in depressive symptoms. Especially treatment-resistant depression, the most severe form of depression, might be a specific subgroup of depression with a dysfunction of the dopaminergic system. A supportive treatment with amphetamine or

ritaline (Stotz et al., 1999) which release dopamine and noradrenaline, improves the symptomatology of such patients.

For many reasons, it can be assumed that the noradrenergic system may be involved in the pathophysiology of bipolar disorders as well. Numerous studies describe an underfunction of the brain noradrenergic system in depressive states. This has been shown indirectly by measuring the noradrenaline metabolism in body fluids suggesting lack on reduced reuptake of noradrenaline, or by neuroendocrine studies with the α_2 receptor stimulants, clonidine (Matussek et al., 1980) or desmethylimipramine (Laakmann et al., 1990), which by measuring the growth hormone secretion, allows the estimation of activity of noradrenergic neurones in brain. In depressive states, a lower noradrenaline output and a lower sensitivity of α_2 receptors, which are indicated by a blunted growth hormone response to clonidine, is reported in contrast to a tendentially higher noradrenaline activity in manic states. The serotonin system which has been in the focus of interest for the last years, interacts with the other transmitters as well. In principal, serotonin modulates in the central nervous system different neuronal activities and, in this way, many physiological and behavioural functions such as sleep, appetite, impulse control, etc. Therefore, low serotonin release and activity is discussed to be the reason for many behavioural abnormalities like suicidal ideas and attempts, agressivity, disturbed sleep, etc. Some of them frequently occur in bipolar patients.

The molecular structures of the three neurotransmitter transporters show a high similarity. For this reason reuptake inhibitors do not act very selectively and often influence the other transmitters as well. Other factors such as the regulation of the release and the sensitivity of various kinds of neurotransmitter receptors may also play a crucial role for the pathophysiology of behavioural abnormalities. Most of these neurotransmitter receptors are coupled to G-protein receptors, whose sensitivity is modifying transmitter activity, too. The effect of mood stabilisers point to the G-protein related receptors (Avisar et al., 1988; Schreiber et al., 1991). Therefore, many theories assume that an abnormality of the signal transduction system is the pathophysiological cause for bipolar disorders.

3. Intracellular signal transduction in bipolar disorders

As pointed out above, many theories are related to the mechanisms of action of psychotropic drugs, which can induce an amelioration the bipolar symptomatology.

Most studies could not demonstrate one common action of antidepressants at the level of monoamine release, reuptake or interaction with the respective receptors. This is not astonishing since the classical and newer antidepressants possess widely different potencies in inhibiting noradrenaline, serotonin and dopamine reuptake. Some of them are specific for one transmitter system, others influence more than one transmitter system at the same time. Additionally, the antidepressants are metabolized extensively through the different P450 cytochrome enzymes.

The resulting metabolites themselves show own pharmacological effects on the neurotransmitter and are often different from the mother compound. Newer hypothesis postulate that the long-term therapeutic action of antidepressants is mediated by postreceptor intracellular targets. This is partly true for antipsychotics as well, which are used as antimanic drugs, and especially for mood stabilizers which interact in different ways with intracellular second messenger systems and the gene expression of proteins involved in transmitter action (Ackenheil, 1998).

Most of the neurotransmitters, such as noradrenaline, serotonin, dopamine acetylcholine, exert their action via postsynaptic receptors which are coupled to guanine nucleotide-binding proteins (G-proteins). The G-proteins are heterotrimeric. They are composed of two functional entities, an α-subunit binding and hydrolysing guanosine triphospate (GTP), and a dimer consisting of β- and γ-subunits (Spiegel et al., 1992; Birnbaumer, 1993). There is a high diversity of the α-subunit with at least four subgroups (Gαs, Gα, Gαq, Gαo) (Raymond, 1995). The Gα subunits regulate different effector proteins. They are active if GTP is bound, inactive if GDP is bound. The interconversion of GDB/GTP bound states is a key step in regulating the G-protein function (Raymond, 1995).

These G-protein coupled receptors stimulate or inhibit mainly three second messenger systems:

adenylyl cyclase (AC), phospholipase C (PLC) and ion channels. The products of this second messenger system, like cyclic AMP, inositol phosphates, diacylglycerol and Ca^{2+} react with different protein kinases which, via different steps, induce the expression of immediate early genes such as c-Fos, C-jun, cyclic AMP response element binding protein (CREP), and lead to a gene expression of transmitter enzymes, receptors and transporters which regulate the neuronal activities. Hypotheses concerning the pathophysiology of bipolar disorders on second messenger systems are based on the effects of mood stabilizing drugs which interfere with these three systems.

