

# The Neurobiology of Bipolar Disorder: Focus on Signal Transduction Pathways and the Regulation of Gene Expression

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**Objective:** This article presents an overview of signal transduction pathways and reviews the research undertaken to study these systems in clinically relevant samples from patients with bipolar disorder (BD).

**Method:** We reviewed the published findings from studies of post mortem brain tissue and blood samples from patients with BD.

**Results:** Although the exact biochemical abnormalities have yet to be identified, the presented findings strongly suggest that BD may be due, at least in part, to abnormalities in signal transduction mechanisms. In particular, altered levels or function, or both, of G-protein  $\alpha$  subunits and effector molecules such as protein kinase A (PKA) and protein kinase C (PKC) have consistently been associated with BD both in peripheral cells and in post mortem brain tissue, while more recent studies implicate disruption in novel second-messenger cascades, such as the ERK/MAPK pathway.

**Conclusions:** Despite the difficulties inherent in biochemical studies of clinically relevant tissue samples, numerous investigations have illuminated the signal transduction mechanisms in patients with BD. These studies also suggest that BD may be due to the interaction of many abnormalities. In this context, novel techniques enabling the study of gene expression promise to assist in untangling these complex interactions, through visualizing the end result of these changes at the level of gene transcription.

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## Clinical Implications

- Understanding the abnormalities underlying bipolar disorder (BD) may lead to a better understanding of current drug effects and novel pharmacotherapy and thus enable more effective treatment of patients with this illness.
- Elucidating verifiable molecular and biochemical markers for BD may assist in developing more robust and effective patient diagnosis.
- A solid understanding of signal transduction pathways and their downstream effects is relevant to all illnesses involving changes in cell signalling or gene expression.

## Limitations

- Currently, the biochemical and molecular abnormalities underlying BD are unknown.
- The abnormalities thought to underlie BD are likely not due to a single defect.
- The functional implications of the research described herein are limited by the lack of knowledge with respect to changes in gene expression as associated with these disorders and the need to develop effective and accurate methods of ascertaining these alterations in clinical samples.

**Key Words:** *signal transduction abnormalities, bipolar disorder, clinical studies, brain, gene expression*

**B**ipolar disorder (BD) is a relatively common illness with episodes of mania and depression and, in most patients, a chronic recurrent course. The burden of illness was previously underappreciated; it spans a continuum from psychosocial impairment to an increased risk of suicide. Treatments available for the disorder have proliferated over the past decade and include a diverse group of agents ranging from lithium to anticonvulsant and novel antipsychotic agents. As our understanding of the specific neurobiology of BD increases, genetic susceptibility genes are increasingly seen as having clear importance in the disorder's etiology. Neurohormonal pathways, such as the hypothalamic-pituitary-adrenal axis and classic monoaminergic neurotransmitter systems, have all been well studied in BD. A more recent focus on the role of excitatory amino acids such as glutamate has emerged with the findings that lithium can regulate reuptake of this amino acid in animal models. The intracellular mechanisms linked to these receptors provide an interesting system that may be central to BD and that has recently been intensively studied in patients with this disorder. (A list of abbreviations and acronyms used in this paper appears on page 144.)

The complexity and diversity of signal transduction pathways continues to emerge; however, several general features can be used to understand the networks. These features have allowed direct investigation in tissue samples from patients with BD. Most neurotransmitter receptors couple to guanine-nucleotide binding proteins (G-proteins). These proteins link receptors to specific enzymes that produce second messengers, or alternatively, they link to specific ion channels. The extracellular signals are integrated, amplified, and transmitted to specific intracellular enzymes, called effectors, which catalyze the production of an extensive array of cascading second messengers. In turn, these messenger molecules act on various protein kinases (1). The activation of these kinases is instrumental in regulating diverse intracellular processes, including gene expression, and in relating these to lasting neurobiological changes (1,2). In deed, the number of findings on abnormalities in signal transduction systems in samples obtained directly from patients is growing.

In the central nervous system (CNS), intracellular signal transduction pathways are uniquely responsible for coordinating the cellular response to information impinging on the cell from multiple sources and time frames. It follows that abnormalities in these pathways may lead to functional imbalance in multiple neurotransmitter pathways, which could account for the diverse clinical features found in BD, such as a recurrent course, mood fluctuations, psychotic features, neurovegetative symptoms, and cognitive impairment. In fact, the higher-order brain functions, such as behaviour,

mood, and cognition, are critically dependent on signal transduction processes for their proper functioning (1). The time lag between the pharmacologic and clinical effects of mood stabilizers also suggests that long-term cellular and molecular events are important in the drugs' mechanism of action. Signal transduction pathways present researchers with a range of targets that may be important for understanding the biological basis of BD and its treatment. In this article, we will briefly describe several signal transduction pathways and review studies that have examined these systems in tissue from patients with BD.

## Signal Transduction Pathways

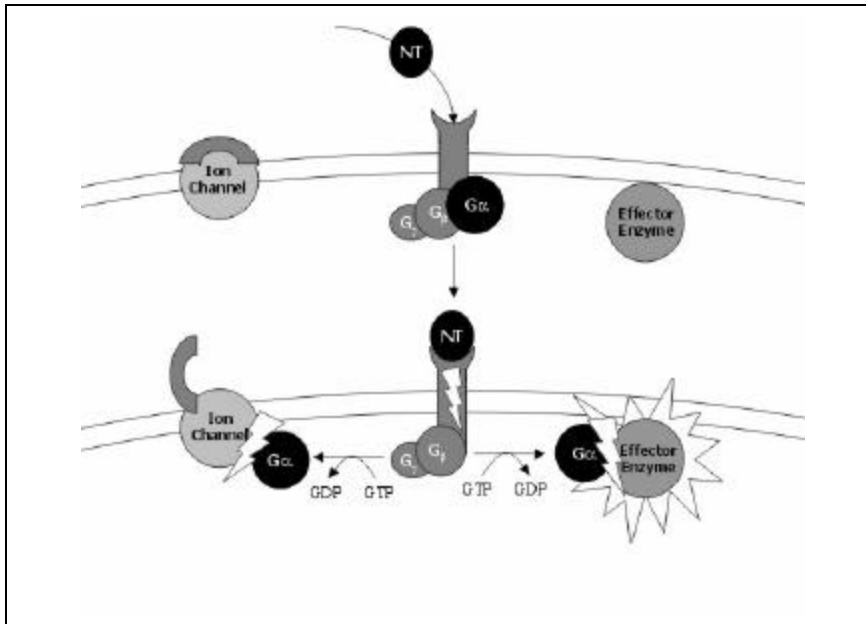
Among the first studies to suggest disturbances in signal transduction in patients with mood disorders were the findings of attenuated  $\beta$ -adrenergic receptor-activated adenylyl cyclase (AC) activity in peripheral cells (platelets and lymphocytes) from patients with unipolar and bipolar depression (3–6). At the same time, no differences were observed in the number or affinity of this type of noradrenergic receptor in patients, compared with control subjects (7,8). This suggested blunted responsiveness or desensitization, rather than a diminished number of  $\beta$ -adrenergic receptors (7,9). Since then, researchers have identified several signal transduction molecules as targets of mood stabilizers and antidepressants. They have also identified abnormalities in these pathways in samples from patients with BD (for review see [10]). It is possible that these drugs correct an underlying signal transduction abnormality in patients. In the following sections, we will proceed downstream along the signal transduction pathway, from coupling of G-proteins to receptors, to direct measurement of second messengers, to kinases and transcription factors, and finally, to regulation of gene expression in nuclei. We will also briefly describe the molecular pathways and the findings in patient samples.

