

## Appendix A14.1

### Older Findings in Manic-Depressive Illness

To supplement the discussion of the neurobiology of bipolar disorder in Chapter 14, here we provide a summary of older but important biological findings in manic-depressive illness that have not been extensively pursued in recent years. These investigations include electrolytes (sodium, magnesium, and calcium), membrane transport studies including red blood cells/plasma lithium ratio, Na/K ATPase studies, and red blood cell cation transport.

#### **Electrolytes: Sodium, Magnesium, and Calcium**

Although some of the earliest biochemical investigations of bipolar disorder focused on electrolytes, very little work has been done in this area in the last 20 years. This might seem curious since, if one were to be guided by the pharmacological bridge strategy of studying parameters related to the action of drugs with wide and important ranges of effects, electrolytes should be of special interest in light of the action of lithium on various endogenous ions (Emrich et al., 1982). In the 1960s, the study of total body water and electrolyte balance in manic-depressive patients was revitalized by a growing appreciation for the importance of sodium, magnesium, calcium, and potassium in nerve cell excitation and synaptic transmission. Interest in electrolytes was further spurred by the discovery that lithium—a cation closely related in physical and chemical properties to the cations involved in nerve function—is an effective pharmacological agent for the treatment of bipolar disorder. The current focus on the possible role of neuropeptides in mood disorders adds another reason to explore this subject, since some of these peptides, such as vasopressin, have a direct regulatory influence on fluid and electrolyte physiology.

Early studies suggested that intracellular sodium may be higher than normal in both depression and mania, but the isotope-dilution methods employed were cumbersome and artifacts were difficult to control. Considering these methodological problems, initial efforts at assessing total-body electrolyte status were never thoroughly followed up, but they did provide important background information for later work on membrane ion transfer mechanisms. The three electrolytes reported to be abnormal in some respect during depressive and/or (hypo)manic episodes are sodium, magnesium, and calcium. Interestingly, abnormalities in potassium are not found as a function of bipolar disorder.

Although there were early reports of abnormalities in sodium concentration in plasma or cerebrospinal fluid (CSF), these findings have not been replicated (Jimerson et al., 1979; Bech et al., 1978). In contrast to direct measures of concentration, use of radioactive sodium permits the study of sodium transfer from plasma to CSF; an early application of this technique revealed decreased sodium transfer in depressed patients as compared with controls (Coppen, 1960). This finding was replicated by Baker (1971), who similarly showed the same deficit in a group of manic patients. Results of a subsequent study (Carroll, 1972) were consistent with decreased sodium transport in both depressed and manic patients. Another group (Glen et al., 1968) had noted decreased salivary sodium transport in manic-depressive patients.

Using red blood cell (RBC) concentrations as a possible index of intracellular sodium in all body compartments, some groups initially found abnormal concentrations in unipolar and bipolar depressed or manic patients. However, more recent studies failed to replicate this finding (Frazer et al., 1983). The other major factors involved in sodium concentrations are the membrane mechanisms responsible for sodium transport—a subject to which we return below.

Despite the meager data, it is still attractive to consider the possibility that bipolar illness may involve a generalized abnormality (perhaps with a genetic basis) that produces altered regulation of some major electrolyte that might be corrected or compensated for by lithium.

Magnesium is of more recent interest because of the positive finding from the large-scale NIMH Collaborative Study of Depression that plasma magnesium is elevated in both depressed and manic patients compared with controls (Frazer et al., 1983). However, the ionized fraction (considered to represent the physiologically active form) was not different among the groups. Moreover, CSF studies revealed no subgroup differences or differences from controls in magnesium concentrations (Jimerson et al., 1979; Mellerup and Rafaelsen, 1981). In the absence of any theoretical reason for incorporating abnormalities of magnesium, we are tempted to view the few findings that have emerged as not specific to the illness.