The AC system is connected to biogenic amine receptors. On this way the production of cyclic AMP is either stimulated by Gs-proteins or inhibited by Gi-proteins. Cyclic AMP reacts with protein kinases. The resulting CREP modifies phosphorylation and regulates gene-expression of proteins, which are relevant for neurotransmitter metabolism and release. Regulation on this level is possible through up- and downregulation of G-proteins or the cyclic AMP catabolyzing enzyme phosphodiesterase.

The PI system is stimulated by neurotransmitter receptors via Gq proteins and activated phosphorlipase C which converts PIP2 to diacylglycerol (DAG) or to INS (1,4,5)P3, diacylglycerol opens Ca^{2+} channels. The maintenance and efficacy of the PI signal system depends mainly on PI P2 which is synthesized from myo-inositol by the enzyme inositol monophosphatase (IMP), being the rate-limiting step.

Furthermore, intracellular Ca^{2+} is released from intracellular stores and stimulates protein kinases. Intracellular Ca^{2+} levels are critically dependent on regulation by ion channels. The intracellular Ca^{2+} levels (50–200 nm) are 10 000-fold lower than extracellular Ca levels. The cytosolic Ca^{2+} concentration increases in the case of cellular stimulation. Hormones, neurotransmitters and electrical activity regulate cytosolic Ca^{2+} concentration by an influx of Ca^{2+} through Ca^{2+} channels into the cytosol and by release of Ca^{+} from internal storage pools. Increased intracellular Ca^{2+} influences synthesis and release of neurotransmitter and receptor signals. The Ca^{2+} calmodulin complex serves as an additional puffer system. Normally, when Ca^{2+} returns to resting levels, many of the biochemical effects are terminated. A Ca^{2+}-dependent ATPase drives Ca^{2+} against the concentration gradient out of the cell or in intracellular storage compartments. The Ca^{2+} removal is regulated through Na^{+}/Ca^{2+} exchange. Ca^{2+} leaves and Na^{+} enters the cell with the help of Na^{+}/K^{+} ATPase energy-dependent processes (Carafoli, 1987).

Under normal physiological conditions a substantial crosstalk occurs between the three second messenger systems. Cyclic AMP interferes with the PI system and the Ca^{2+} levels. The three different signal transduction systems are not acting independently. The crosstalk between receptor-mediated second messenger systems may thus modulate the signal integration and coordinates the cell function.

Interestingly, all three second messenger systems are discussed to be involved in the pathophysiology of bipolar disorders. The action of mood-stabilising drugs, such as lithium, carbamazepine, sodium valproate and calcium antagonists, which interfere with all three signal transduction systems, justify the major arguments of an abnormality on this level of cell function. Studies with either peripheral blood cells or with post-mortem brain tissue support these theories. Peripheral lymphocytes are considered as models for neuronal cells since they share a lot of common characteristics with neuronal cells. Lymphocytes express neurotransmitter receptors on their cell membranes. These receptors again are connected via G-proteins to second messenger systems such as AC and PI, which also stimulate intracellular Ca^{2+} secretion in these cells, the expression of immediate early genes, c-Fos, c-Jun and the secretion of cytokines.

With respect to G-protein function, there are some interesting findings on lymphocytes and platelets of bipolar patients. Most of the studies show an increased activity of G-proteins connected to cyclic AMP production (Schreiber et al., 1991; Young et al., 1994; Perez et al., 1995) or to the PI system (Brown et al., 1993; Friedman et al., 1993).

A very promising finding, combining molecular genetic studies and intracellular Ca^{2+} measurement, shows a higher frequency of a functional human G-protein β_3 subunit variant (Siffert et al., 1998),

associated with higher Ca^{2+} influx. The combination of molecular genetic studies and biochemical findings offer new perspectives for the future research and overcomes the problems of clinical heterogeneity.

4. Mechanism of action of mood stabilisers

Lithium is the first 'drug of choice' for long-term treatment of bipolar disorders. Since one-third of bipolar patients may be partially or completely refractory to lithium therapy, anti-epileptic drugs, such as carbamazepine or sodium valproate, are additionally used quite frequently for the treatment of bipolar disorders (Post et al., 1998).

There is a huge and extensive literature on the mechanism of action of lithium in relation to bipolar disorders. Most of the studies had been carried out in animals and showed that lithium increases synthesis and turnover of serotonin in presynaptic neurons, at least partly by increasing the uptake of the serotonin precursor tryptophan. Lithium mediates the sensitivity of postsynaptic 5HT1A receptors and, similarly, as antidepressants, decreases β-adrenergic receptor-mediated stimulation of adenylate cyclase (Price et al., 1990).