## G-Proteins

G-proteins are an integral part of the intracellular signaling pathway, in that they link receptors in the membrane to diverse intracellular effector molecules and responses (see Figure 1). G-proteins consist of 3 subunits: an  $\alpha$  subunit that binds and hydrolyzes guanosine triphosphate (GTP), and  $\beta$  and  $\gamma$  subunits that are tightly bound to one another (11). This hetero-oligomeric protein structure allows for the coupling of a wide variety of receptors to the same or different signal transduction systems, leading to near infinite combinations. Even modest changes in the levels of the G-proteins have the potential to markedly alter the orderly progression of events from the membrane receptors to their intracellular targets.

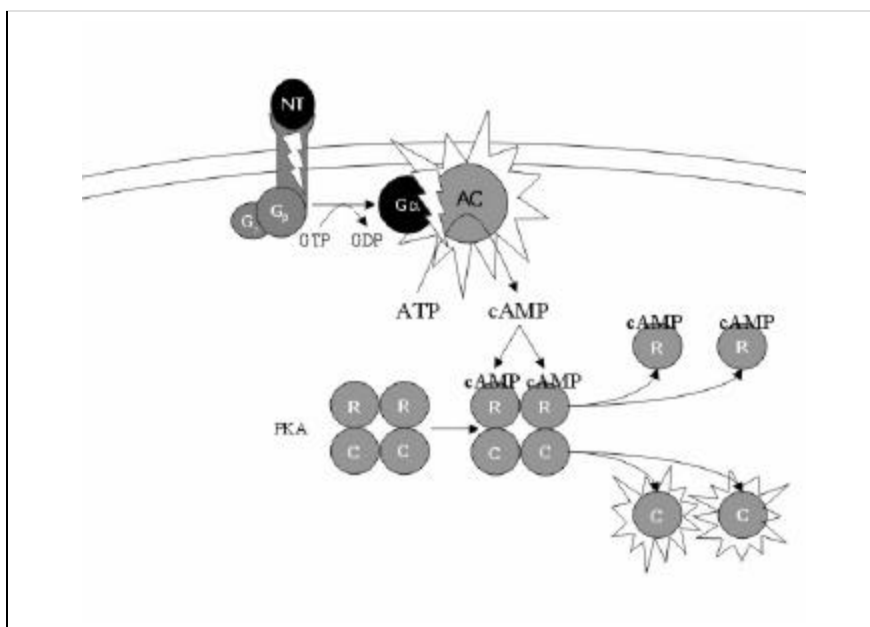
The interest in studying G-proteins in BD (see Table 1) was largely prompted by an initial studies: these found that lithium attenuates the function of several G proteins, including the stimulatory subtype  $G\alpha_s$  (12–14). Young and others (15,16) described increased  $G\alpha_s$  (but not  $G\alpha_i$ ,  $G\alpha_o$ , or  $G\beta$ ) levels in frontal, temporal, and occipital cortex obtained post mortem from subjects with BD. Further, these increases appear to have functional relevance, because they were correlated with the activity of AC, the major effector enzyme coupled to  $G\alpha_s$ , in the same brain tissue samples. These findings were replicated and also extended in another study with a different collection of brain tissue. Using [ $^{35}$ S]GTPS binding, a specific binding

assay for G-proteins, and other methods to measure the function of G-protein  $\alpha$  subunits, the investigators found evidence to support both increased abundance of G-proteins and increased function in the frontal cortex of subjects with BD (17). In a much larger sample of subjects from the Stanley Foundation Neuropathology Consortium, we recently reported that, while there were no overall differences in  $G\alpha_s$  levels among patients compared with control subjects, an increase was evident in subjects not on lithium at the time of death, compared with those on the medication (18). The treatment before death of patients in this sample may have been more aggressive than that in earlier samples; this may partly explain the failure to



**Figure 1.** G-protein coupled signal transduction. Neurotransmitters (NT) bind to G-protein coupled transmembrane receptors, which interact with G-proteins composed of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits. Receptor activation induces a conformational change in receptor associated G-protein, resulting in the exchange of GDP for GTP on the  $\alpha$  subunit. The  $G\alpha$  subunit then stimulates an effector enzyme or certain ion channels, resulting in the accumulation of various second messengers and initiation of intracellular signaling cascades.

Table 1. G-protein signalling in bipolar disorder		
		Study
Postmortem cerebral cortex	$\uparrow G\alpha_s$ , $\leftrightarrow G\alpha_i$ , $G\alpha_o$ , and $G\beta$ levels	(15,16)
	$\leftrightarrow G\alpha_s$ mRNA levels	(29)
	$\uparrow$ Coupling of 5-HT receptors to membrane G-proteins; $\uparrow$ GOC levels	(17)
	$\uparrow$ ADP-ribosylation of $G\alpha_i$ and $G\alpha_o$ ;	(18)
	$\uparrow G\beta$ coprecipitation with $G\alpha_i$ $\downarrow G\alpha_s$ levels in Li-treated subjects	
Leukocytes and platelets	$\uparrow G\alpha_s$ and $G\alpha_i$ levels in depressed patients	(8)
	$\uparrow G\alpha_s$ levels in leukocytes of BD patients; $\downarrow G\alpha_{q/11}$ and $\uparrow$ ADP ribosylation in platelets from Li-treated patients	(21)
	$\downarrow$ Agonist-induced Gpp(NH)p binding in depression; $\downarrow G\alpha_s$ levels	(33)
	$\uparrow$ Agonist-induced Gpp(NH)p binding and $G\alpha_s$ and $G\alpha_i$ levels in mania and $\downarrow$ in depression	(20)
	$\uparrow G\alpha_s$ levels in platelets of BD types I and II, irrespective of treatment; $\leftrightarrow$ in MNLs	(22)
	$\uparrow G\alpha_s$ levels in depressed and Li-treated patients	(23)
	$\downarrow G\alpha_s$ levels in Li-treated patients	(153)
	$\leftrightarrow G\alpha_s$ levels in Li-treated BD type I patients	(25)