In contrast, data suggest a solid pharmacological bridge to the electrolyte calcium in mood disorders, an increase of which has been associated with depressive symptoms, while hypocalcemia is often accompanied by mood instability, irritability, and hyperactivity (Katzman and Pappius, 1973). For methodological reasons, direct studies of blood calcium are difficult to interpret. Measures of CSF calcium are less problematic, and beginning with a study more than 80 years ago (Weston and Howard, 1922), four of seven studies have found significantly higher while none have found lower concentrations in depressed patients versus controls. With regard to the unipolar/bipolar distinction, however, there is one study reporting no effect of electroconvulsive therapy (ECT) on CSF calcium. Finally, in a small group of unmedicated

bipolar patients, CSF calcium was higher in depression than in mania. Overall, the evidence supports the notion of increased CSF calcium in bipolar depression. Whether this finding can be related to the neurotransmitter alterations discussed in online Appendix A14.2 remains to be seen. Nonetheless, it suggests that systematic studies of drugs affecting calcium balance and/or transport, such as calcitonin and calcium channel blockers, may be of particular relevance for bipolar disorder. As we discuss in detail later, there is considerably more evidence for abnormalities in intracellular calcium in bipolar disorder.

### **Membrane Transport Studies**

#### *Red Blood Cell/Plasma Lithium Ratio*

Instead of focusing primarily on the absolute amount of a substance (e.g., electrolytes, as discussed above) in various compartments, some investigators have studied membrane transport functions more directly. Alterations of enzyme-dependent ion transfer systems in membranes could account for any abnormalities in concentrations. The major focus, however, has not been on transport of sodium or calcium, but on lithium. It was observed in patients that although lithium in RBC is usually about 50–60 percent of that in plasma—the RBC/plasma lithium ratio—there was wide variability in the ratio among individuals, which appeared to reflect both genetic and clinical response characteristics. The mechanisms underlying the ratio involve a sodium-lithium energy-dependent countertransport system; thus there is a correlation between the activity of the RBC countertransport system measured in vitro in cells taken from patients and the RBC lithium ratio observed in vivo when the patients are treated with lithium.

The usual methodological problems accompany actual studies of these parameters, especially with regard to patient selection and, importantly, the length of periods on and off lithium. When data from 13 studies comparing the in vivo lithium ratio in treated unipolar and bipolar patients are pooled, however, a significantly higher ratio is found in the bipolar patients (Goodwin and Jamison, 1990). Consistent with this observation, 3 of 5 studies showed decreased activity of the RBC sodium-lithium countertransport system in bipolar patients as compared with controls; decreased transport out would be expected to result in higher RBC levels of lithium in those with bipolar disorder. For a listing of studies on the RBC/plasma lithium ratio, including sample sizes and levels of significance, see Table A14-1.

Table A14.1  
RBC/Plasma Lithium Ratio in Bipolar Disorder (BPD) and Depression (UP)

Study	BPD $\pm$ SEM (N)	UP $\pm$ SEM (N)	Control $\pm$ SEM (N)	Significance
Elizur et al., 1972	0.3 $\pm$ 0.02 (16)	0.28 $\pm$ 0.03 (9)		NS
Mendels and Frazer, 1973 <sup>1</sup>	0.51 (9)	0.41 (4)		
Rybakowski et al., 1974	0.54 $\pm$ 0.02 (28)	0.55 $\pm$ 0.04 (11)		NS
Soucek et al., 1974	0.47 $\pm$ 0.02 (36)	0.45 $\pm$ 0.03 (12)		NS
Cazzullo et al., 1975	0.60 $\pm$ 0.04 (11)	0.44 $\pm$ 0.04 (12)		p <.01
Albrecht and Muller-Oerlinghausen, 1976	0.34 $\pm$ 0.02 (19)	0.33 $\pm$ 0.02 (9)		NS
Lyttkens et al., 1976	0.45 $\pm$ 0.03 (37)		0.37 $\pm$ 0.02 (16)	p <.05
von Knorring et al., 1976 <sup>2</sup>	0.56 (28)	0.50 (33)		
Ramsey et al., 1979 <sup>3</sup>	0.61 $\pm$ 0.04	0.38 $\pm$ 0.04		p <.001
Frazer et al., 1978	0.54 $\pm$ 0.04 (24)	0.41 $\pm$ 0.04 (12)		p <.05
Kim et al., 1978	0.51 $\pm$ 0.02 (64)	0.39 $\pm$ 0.05 (15)		p <.02
Mendlewicz et al., 1978	0.59 $\pm$ 0.07 (3)	0.62 $\pm$ 0.07 (3)		NS
Rybakowski et al., 1978	0.52 $\pm$ 0.02 (79)	0.47 $\pm$ 0.03 (34)	0.43 $\pm$ 0.01(49)	NS
Ramsey et al., 1979	0.52 $\pm$ 0.02 (49)	0.41 $\pm$ 0.03 (23)		p <.001
Szentistvanyi and Janka, 1979	0.50 $\pm$ 0.02 (52)	0.38 $\pm$ 0.02 (32)		p <.001
Mallinger et al., 1980 <sup>4</sup>	0.31 (5)	0.31 (8)		
Liebermann and Stokes, 1980 <sup>5</sup>	0.55 $\pm$ 0.21 (133)		0.35 $\pm$ 0.04 (6)	
Del Vecchio et al., 1981 <sup>6</sup>	0.38 (18)	0.36 (22)		NS
Ostrow and Davis, 1982 <sup>7</sup>	0.55	0.35 (5)	0.39 (6)	p <.001
Ryan et al., 1989 <sup>8</sup>	0.61 $\pm$ 0.18 (53)		0.57 $\pm$ 0.18 (42)	NS
Dafflon et al., 1999 <sup>9</sup>	1.59 (16)	1.78 (46)	1.68 (39)	NS