The effects of lithium on intracellular signal transduction systems are more important. There is accumulating evidence that lithium decreases G-protein functionality (Avisar et al., 1988) and by such a way inhibits cyclic AMP production. The resulting hypothesis of a hyperfunctionality of G-proteins in bipolar patients was described in a convincing manner by Schreiber et al. (1991). This hypothesis is supported by clinical studies showing an increase of cyclic AMP signalling in bipolar patients. Increased forskolin-stimulated adenylate cyclase activity and increased [³H]cyclic AMP binding in post mortem brains as well as an increased cyclic AMP-dependent protein phosphorylation in platelets of bipolar patients have been reported (Risby et al., 1991).

Another pathway of research focuses on the effect of lithium on the PI cycle. Lithium in therapeutically relevant concentrations is an inhibitor of the rate-limiting enzyme, the inositol monophosphatase (IMP) for PI P2. The inositol depletion hypothesis (Berridge and Irvine, 1989; Jope et al., 1996) assumes a lack of free inositol in bipolar patients. Lithium causes a reduction in the synthesis of phosphoinositol (PI) which is necessary for the signalling pathway. According to this theory, the IMPase activity is postulated to be elevated in bipolar disorders resulting in diminished inositol levels which accelerate cellular responses to neurotransmitter stimulation. The inhibition of IMPase activity by lithium can restore intracellular inositol levels. Alternatively, treatment with Inositol restoring the Inositol levels, has beneficial effects (Benjamin et al., 1995). An ultimate effect more downstream is the decrease of protein kinase C (PKC), signalling an altered regulation of gene expression. Newer research studies, applying new molecular biological techniques such as differential displays, have shown that treatment with lithium expressed four differential gene products, which, unfortunately, could not be completely identified so far. One of the gene products is most probably a gene for the enzyme 2,3-cyclic nucleotide-3-phosphodiesterase type II (CNPase II) which is markedly increased after lithium treatment (Wang and Young, 1997). Phosphodiesterases catabolyse cyclic AMP and cyclic GMP. Further studies of this kind may be helpful for an understanding of the therapeutic effect of lithium and its involvement in the regulation of signal transduction pathways.

Another target of lithium as well as of carbamazepine and valproate is the intracellular Ca^{2+} level. There are some results which show a decreased activity of Na^+,K^+-ATPase in bipolar patients which regulates Ca^{2+} flow. It is well known that lithium accumulates intracellularly by replacing Na which in turn decreases intracellular Ca^{2+}. Additionally, lithium and carbamazepine stimulate Na^+/K^+-ATPase activity directly which is an important step for the reduction of intracellular Ca^{2+} levels. Na^+/K^+-ATPase has been reported to be decreased on red blood cells of bipolar patients. This enzyme regulates intracellular Na^+ and consequently the Na^+/Ca^{2+} exchange. Dubovsky and colleagues found elevated intracellular free Ca^{2+} concentrations in platelets and lymphocytes of manic and depressed bipolar patients (Dubovsky et al., 1989). Incubation with lithium in therapeutic concentrations could reduce resting and

stimulated levels of Ca^{2+} (Dubovsky et al., 1994). According to this theory, slightly elevated intracellular free Ca^{2+} levels raise cell metabolism to a maximum, whereas higher Ca^{2+} levels lower Na^+/K^+-activated ATP, thus reducing the metabolic rate of the cells. Excessive intracellular free Ca^{2+} is cytotoxic and leads to cell death by activating Ca^{2+}-dependent proteases and phosphorlipase A. Slightly elevated Ca^{2+} levels may occur in manic states with higher cellular activity. Excessive Ca^{2+} levels might reduce cellular activity leading to depression. There are obvious links between these Ca^{2+} findings and those in cyclic AMP and PI. INS(1,4,5)P3 binds to a receptor that liberates Ca^{2+} from its intracellular storage places. That is why the increased PI system activity is accompanied by elevated intracellular Ca^{2+} levels. Additionally, in some tissues, Gαs protein couples to Ca^{2+} channels (Yatani et al., 1988) and, in this way, increases intracellular Ca^{2+} levels. Both increased PI signalling as well as increased levels of Gα subunits in bipolar patients lead to higher cytosolic Ca^{2+} levels. Interestingly, Ca^{2+} channel blockers have been reported to be therapeutically effective (Höschl, 1991). Among them the highly lipid soluble A type Ca^{2+} channel antagonist nimodipin is reported to improve manic as well as depressive episodes (Walden et al., 1995).