**Figure 2.** cAMP signaling system. The G $\alpha$  subunit (G $\alpha_s$ , G $\alpha$ ) released upon neurotransmitter binding stimulates AC, which then converts ATP to cAMP. As a second messenger, cAMP activates cAMP-dependent PKA, by binding to the regulatory (R) domains, and inducing the dissociation of the catalytic (C) domains.

detect a difference between the larger group of subjects with BD and control subjects.

Studies of peripheral blood cells have largely confirmed the above findings and have also explored the relation between G-protein signaling and mood state. Schreiber and associates first reported enhanced binding of [ $^3$ H]Gpp(NH)p in mononuclear leukocytes (MNLs) of patients with mania, implicating increased G-protein levels and enhanced receptor-mediated G-protein activation in this patient group (19). Since then, several studies have found an increase in both level and function of G-protein subunits in manic and euthymic states (19–22). At least 2 studies found increased G $\alpha$  levels in MNLs from unmedicated patients with bipolar depression (23,24), whereas another suggested that the levels of this coupling G-protein may be more directly linked to mood state, with increased levels in mania and decreased levels in depression (20). At least 1 study of a larger sample found that increased levels might be present in both drug-free patients and in those on various mood stabilizing medications (22). Studies of platelets from patients with BD have also shown differences in G-protein levels (21,22). However, Alda and colleagues measured G $\alpha_s$  levels in transformed lymphoblasts from lithium-responsive patients with BD and found no differences, compared with control subjects (25). This suggests that either mood state or cell type may be an important factor in determining whether G $\alpha_s$  levels are detectable in blood cells from patients with BD.

It has proved more difficult to identify the mechanisms responsible for observed G-protein abnormalities. Linkage studies of BD and the gene coding for G $\alpha_s$  have yielded negative results (26–28), and, similarly, the gene-expression levels

of G $\alpha_s$  do not appear to be altered in post mortem brain tissue taken from subjects with BD (29). The mechanisms that determine G-protein subunit levels are very complex. It has yet to be determined whether G-protein abnormalities are directly involved in BD or whether they represent a secondary manifestation of dysfunction in another pathway. Without an understanding of the causes of any apparent differences in G $\alpha_s$  levels, it has been harder to further develop the G-protein hypothesis of BD and its treatment. On the whole, G-protein studies suggest that altered G $\alpha$  levels or function, or both—perhaps through increased receptor–G-protein coupling—play an important role in the biological basis of BD.

### Cyclic Adenosine Monophosphate (cAMP)-Generating Pathway

Following receptor activation, G-proteins interact with several enzymes called effectors. One well-characterized pathway is the coupling of stimulatory or inhibitory G-protein subunits to the enzyme AC (see Figure 2) (11). Multiple forms of AC catalyze the production of cAMP, an important second messenger, from adenosine triphosphate (ATP). The production of cAMP by this enzyme is balanced through its rapid degradation by phosphodiesterases: another enzyme with multiple intracellular subtypes (30). cAMP in turn regulates many cellular functions, such as metabolism and gene transcription. The major target for cAMP is yet another enzyme, cAMP-dependent protein kinase, also known as protein kinase A (PKA). This enzyme is a critical step in linking short-term changes in neurotransmitter signaling to lasting neurobiological changes (see below) (31,32).

Table 2. cAMP signalling in bipolar disorder		
		Study
Postmortem cerebral cortex	↑ Forskolin-stimulated cAMP production	(15,16)
	↓ [ <sup>3</sup> H]-cAMP binding	(35)
	↔ AC levels	(154)
	↑ Maximal and basal cAMP-dependent PKA activity; ↓ PKA EC50 for cAMP	(38)
	↓ Forskolin-stimulated AC; ↓ CREB levels in anticonvulsant-treated subjects	(18)
Leukocytes and platelets	↓ PGE1-stimulated cAMP in depressed MDD and BD patients ↓ NE Inhibition of PGE-1 stimulated cAMP production	(41)
	↓ Isoproterenol-stimulated cAMP production in depressed MDD and BD patients	(7) (9)
	↓ Forskolin-stimulated AC activity subsequent to Li treatment	(5)
	↓ Basal and stimulated AC activity in Li-treated patients	(6)
	↓ Agonist-induced Gpp(NH)p binding in manic patients	(19)
	↑ cAMP dependent protein phosphorylation in euthymic patients	(40,42)
	↑ Basal and cAMP-stimulated protein phosphorylation after Li treatment	(36)
	↑ Basal and NaF stimulated; ↓ isoproterenol-induced cAMP formation in subjects with high Ca <sup>2+</sup> levels	(101)
	↑ PKA catalytic subunit levels vs untreated euthymic BD and control subjects; ↔ PKA regulatory subunit levels; ↑ rap 1 levels	(39)