<sup>1</sup>Data reanalyzed. SD and significance not calculated.

<sup>2</sup>Data reanalyzed. Means of Recovered and Acute BPD and UP. Cycloid psychotic patients excluded. SD and significance not calculated.

<sup>3</sup>N (sample size) not mentioned.

<sup>4</sup>Data reanalyzed. Cycloid psychotic patients excluded. SD and significance not calculated.

<sup>5</sup>133 affective outpatients, heterogeneous diagnostic group. Significance not calculated.

<sup>6</sup>Data reanalyzed. Means of Responders and No Responders patients. Cycloid psychotic patients excluded.

<sup>7</sup>BPD group correspond to BPD-I patients. BPD-II RBC/Plasma Lithium Ratio 0.294. Significance referred to the mean of BPD-I group and the mean of the other subtype groups of patients (including 6 schizoaffective patients).

<sup>8</sup>Controls are nonbipolar patients.

<sup>9</sup>Means estimated from graph.

Table updated from Goodwin and Jamison, 1990.

Again, interpretation is confounded by the apparent long-term inhibitory effects of lithium treatment on the system. Taken together, however, the data still suggest that some bipolar patients may have an abnormality in the membrane processes responsible for the transport of sodium into and lithium out of the cell.

#### *Na/K ATPase Studies*

For over 50 years, it has been known that lithium undergoes active transport across cell membranes (Zerahn, 1955). Both membrane transport systems and ion channels play a role in the

regulation of intracellular lithium. Transport systems may be either ATP-driven, like Na/K ATPase, or driven by the net free energy of transmembrane concentration gradients, like the sodium-calcium exchanger. These transport systems are likely to be relevant to the regulation of lithium in the cell body, as they essentially regulate all steady-state intracellular ion concentrations. Numerous studies have characterized the membrane transport of lithium and its interaction with other cations in both the brain and peripheral tissues in an effort to address a potential mode of action of the drug in the treatment of bipolar disorder<sup>1</sup>.

Early evidence suggested that in excitable cells, lithium influx occurs primarily through the voltage-sensitive Na<sup>+</sup> channel.<sup>2</sup> Upon activation of the channel, lithium entry has been shown to occur, especially during the depolarization phase, wherein lithium rushes into the cells at the expense of Na<sup>+</sup>. This property of lithium may be reflected in the increase in plasma levels of lithium occurring as a patient becomes euthymic following treatment for an acute manic episode (Degkwitz et al., 1979). Additional evidence in neuroblastoma-glioma hybrid cells indicates that lithium may also use the ouabain-sensitive Na/K ATPase, but this was not observed in neurons in primary culture (Richelson 1977; Gorkin and Richelson, 1981). Extrusion of lithium from the cell appears to depend on the gradient-dependent Na<sup>+</sup>-Li<sup>+</sup> exchange process, wherein intracellular lithium substitutes for the intracellular Na<sup>+</sup> (Sarkadi et al., 1978; Hitzemann et al., 1989). However, although there is evidence that lithium enters the cell equally displacing Na<sup>+</sup> in excitable cells, it does have a tendency to accumulate in the cell, since its removal is less efficient than that of Na<sup>+</sup> (Coppen et al., 1967; El-Mallakh 1990). It is thought that Na K/ATPase may play an indirect role because it establishes the Na<sup>+</sup> gradient in neurons; the greater the Na<sup>+</sup> gradient, the greater is the rate of Na<sup>+</sup> efflux through the Na<sup>+</sup>-Li<sup>+</sup> exchange. Over the years, clinical studies of patients with bipolar disorder have provided evidence for an increase in Na<sup>+</sup> retention and intracellular Na<sup>+</sup>;<sup>3</sup> a decrease in Na/K ATPase activity;<sup>4</sup> and, more recently, an increase in intracellular calcium in peripheral blood cells in both mania and depression (Dubovsky et al., 1991, 1992b). Lithium treatment has been shown to result in a reduction of intraerythrocyte Na<sup>+</sup> (Hermoni et al., 1987; Hitzemann et al., 1989), and studies using Fura 2-AM fluorescence have revealed a lithium-induced reduction of Ca<sup>2+</sup> in platelets of bipolar patients (Dubovsky et al., 1991). Because free calcium ion concentration tends to parallel free sodium concentration, this observation may account for the lithium-induced reduction in free Ca<sup>2+</sup> ion concentrations noted previously (Mullins and Brinley, 1967; Torok, 1989).