There is another new exiting candidate for the mechanism of lithium action (Agam and Levine, 1998). The enzyme glycogen synthase kinase 3 (GSK 3) is involved in the regulation of at least three intracellular signal transduction cascades, the WNT which is responsible for neuronal development, mitogen-activated protein kinase (MAPK) and phosphatidylinositol (PI)-3 kinase. The lithium effect on GSK 3 can explain the teratogenic effects of lithium as well as the therapeutic effect. The teratogenic effects may result from the activation of the WNT pathway, which is responsible for development (Moon et al., 1997), whereas the therapeutic effects are mediated via the MAPK and the PI-3 signal transduction systems. Final proof has to be given if there is indeed a dysfunction of the GSK 3 as an etiological effector in bipolar disorders. Only one report of a dysfunction of this protein kinase in lymphocytes of schizophrenic patients points in this direction (Yang et al., 1995). Anyway, the discovery of the lithium inhibition of enzyme GSK 3 opens a new perspective in the research of bipolar disorders.

5. Sensitisation and kindling

The models of sensitisation and kindling have been developed on the basis of animal experiments (Post, 1976; Post and Weiss, 1996). They are interesting theoretical constructs, showing that the phenomena of recurrence and cyclicity can be explained and that due to conditioning factors the frequency of episodes may increase. Sensitisation is induced in animals by repeated application of the psychostimulant cocaine, kindling by repeated electrophysical stimulation. As shown, treatment with mood stabilizers can prevent these effects. It can be speculated that in bipolar disorders similar mechanisms trigger these symptoms. In human beings sensitisation and kindling can only be shown indirectly. Conditioning factors which induce sensitisation and kindling can stress-related live events, for example, a provocation of episodes with psychotropic drugs or unknown intracellular events as for long-term potentiation. Such processes are observed in other medical disorders and probably in normal and abnormal behaviours as well. If untreated, epileptic seizures occur with increased frequency. Although disorders or obsessive compulsions may be related to similar mechanisms as well, normal learning can be based on a similar mechanism.

6. Neuroanatomy and neuroimaging

New anatomic models, resulting from animal experiments can be tested with research of brain imaging methods. In the centre of interest remains the limbic system, especially the nucleus accumbens and the limbic thalamic circuits which are connected to the limbic system. There are some reports that ventricular enlargement appears to occur in bipolar disorders like schizophrenia, but there is no clear relationship to clinical parameters (Raz and Raz, 1990; Elkis et al., 1995). Also, there does not seem to be a high specificity for a single psychiatric disorder. More promising are investigations with magnetic resonance imaging, allowing the measure-

ment of subcortical hyperintensities, which indicate other abnormalities. Altshuler et al. (1995) reported an increase of periventricular subcortical hyperintensities in bipolar patients. This finding was supported by two other studies (Kato et al., 1998; Volz et al., 1998). However, despite the increasing advanced methodology no convincing results have been reported so far. This may be due to the heterogenic clinical picture and the problems related to manic symptomatology which makes it very difficult to carry out such kind of studies during manic episodes. Another interesting result has been observed with ^{31}P magnetic resonance spectroscopy that allows the in vivo measurement of biochemical molecules. Phosphor monoesters were increased in patients treated with lithium in manic and in depressive states (Kato et al., 1994). Decreased PH values as well as decreased phosphocreatinine levels were reported in the same patients. These results have been replicated by another group but need further clarification.

7. Future perspectives

The diagnosis of bipolar disorders is continuously improved and broadened. Molecular genetic and biological research is faced with the problem of clinical heterogeneity and, therefore, despite the huge number of studies, no conclusive results exist. There is clear evidence for an abnormality of the neurotransmitter function or regulation. Dopamine, noradrenaline and serotonin may contribute to the pathophysiology of bipolar disorders. Studies of intracellular signalling offer possibilities to understand both kinds of behaviour, depressive and manic symptomatology. The action of drugs, either provoking bipolar symptoms or having beneficial therapeutic effects, offer perspectives for future research projects. The subgrouping of patients due to responses to treatment is another perspective for defining bipolar phenotypes. Coupling of biochemical results and pharmacological responses with molecular genetic genotyping will be the perspective of the future.

The animal models of sensitisation and kindling have a scientific theoretical value, which is difficult to prove in patients, but may be helpful in understanding the therapeutic effects of mood stabilizers.

Neuroimaging studies have failed to produce specific disorder-related findings, but in combination with neuropsychological paradigms they are promising in the future. Thus, basic and clinical research have to plan future studies in a collaborative manner.

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