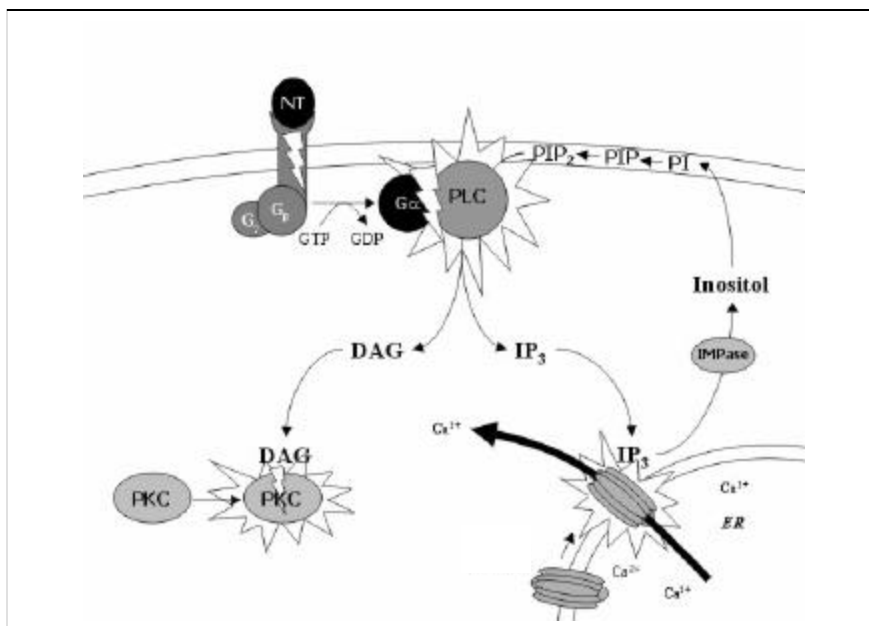
Several studies have reported that basal and receptor-activated AC activities are increased in patients with BD (see Table 2). These changes may be linked to disturbances in the G-protein  $\alpha$  subunits (3–5,15,16,19,20,33,34) described in the previous section. Further, the activity of this enzyme correlates significantly with treatment or mood state: studies demonstrate decreased AC activity in subjects with depression and in patients with euthymia that recurs after lithium treatment (20,33,34).

As described above and reviewed elsewhere, PKA is the major target of cAMP. PKA is a complex protein made up of regulatory (R) and catalytic (C) subunits. A postmortem study found that [<sup>3</sup>H]cAMP binding to the PKA (R) subunits was reduced in the cerebral cortex of patients with BD (35), which might be due to altered synthesis or protein degradation. This is known to occur in the presence of increased cAMP signalling (for a review, see [36]). More recently, a postmortem brain tissue study found that the activity of this enzyme was increased in the temporal cortex of patients with BD (37). Subsequent analysis of the specific PKA subunits suggests that elevated PKA activity in BD results from a state-related imbalance in the specific PKA subunits (38). Several studies with large numbers of patients with BD in various mood states before and after treatment, have also found evidence of increased PKA levels and activity with increased levels of several downstream markers in peripheral cells (39). These postmortem brain tissue findings are interesting, and suggest that numerous components of the G-protein-coupled, cAMP signalling pathway are activated in patients with BD (38,40,41).

### Phosphoinositide (PI) Pathway

Many neurotransmitter receptors are coupled to an other signalling pathway, involving the phosphatidylinositol-specific phospholipase (PLC) enzyme, by the G-protein isoforms G<sub>q</sub>/G<sub>11</sub>, (42) (see Figure 3). The activation of these receptors stimulates PLC, which in turn induces the hydrolysis of the inositol-containing phospholipid phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to 2 second messengers: 1,2-diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP<sub>3</sub>) (43). By binding to an IP<sub>3</sub>-specific receptor on the endoplasmic reticulum (ER) surface, IP<sub>3</sub> stimulates the release of intracellular-stored calcium from the smooth ER into the cytosol (44). DAG, on the other hand, activates protein kinase C (PKC), which comprises another family of kinases (43). Further, because inositol crosses the blood-brain barrier poorly, cells must maintain a sufficient supply of *myo*-inositol for the resynthesis of PIP<sub>2</sub> and the maintenance and efficiency PI-mediated signal transduction. This supply of *myo*-inositol thus depends on the dephosphorylation of inositol phosphates. The enzyme that catalyzes this reaction, inositol monophosphatase (IMPase), thus plays a crucial role in the PI-signalling pathway (45).

There is strong evidence of PI-signalling abnormalities in peripheral cells and postmortem brain tissue obtained from subjects with BD (see Table 3). Initial investigations



**Figure 3.** PI-generated second messenger system. The binding of a ligand activates receptors coupled to a G-protein (G<sub>q</sub>). The G<sub>αq</sub> subunit dissociates and activates PLC, which catalyzes the hydrolysis of PIP<sub>2</sub> and generates the second messengers IP<sub>3</sub> and DAG. IP<sub>3</sub> releases calcium from the ER, and is metabolized by either phosphorylation to IP<sub>4</sub> or dephosphorylation to IP<sub>2</sub>. Subsequently, PI3-kinase phosphorylates IP<sub>4</sub>. Finally, IMPase dephosphorylates these substrates, producing inositol, which replenishes the phospholipid content of the membrane. DAG, on the other hand, activates PKC (synergistically with Ca<sup>2+</sup> in most cases), which is then free to phosphorylate various substrate molecules.

Table 3. PI signalling in bipolar disorder		
		Study
Postmortem cerebral cortex	↑G <sub>αq/11</sub> and PLC-β immunoreactivity; Gβ	(69)
	↓GTPγS and NaF-stimulated [ <sup>3</sup> H]PI hydrolysis in BD vs Li-treated and control subjects; ↔Ca <sup>2+</sup> stimulated PLC activity	(60)
	↑PKC activation; ↑PMA and phorbol-ester induced PKC translocation; ↑cytosolic α and membrane-associated γ and ε-PKC isozyme levels; ↓cytosolic ε-PKC levels	(69)
	↔IMPase activity in depressed patient samples	(46)
	↓Inositol levels in frontal cortex; ↔IMPase activity	(49)
Platelets	↓PLC activity in Li-treated euthymic patients	(6)
	↑Membrane-bound vs cytosolic PKC activity; ↑5-HT elicited PKC translocation; ↓basal and 5-HT elicited PKC activity following 2 weeks of Li treatment	(64)
	↑PIP <sub>2</sub> levels in manic patients	(52)
	↑PIP <sub>2</sub> levels manic vs untreated euthymia; ↓Li-treated vs manic; ↔between Li treated vs untreated euthymia	(54)
	↓PIP <sub>2</sub> in Li-treated euthymic patients; ↔in other phospholipids	(55)
	↑Basal PKC activity in mania; ↓PKC responsiveness to PMA/thrombin in depression; ↑PKC responsiveness to 5-HT; ↔PMA induced translocation	(65)
	↔PKC-α levels	(155)
	↓PIP <sub>2</sub> following Li treatment; ↔in other phospholipids	(56)
	↓PIP <sub>2</sub> in Li-treated patients; cytosolic PKC-α levels; no correlation between PLC and PIP <sub>2</sub> measures	(57)
	↑Membrane PIP <sub>2</sub> levels in depressed patients; ↔in other phospholipids	(53)
Erythrocytes	↓Inositol 1-phosphatase activity in Li-treated patients	(50)