It has been suggested that an alteration in the activity of the Na/K ATPase pump could result in significant changes in neuronal excitability and may represent a pathogenesis for mood disorders.<sup>5</sup> However, clinical studies in RBC over the years have reported conflicting data in

bipolar patients, with a reduction in Na/K ATPase activity noted predominantly in both unipolar and bipolar depression.<sup>6</sup> Multiple factors, such as psychotropic drugs, circulating hormones, and diet, have probably contributed to much of this variability (Swann, 1984, 1988; Wood et al., 1989).

Looney and el-Mallakh (1997) conducted a meta-analysis of the available literature on Na/K ATPase pump activity in bipolar disorder. They found a significant (but small to moderate) mood-state related decrease in Na/K ATPase activity in both manic and bipolar depressed patients compared with euthymic bipolar patients, but not when ill patients were compared with normal controls. In a subsequent study, Rose and colleagues (1998) determined Na/K ATPase alpha subunit expression in postmortem temporal cortex gray matter from individuals suffering from bipolar disorder, schizoaffective disorder, and schizophrenia, and matched normal controls. They found that bipolar individuals exhibited a significant reduction in abundance of the alpha 2 isoform of Na/K ATPase compared with normal controls. By contrast, schizophrenic and schizoaffective brains were not significantly different from those of normal controls.

Early studies in frog muscle found that lithium is a poor substrate for Na/K ATPase (Keynes and Swan, 1959). Studies in whole brain of animals revealed an acute inhibition of Na/K ATPase activity with lithium. There was evidence that chronic lithium treatment resulted in an inhibition of the Na/K ATPase enzyme in synaptosomal membrane fractions from brain, which appeared to be regionally specific to the hippocampus (Swann et al., 1980; Guerri et al., 1981). Furthermore, this inhibition represented a reduction in the  $V_{max}$  of the enzyme, with no apparent change in affinity ( $K_m$ ), and was selective for neurons having the enzyme subtype with high affinity for ouabain binding. Similar observations of lithium inhibition of Na/K ATPase have been made in peripheral neurons and have been attributed to an action of lithium competing for the intracellular  $Na^+$  activation site of the enzyme (Ritchie and Straub, 1980).

On the other hand, studies of erythrocyte membranes in lithium-treated patients have revealed increased activity of Na/K ATPase.<sup>7</sup> (See Table A14-2.) These data have been partially accounted for by a lithium-induced inhibition on Na/K ATPase activity mediated through intracellular interaction with the  $Na^+$  binding site, and concomitant activation, mediated through an extracellular K site (Lazarus and Muston, 1978). However, while flux of lithium through voltage-dependent sodium channels may contribute to the regulation of steady-state lithium homeostasis within the cell, it is likely that the gating of lithium via ion channels may be more physiologically relevant at the synapse. In the local environment of a dendritic spine, where the surface-to-volume ratio becomes relatively large, the lithium component of a synaptic current can

theoretically cause significant increases in local lithium concentration following a train of synaptic stimuli. This remains a fertile area for future investigation.