found no differences in free inositol levels in unmedicated patients with BD (46,47), although 1 study observed reduced incorporation of inositol to PI intracellular pools in this patient group (46). Recent post mortem brain studies found decreased free inositol levels in the frontal cortex of patients with BD, but no change in IMPase activity (48). The activity of this enzyme, which leads to the release of free inositol, has also been studied in patients with BD. No difference in this enzyme's activity was found in erythrocytes of unmedicated patients, compared with control subjects, although lithium had an inhibitory effect (49). An inhibitory effect of lithium is consistent with preclinical observations of this drug in animal models. Recent findings from magnetic resonance imaging (MRI) studies also support the ability of lithium to regulate IMPase, but a temporal dislocation between lithium-induced *myo*-inositol depletion and clinical improvement was seen (50). It is possible that depletion of inositol levels may be an initiating event in lithium's mechanism of action, rather than an ongoing factor in its clinical effects.

Researchers have also examined the relative content of membrane phosphoinositides, with a particular emphasis on the major PLC substrate  $PIP_2$ , under various mood and treatment states. Brown and colleagues (51) were the first to show increased levels of  $PIP_2$  in the manic state of BD, a finding that was recently also observed in platelets of patients in the depressed phase (52). Since  $PIP_2$  is the precursor of  $IP_3$  and DAG, the authors suggested increased PI signaling as a possible outcome of their findings (51,52). There is a recent case report of a patient in whom  $PIP_2$  membrane levels increased in the course of cycling into mania and normalized with a return to euthymia subsequent to lithium treatment (53). Several subsequent studies reported a significant reduction specific to platelet  $PIP_2$  levels in lithium-treated euthymic patients with BD, compared with control subjects (54–56). Together, these studies strongly suggest that lithium may blunt PI signaling (54).

The G-protein  $G_q$  and  $G_{11}$  isoforms that mediate signal transduction along this pathway are related to the other subtypes of G-proteins that we discussed in previous sections (42,57,58). One post mortem brain study reported increased  $G_{\alpha_{q/11}}$  and PLC levels in the occipital cortex of subjects with BD (59). A second study observed decreased PI-coupled G-protein activation in the same region (60). The authors suggest an adaptive increase in  $G_{\alpha_{q/11}}$  expression as a result of deficient PI-signaling activity in BD. They also point out alternatively that long-term lithium treatment could have confounded the results (60). In peripheral blood cells, no significant differences in  $G_{\alpha_{q/11}}$  levels were found in unmedicated subjects with BD, although decreased levels were found in lithium-treated subjects, relative to control subjects (21). The importance of the PLC enzyme is further supported by the

recent findings of linkage to the gene for 1 member of the PKC family in patients with lithium-responsive BD (61,62). Taken together, the evidence suggests that G-protein-coupled PI signaling may be attenuated in patients with BD. This is in contrast to the preponderance of findings (reviewed above) of increased G-protein coupling to cAMP in this disorder. Thus, there may be a functional imbalance between these 2 pathways; it may be highly relevant to understanding the causes of BD, and it would not have been found without this shift in focus to the intracellular level.

PKC, an important intracellular enzyme in the PI pathway, has stimulated much interest in recent years. Friedman and coworkers demonstrated increased platelet-PKC activity in the manic state of subjects with BD (63,64). These findings were seen as further confirmation of impaired PI signaling in BD, because intracellular DAG levels activate PKC. In addition, increased serotonin-stimulated PKC activation was found by another group of researchers in platelets from patients in the manic state, which was decreased to levels observed in control patients following lithium treatment (63). On the other hand, PKC levels in platelets from euthymic lithium-treated patients with BD were no different from those of control subjects (55,56). The relevance of these clinical findings is further supported by consistent reports of lithium-mediated inhibition of PKC activity in animal studies (65–67). More recently, PKC levels and activity were measured in post mortem brain tissue from subjects with BD and found to be increased in the frontal cortex, compared with control subjects (68). Indeed, these findings may be very specific to the diagnosis of BD and not found in various other psychiatric disorders (63,64,69,70).

Elevated PKC activity in BD that may be blocked by lithium treatment may be a clinically relevant finding. Manji and coworkers have begun to study PKC inhibitors in the treatment of this disorder (10). They have published pilot studies of tamoxifen, a synthetic, nonsteroidal antiestrogen widely used to treat breast cancer. Recently, this drug has also been found to be a selective PKC inhibitor. Interestingly, preliminary findings from a small sample are so far promising and provide evidence that this medication has some antimanic qualities (71). These results await confirmation by large-scale, randomized double-blind placebo-controlled studies; however, they clearly illustrate the clinical importance of the signal transduction abnormalities that continue to be reported in patients with BD.

### Intracellular Calcium Signalling

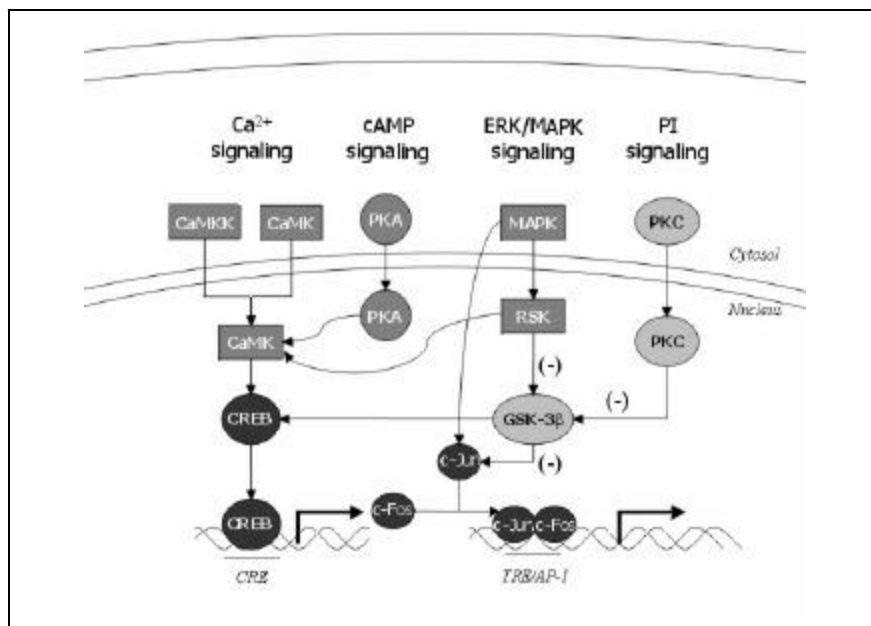
Although the importance of the calcium ion in synaptic transmission and neurotransmitter release is well established, it has become increasingly apparent that calcium has a critical role in mediating diverse intracellular events. These include synaptic plasticity, cell survival, and excitotoxic cell death

Table 4. Calcium signalling in Bipolar Disorder		
		Study
Erythrocytes	↓Na <sup>+</sup> /K <sup>+</sup> -ATPase activity in depressed patients	(114,115,116)
	↑Ca <sup>2+</sup> -ATPase activity in mania and depression	(111)
	↔Ca <sup>2+</sup> response: ↑Ca <sup>2+</sup> -ATPase levels in mania and depression	(112)
Neutrophils	↑fLMP-stimulated Ca <sup>2+</sup> responses in untreated mania and depression; ↓stimulated Ca <sup>2+</sup> responses in Li-treated patients	(157)
	↓fLMP-stimulated Ca <sup>2+</sup> responses in Li-treated patients	(158)
Leukocytes and platelets	↑Basal and stimulated Ca <sup>2+</sup> levels in mania and depression	(86–90)
	↑5-HT stimulated Ca <sup>2+</sup> response in mania and depression	(92)
	↑Basal Ca <sup>2+</sup> levels in Li-treated patients; ↑ thrombin-stimulated Ca <sup>2+</sup> response; ↑ stimulated Ca <sup>2+</sup> response in vitro with Li	(108)
	↑5-HT-stimulated Ca <sup>2+</sup> response in depressed patients	(98,104,105,106)
	↑PAF and thrombin stimulated Ca <sup>2+</sup> response in untreated BD	(102)
	↔Basal or stimulated Ca <sup>2+</sup> in Li-treated patients; ↑serum and 5-HT stimulated intracellular Ca <sup>2+</sup> levels	(95)
	↔Basal or stimulated Ca <sup>2+</sup> with chronic Li treatment or in vitro	(93)
	↑Basal Ca <sup>2+</sup> in euthymic patients	(96)
	↑5-HT stimulated Ca <sup>2+</sup> responses in manic patients	(107)
	↔Ca <sup>2+</sup> uptake in mania or depression; ↓Ca <sup>2+</sup> uptake following in vitro Li treatment	(94)
	↑basal Ca <sup>2+</sup> concentration; ↓percent change in phyto-hemagglutinin stimulated vs. basal Ca <sup>2+</sup> levels in BD type I BD	(109)
	↑Basal and stimulated Ca <sup>2+</sup> concentration; ↔between types, med state or severity	(91)
	↑Basal and NaF stimulated and ↓isoproterenol stimulated cAMP formation in BD subjects with high basal Ca <sup>2+</sup> levels:	(101)
↑5-HT-induced Ca <sup>2+</sup> response correlated with response to mood stabilizers treatment in a longitudinal study	(103)	
↔Basal or 5-HT induced Ca <sup>2+</sup>	(97)	

(72–75). Consequently, the mechanisms by which changes in intracellular calcium levels can lead to diverse, long-lasting biochemical alterations have been a target of directed investigation. Cells have 2 major sources of calcium—the extracellular milieu, and the ER (76). After stimulation, the calcium concentration in the cytosol rises rapidly, from approximately 100nM to values in the mM range (77). At high intracellular concentrations, however, Ca<sup>2+</sup> downregulates its signalling by inhibiting IP<sub>3</sub> receptor sensitivity (44) and stimulating the hydrolysis of IP<sub>3</sub> (78). Return of intracellular free calcium to resting levels terminates many of its cellular effects. This gradient is reestablished and maintained by the action of membrane-associated Ca<sup>2+</sup>-ATPases (Ca<sup>2+</sup> pumps), which drive Ca<sup>2+</sup> against a steep concentration gradient, either out of the cell or into intracellular stores (77), or through energy-dependent Na<sup>+</sup>/Ca<sup>2+</sup> exchange, which pumps Ca<sup>2+</sup> out of, and Na<sup>+</sup> into, the cytosol of the cell (79,80).

Inside the cytosol, Ca<sup>2+</sup> in turn acts with several regulatory proteins. Calmodulin, a small Ca<sup>2+</sup>-binding protein, acts as an intracellular Ca<sup>2+</sup> sensor and is critical in the regulation of diverse cellular events (81). After binding Ca<sup>2+</sup>, the Ca<sup>2+</sup>/calmodulin (CaM) complex regulates several other enzymes, including the CaM-dependent protein kinases (CaMKs) (81). CaMK I, IV, and certain CaMK II isoforms may be specifically involved in mediating transcriptional activation of gene expression in response to changes in Ca<sup>2+</sup> fluctuations in the cytosol (82,83).

The calcium-signalling system has increasingly been the focus of investigation in BD (see Table 4). Initial studies in calcium signalling by Carman and others uncovered a significant correlation between transient increases in serum Ca<sup>2+</sup> levels and the switch into mania (84). Direct measurements of intracellular free calcium have largely supported and extended these observations, with Dubovsky and colleagues (85–90) describing increased baseline Ca<sup>2+</sup> concentration in



**Figure 4.** Regulation of gene expression. Signal transduction systems transmit extracellular events to intracellular responses by modulating the activation state of key protein kinases. These protein kinases, which include CaMK, PKA, PKC, and elements of the MAPK cascade, in turn modulate the activity of transcription factors such as CREB and AP-1. Following activation, CREB binds to a CRE in various target genes. This in turn regulates the transcription of *c-fos*, which combines with *c-jun* to form the AP-1 class of transcription factors. AP-1 may then bind to its own consensus sequence, the TRE site. Both *c-jun* and CREB are both regulated by GSK3β.

platelets and leukocytes from unmedicated patients in both manic and depressed states. These Ca<sup>2+</sup> studies are intriguing, although not all investigators have been able to confirm these findings (91–97). Further, calcium communicates directly with the primary effector molecules of the PI-signaling pathway, and increased PI signaling might be expected to be accompanied by increased levels of intracellular calcium. Given that Ca<sup>2+</sup> is necessary for PKC activation, many of the previously described findings with respect to elevated PKC activity and translocation in patients with BD may be at least partly a consequence of increased affinity of certain PKC isozymes to Ca<sup>2+</sup> (64). Evidence also supports the notion that Ca<sup>2+</sup> channels may be coupled to Gα<sub>s</sub> in some tissues (98,99); this suggests that the findings of increased Gα<sub>s</sub> levels as associated with BD may result in increased cytosolic Ca<sup>2+</sup> concentrations—a notion supported by a recent study by Emamghoreishi and others (100). This is another example in which dysfunction at the level of 1 pathway may disrupt the intricate crosstalk between various signal transduction systems (100). This again illustrates how the shift in focus from neurotransmitters and receptors to the shared intracellular pathways that integrate receptor activity may be critical in explaining the causes of BD.