Table A14.2

Published Studies of Erythrocyte Na/K-ATPase Activity in Bipolar Patients

Study	Ni	Nc	Na/K-ATPase Activity	P
<b>Manic vs. Bipolar Recovered (1)</b>				
Naylor et al., 1976	22	15	Decreased	ns
Naylor et al., 1980	13	17	Decreased	<.015
Akagawa et al., 1980	11	4	Increased	<.01
Nurnberger et al., 1982	7	17	Decreased	ns
Hokin-Neaverson and Jefferson, 1989a,b	16	18	Decreased	<.05
Reddy et al., 1989, 1992	44	44	Decreased	.01 paired
<b>BPD Depressed vs. BPD Recovered</b>				
Naylor et al., 1976	8	3	Decreased	ns paired
Choi et al., 1977	5	5	Decreased	.028 paired
Naylor et al., 1980	19	17	Decreased	ns
Rybakowsky et al., 1981	8	8	Decreased	<.05 paired
Nurnberger et al., 1982	19	17	Decreased	<.01
Hokin-Neaverson and Jefferson, 1989a,b	14	18	No change	ns
<b>Manic vs. Normal Controls (1)</b>				
Naylor et al., 1976	22	15	No change	ns
Scott and Reading, 1978	8	10	No change	ns
Akagawa et al., 1980	11	15	Increased	<.01
Nurnberger et al., 1982	7	16	No change	ns
Hokin-Neaverson and Jefferson, 1989a,b	16	53	Decreased	<.001
Reddy et al., 1989, 1992	62	66	No change	ns
<b>BPD Depressed vs. Normal Controls</b>				
Hesketh et al., 1977	12	10	No change	ns
Choi et al., 1977	5	5	Decreased	.018
Rybakowsky et al., 1981	8	16	Decreased	<.05
Nurnberger et al., 1982	19	16	No change	ns
Hokin-Neaverson and Jefferson, 1989a,b	14	53	No change	ns
<b>BPD Recovered vs. Normal Controls (2)</b>				
Naylor et al., 1976	15	15	Increased	ns
Akagawa et al., 1980	4	15	No change	ns
Rybakowsky et al., 1981	8	16	No change	ns
Nurnberger et al., 1982	17	16	No change	ns
Thakar et al., 1985	54	28	No change	ns
Alexander et al., 1986	23	24	No change	ns
Hokin-Neaverson and Jefferson, 1989a,b	18	53	No change	ns

Note: Ni = sample size in ill group; Nc = sample size in comparison group; Ns = not significant.

Source: Modified and reproduced with permission from El Mallakh and Wyatt, 1995, who have done a review, and Looney and El-Mallakh, 1997, who have done a meta-analysis, including all the studies. The meta-analysis confirmed the reviewed findings, showing a significant mood-state-related decrease in Na,K-ATPase activity in both manic and bipolar depressed patients when compared to euthymic bipolar patients, but not when ill patients were compared to normal controls. The overall change can be characterized as small to moderate in magnitude. These results provide support for a mood-state-related decrease in erythrocyte membrane Na,K-ATPase activity (rather than a trait-related phenomenon) in both ill phases of bipolar illness, although the evidence is much stronger for depression than for mania. The decreased activity among bipolar patients occurs independently of the type of treatment.

### *Red Blood Cell Cation Transport*

RBC has served as a cell model for a series of clinical investigations over the years, as it shares lithium transport properties with neurons and is easily accessible (Bach and Gallicchio, 1990; Mota de Freitas et al., 1990). At therapeutic levels, influx of lithium into the RBC occurs predominantly through passage as a cation through the “leak,” or passive diffusion pathway. Additional routes of entry for lithium include an  $\text{Na}^+$  ( $\text{Li}^+$ )- $\text{K}^+$  cotransport pathway, as well as the anion exchange pathway, wherein lithium’s small size and high charge density permit its anionic transport in complex with bicarbonate. Efflux of lithium occurs primarily through the  $\text{Na}^+$ - $\text{Li}^+$  countertransport pathway, with additional routes through the passive “leak” pathway and (to a lesser extent) the Na/K ATPase pump. There is no evidence that lithium treatment alters the transport properties of either the “leak” or  $\text{Na}^+$  ( $\text{Li}^+$ )- $\text{K}^+$  cotransport pathways.