An alternative approach has been to stimulate Ca<sup>2+</sup> flux in peripheral cells from patients, using various drugs. Stimulating platelets from unmedicated patients in both the depressed and manic state with platelet-activating factor and thrombin significantly increased calcium response, compared with euthymic, treated subjects with BD, subjects with major depressive disorder (MDD), and control subjects (85,86–89,101). Likewise, activation of serotonin 5-HT<sub>2A</sub> receptors produced consistently elevated Ca<sup>2+</sup> response, both in patients with bipolar depression and in those with unipolar

depression, as reported in several studies by diverse laboratories (91,96,97,102–105). An other study of unmedicated patients with manic and euthymic BD further confirms the finding of increased 5-HT-stimulated Ca<sup>2+</sup> responses in mania (106). Not surprisingly, it has been suggested that elevated Ca<sup>2+</sup> responses may be a state-dependent variable that normalizes with remission of mood (85). Some findings, however, suggest that, since these abnormalities persist into euthymia, they may be trait-dependent (95,103,105,107,108). In the sole study to date on the downstream target of Ca<sup>2+</sup>, no differences were found in CaMK immunoreactivity in post-mortem cerebral cortex tissue of subjects with BD (109).

Further confirmation of calcium-signaling abnormalities in BD is provided by reports of increased activity of the Ca<sup>2+</sup>-ATPase pump in red blood cells from manic and depressed BD patients (110,111), as well as lithium-treated BD patients (112), compared with matched control subjects. Several studies have also described significantly lower Na<sup>+</sup>-K<sup>+</sup>-ATPase activity, which regulates Na<sup>+</sup>/Ca<sup>2+</sup> exchange, in red blood cells of patients in the depressed state (113–116).

### Regulation of Gene Expression

One important consequence of the activation of these diverse pathways is the production or activation of a family of proteins called transcription factors. These molecules bind to DNA and regulate the expression of a wide variety of genes. The complexity of this process and the numerous players involved continue to become evident with the extensive knowledge acquired in the human genome project (see Figure 4). One transcription factor that has been implicated and studied in BD is the cAMP-responsive element-binding protein (CREB) (117,118). CREB resides in the nucleus and spends

List of abbreviations and acronyms			
<b>AC</b>	adenyl cyclase	<b>GTP</b>	guanosine triphosphate
<b>ADP</b>	adenosine diphosphate	<b>IMPase</b>	inositol monophosphatase
<b>AP 1</b>	activator protein 1	<b>IP<sub>3</sub></b>	inositol 1,4,5-triphosphate
<b>ATP</b>	adenosine triphosphate	<b>Li</b>	lithium
<b>ATPase</b>	adenosine triphosphatase	<b>MAPK</b>	mitogen-activated protein kinase
<b>CaM</b>	Ca <sup>2+</sup> /calmodulin	<b>MDD</b>	major depressive disorder
<b>CaMKs</b>	CaM-dependent protein kinases	<b>MNLs</b>	mononuclear leukocytes
<b>CAMP</b>	cyclic adenosine monophosphate	<b>MRNA</b>	messenger ribonucleic acid
<b>CDNA</b>	complementary DNA	<b>P13-kinase</b>	phosphatidylinositol 3-kinase
<b>CRE</b>	cAMP-response element	<b>PAF</b>	platelet activating factor
<b>CREB</b>	cAMP-responsive element-binding protein	<b>PGE</b>	prostaglandin E
<b>DAG</b>	1,2-diacylglycerol	<b>PI</b>	phosphoinositide
<b>DD</b>	Differential display	<b>PIP<sub>2</sub></b>	phosphatidylinositol 4,5-bisphosphate
<b>ER</b>	endoplasmic reticulum	<b>PKA</b>	protein kinase A, cAMP-dependent protein kinase
<b>ERK</b>	extracellular signal-regulated kinase	<b>PKC</b>	protein kinase C
<b>FLMP</b>	bacterial peptide	<b>PLC</b>	phosphatidylinositol-specific phospholipase
<b>G-proteins</b>	guanine-nucleotide binding proteins	<b>PMA</b>	phorbol ester
<b>GDP</b>	guanosine diphosphate	<b>Rap 1</b>	rapamycin-associated protein 1
<b>Gpp(NH)p</b>	guanylylimidodiphosphate	<b>SAGE</b>	serial analysis of gene expression
<b>GSK3<math>\beta</math></b>	glycogen synthase kinase 3 $\beta$	<b>TRE</b>	12-O-tetradecanoylphorbol-13-acetate-response element

most of its time in an inactive form. Its activation occurs after phosphorylation at a particular amino acid (Ser-133) by a number of protein kinases, including those that are downstream targets of the signaling pathways discussed earlier in this article (PKA, MAPKs such as RSK1-3, and CaMKs) (119). Once phosphorylated the CREB protein, now called pCREB, binds to a specific site in the promoter region of target genes, known as the cAMP-response element (CRE). This leads to the production of messenger ribonucleic acid (mRNA), which is the blueprint for the synthesis of new proteins (120). This is a critical step: in many ways it is the final link coupling the rapid fluctuations in neurotransmitter levels and receptor binding to the production of new proteins that can permanently alter the function or structure of specific brain regions.

Many studies have examined the effects of pharmacotherapy on transcription factor activity in cell lines and animal models. Nibuya and others demonstrated that chronic antidepressant treatment increased rat hippocampal CREB protein and mRNA levels, as well as the binding of CREB to the CRE (121), a finding confirmed in postmortem brain samples from subjects with MDD (122). In this same clinical study, Dowlatshahi and others measured the levels of CREB in temporal and occipital cortices of subjects with BD, MDD, schizophrenia (SCZ), and control subjects (18). While they were unable to observe any significant association of CREB levels with BD, decreased levels were observed in subjects who died as a result of suicide and in those treated with anticonvulsants at the time of death. This later finding, which

is opposite to that observed with antidepressant treatment, supports studies in both rat brain and cultured cells (123–125). Further, it is consistent with the effects of lithium treatment on the signal transduction pathways (see above) and is reminiscent of the opposing clinical effects of antidepressants and anticonvulsants in depression and mania, respectively.

Recently another modulator of CREB, glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ), has been identified. GSK3 $\beta$  is a highly conserved serine-threonine protein kinase regulated by several signal transduction cascades (126–128). This protein plays a critical role in regulating long-term nuclear events. It can also phosphorylate CREB at a different site, which can further regulate or fine-tune the activity of this transcription factor (119). In addition, GSK3 $\beta$  regulates microtubules (129), neurofilaments (130), myelin-basic protein (131), nerve-growth factor (132), and tau (133) in brain tissue. Therefore, GSK3 $\beta$  further refines the complex patterns of gene expression in the CNS. There has been considerable interest in this kinase, since it is a major target of lithium and possibly other mood stabilizers, like valproate (134,135). Indeed, lithium has been shown to reduce neuronal death in cellular models, and one of the major factors involved appears to be GSK3 $\beta$  (136–139). Several studies have measured the levels of GSK3 $\beta$  in postmortem brain samples from subjects with BD and found no differences from control subjects (140,141). Interestingly, differences were observed in the level of phosphorylation of a protein (tau), which is a downstream target for this enzyme in patients with BD. This suggests that

functional differences in this signaling pathway could be associated with changes in gene expression.

Gene expression is critical to the maintenance of cellular viability and function and has also been strongly implicated in the neuronal changes thought to underlie BD. Recent studies have attempted to associate diagnosis or treatment with changes in gene expression by using various techniques with the ability to simultaneously analyze expression of thousands of genes at a time. These powerful new tools thus hold out the exciting prospect of screening large numbers of genes for differential regulation of factors that may be relevant to the underlying disease process or pharmacotherapy. Differential display (DD), serial analysis of gene expression (SAGE), and complementary DNA (cDNA) expression arrays are 3 such techniques that have produced promising results in both clinical and preclinical samples (142–146). These methods should be widely applied to clinical samples from patients with psychiatric disorders, because they have been extremely helpful in understanding the pathophysiology and treatment response in various conditions—most notably, cancer.

## Discussion

There is convincing evidence of signal transduction abnormalities associated with BD. The findings supporting cAMP-signaling abnormalities in BD are extensive, and suggest increased levels of stimulatory G-protein,  $G\alpha_s$ , at least in the manic state. These reports are supported by observed abnormalities further downstream—in elevated AC-mediated cAMP production and PKA activation. Studies of G-protein-coupled PLC activity have been less conclusive, although strong evidence of linkage to the gene for 1 type of PLC in BD suggests that the function of this enzyme should be more fully studied. In the PI pathway, a set of findings including increased  $PIP_2$  levels and PKC activity has generally implicated alterations in this signaling pathway. Increased  $Ca^{2+}$  responses in both peripheral blood cells and post mortem brain tissue of subjects with BD have been observed by several independent laboratories, broadly supporting the findings in PI signaling. Despite attempts to control for the use of medications, the possibility that treatment with antidepressants or mood stabilizers may be at least partly responsible for some of the observed changes can not be discounted (18). Further, extensive crosstalk between the cAMP- and the PI- and calcium-signaling pathways confounds the elucidation of clear loci of major effect in this pathway.

Given the complexity of intracellular communication, more recent studies have implicated the involvement of other signal transduction pathways in BD, including the ERK/MAPK cascade. The last few years have witnessed considerable interest in this pathway, in light of the recent focus on developmental and kindling models as etiologically relevant in mood

disorders research (147–151). The findings of altered Rap1b levels, a downstream target of the MAPK pathway, in platelets of patients with BD lends support to the relevance of this pathway in BD. In addition, recent studies suggest that mood stabilizer-mediated GSK3 $\beta$  regulation may correct pathophysiological dysfunction at other loci in patients with BD. However, further study is needed to fully understand the role of GSK3 $\beta$  and its pharmacotherapy in BD.

Although conclusive results have not yet been observed, compelling evidence from diverse independent research studies suggests that abnormalities in second-messenger systems play an important role in the pathophysiology of BD. Further confirmation of these findings awaits a more detailed examination of the end results of these abnormalities within the nucleus. In this regard, significant advances in molecular technology, such as DD, SAGE, and cDNA array hybridization, have enabled researchers to examine the changes in gene expression in various animal models and cell culture systems. Our lab has undertaken to extend these techniques to clinical samples, and we recently published a cDNA array study in post mortem brain samples of subjects with BD (142). These results, in combination with work in progress at many different research centres, promise to further our understanding of signal transduction abnormalities in the context of a complex, multifactorial disease such as BD.

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## 143. B in N **Résumé : La neurobiologie du trouble bipolaire : accent sur les voies de transduction de signal et le contrôle de l'expression génique**

**Objectif :** Cet article présente un aperçu des voies de transduction de signal et examine la recherche en entreprise pour étudier ces systèmes dans des échantillons cliniques significatifs de patients souffrant de trouble bipolaire (TB).

**Méthode :** Nous avons examiné les résultats publiés d'études du tissu cérébral d'autopsie et du sang prélevés chez des patients souffrant de TB.

**Résultats :** Bien que les anomalies biochimiques ex aucto de meurent en core à déterminer, les résultats présentés indiquent fortement que le TB puisse être attribuable, en partie du moins, aux anomalies des mécanismes de transduction de signal. En particulier, des niveaux altérés ou une fonction altérée, ou les deux, des sous-unités de la glycoprotéine et des molécules effectrices comme la protéine kinase A (PKA) et la protéine kinase C (PKC) ont régulierement été associés avec le TB tant dans les cellules périphériques que dans le tissu cérébral d'autopsie, tandis que des études plus récentes impliquent un dérèglement des cascades du nouveau second messager, comme la voie ERK/MAPK.

**Conclusions :** Malgré les difficultés inhérentes aux études biochimiques d'échantillons de tissu utiles sur le plan clinique, de nombreuses recherches ont fait la lumière sur les mécanismes de transduction de signal chez les patients souffrant de TB. Ces études indiquent également que le TB puisse être attribuable à l'interaction de nombreuses anomalies. Dans ce contexte, les nouvelles techniques permettent l'étude de l'expression génique promet d'aider à démêler ces interactions complexes, au moyen de la visualisation des résultats finaux de ces changements au niveau de la transcription génique.