Although early studies suggested that the RBC/plasma lithium ratio was related to a history of bipolar disorder and that a higher ratio was associated with a clinical response to lithium treatment, it was soon evident that there was large variation among individuals, precluding adequate replication.<sup>8</sup> These investigations, however, led to the hypothesis that the pathogenesis of affective disorders is related to membrane dysfunction (Ehrlich and Diamond, 1980).

This work was followed by a series of studies using lithium transport properties in RBC as a genetic marker, and revealing a reduction in  $\text{Na}^+$ - $\text{Li}^+$  transport rates in a subgroup of bipolar patients and some family members.<sup>9</sup> Here again, variability of data both within and among patients contributed to the failure to replicate these findings in other studies.<sup>10</sup> These data were also confounded by the fact that lithium treatment results in a progressive inhibition of  $\text{Na}^+$ - $\text{Li}^+$  countertransport (Ehrlich et al., 1981, 1983), and a history of hypertension is associated with elevated rates of  $\text{Na}^+$ - $\text{Li}^+$  transport (Canessa et al., 1980, 1987). Investigators who recently studied 22 bipolar patients using the RBC apparent rate constant for lithium efflux ( $K_{\text{exch}}$ ) suggest this index may serve to predict risk for failure of maintenance therapy at 1 year (Mallinger et al., 1997).

Although these data are of considerable interest, we must be cautious about direct extrapolation from a nonnucleated peripheral cell model to one involving excitable nucleated neuronal cells within the brain. Moreover, recent data (e.g., on Na/K ATPase) support the evolution of specific gene products expressed and post-translationally regulated uniquely not only to neurons, but also among brain regions.<sup>11</sup> Thus while the erythrocyte may be used as a peripheral model for lithium transport, extrapolations to lithium homeostasis in the brain or to potential genetic markers for variations in ionic homeostatic processes in the brain underlying the

pathophysiology of a disease such as bipolar disorder remain highly speculative. On the other hand, a better understanding of activity-dependent mechanisms via ligand-gated ion channels for creating localized increases of intracellular lithium at sites of high synaptic activity may be critical for lithium's therapeutic specificity and ability to regulate synaptic function in the brain.

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<sup>1</sup> Bach and Gallicchio 1990; Mota de Freitas et al., 1990; Riddell et al., 1990

<sup>2</sup> Keynes and Swan, 1959; Carmiliet, 1964; El-Mallakh, 1990

<sup>3</sup> Coppen and Shaw, 1963; Coppen et al., 1966; Naylor et al., 1970, 1971

<sup>4</sup> Naylor et al., 1980; Naylor and Smith, 1981; Nurnberger et al., 1982; Hokin-Neaverson and Jefferson, 1989a, 1989b.

<sup>5</sup> Hokin-Neaverson et al., 1974; Naylor and Smith, 1981; El-Mallakh, 1983

<sup>6</sup> Glen and Reading, 1973; Hokin-Neaverson et al., 1974; Naylor et al., 1974b; Choi et al.,

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1977; Akagawa et al., 1980; Sengupta et al., 1980; Nurnberger et al., 1982; El-Mallakh, 1983; Dagher et al., 1984; Strzyzewski et al., 1984; Alexander et al., 1986; Hokin-Neaverson and Jefferson, 1989b; Reddy et al., 1989.

<sup>7</sup> Naylor et al., 1974a, 1980; Hokin-Neaverson et al., 1976; Dick et al., 1978; Johnson et al., 1980; Bunney and Garland-Bunney, 1987; Mallinger et al., 1987; Swann, 1988; Reddy et al., 1989; Wood et al., 1989.

<sup>8</sup> Mendels and Frazer, 1973; Ramsey et al., 1979; Szentistvanyi and Janka, 1979; Richelson et al., 1986

<sup>9</sup> Pandey et al., 1977, 1987; Frazer et al., 1978; Ostrow et al., 1978; Sarkadi et al., 1978; Ehrlich and Diamond, 1979, 1980; Ramsey et al., 1979; Szentistvanyi and Janka, 1979; Shaughnessy et al., 1985.

<sup>10</sup> Greil et al., 1977; Mallinger et al., 1983; Dagher et al., 1984; Egeland et al., 1984; Richelson et al., 1986.

<sup>11</sup> Grillo et al., 1994; Munzer et al., 1994; Sahin-Erdemli et al., 1995; Arystarkhoua and Sweadner, 1996; Lecuona et al., 1996; Malik et al., 1996.