

Appendix A14.3

The Switch Process in Bipolar Disorder

To supplement the discussion of the neurobiology of bipolar disorder in Chapter 14, here we provide additional information on the biological correlates of the switch process, focusing on the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes, the serotonergic, dopaminergic, and noradrenergic systems, and related neuropeptides.

It is our contention that, along with cyclicity, the switch process is one of the fundamental and defining characteristics of bipolar disorder. Thus a greater understanding of the molecular and cellular underpinnings of the switch process could greatly enhance understanding of the neurobiology of the disorder. Unfortunately, the immense practical difficulties inherent in studying medication-free bipolar patients longitudinally have greatly hampered investigators' ability to collect much-needed data concerning this critical facet of the illness. Nevertheless, important clues have been found, most notably with respect to the catecholaminergic systems and neurotrophic cascades.

The Role of Glucocorticoids

Since the early 1950s, the administration of hypothalamic-pituitary-adrenal (HPA) exogenous hormones has been reported to produce psychiatric symptomatology in some patients, particularly mood elevation after the administration of adrenocorticotrophic hormone (ACTH) and cortisone (Ritchie, 1956; Clark et al., 1953). A review of the literature until 1983 reports that the incidence of psychiatric symptoms in patients receiving corticoids was 5.7–27.6 percent (weighted averages) in uncontrolled studies, and 6.3–32 percent in controlled studies (Lewis and Smith, 1983). All of these cases were medically ill patients, and the onset of psychiatric symptoms occurred within 1 day to several weeks after initiation of treatment with glucocorticoids. Approximately 50 percent of these cases corresponded to mania/psychosis symptomatology (Lewis and Smith, 1983). These psychiatric symptoms were clearly induced in a dose-response fashion, as was established in the 1970s (Boton et al., 1972), with higher proportions of symptom induction seen in patients who received doses close to 80 mg/day.

Recent prospective studies have also shown that administration of glucocorticoids induces symptoms that are mainly manic/hypomanic in nature. In 50 patients with multiple sclerosis treated with glucocorticoids, 20 percent showed an elevation in mood, and one patient

developed full mania (Minden et al., 1988). In another group of 50 ophthalmologic patients who received methylprednisolone or fluocortolone (180 mg/day prednisone equivalent), 34 percent developed manic/hypomanic symptoms with no psychoses (Naber et al., 1996); these changes occurred during the first 3 days of treatment. Stronger evidence comes from studies in asthmatic patients who received prednisone 40 mg/day for 7–14 days in whom manic/hypomanic symptoms were reported as a group (Brown et al., 2002). A higher proportion of hypomania was found in a healthy volunteer study, in which 12 subjects received prednisone 80 mg/day for 5 days, and 66 percent developed mild hypomania (Wolkowitz et al., 1990).

Induction of hypomanic/manic symptoms has been further reported shortly after the use of glucocorticoids in medically ill patients: mania was observed after 3 days of beclomethasone inhaler in an asthmatic child (Turktas et al., 1997) and after 3 days in ophthalmologic patients (Naber et al., 1996); after 2 days of use of a budesonide inhaler by an asthmatic child (Lewis and Cochrane, 1983); and after 1 day of hydrocortisone plus fludrocortisone in a patient suffering from Addison's disease (Ur et al., 1992).

Patients suffering from bipolar disorder are particularly susceptible to developing hypomanic/manic symptoms. A recent study, in which clinical charts from patients referred for consultation to a psychiatric division were reviewed, found that in 9 bipolar patients who presented psychiatric symptoms secondary to the use of corticoids (prednisone, betamethasone, methylprednisolone), 77 percent rapidly developed manic/hypomanic syndromes (Wada et al., 2000). Bipolar patients using a beclomethasone inhaler (Goldstein and Preshkorn, 1989; Phelan, 1989), as well as those using the androgen hormone dehydroepiandrosterone (DHEA) (Vacheron-Trystram et al., 2002), have been found to develop mania. In addition, the single administration of triamcinolone in a celiac plexus block was found to produce manic episodes in two bipolar patients (Fishman et al., 1996).

This last case confirms evidence that susceptible patients—those suffering from bipolar disorder—can develop manic symptomatology after the administration of even a single dose of glucocorticoids and within a short period of time (Fishman et al., 1996). This relationship between administration of glucocorticoids and the switch process is more striking when one considers that the administration of prednisone 40–60 mg on alternate days (in an on/off fashion) was able to induce rapid-cycling symptomatology in three patients (Sharfstein et al., 1982). They developed manic symptoms on the days they received prednisone; the opposite occurred on the days they did not receive the drug, with patients relapsing into depression.

The Role of the HPA Axis

Several investigators have examined bipolar patients longitudinally and observed significant hypercortisolemia (and/or elevations of urinary cortisol metabolites) during the depressed but not manic state (Goodwin and Jamison, 1990). Both unipolar and bipolar depressed patients have higher urinary free cortisol levels than patients in the manic phase or healthy controls, although the urinary free cortisol levels in manic patients in this study were significantly lower than those in normal controls (Linkowski et al., 1994). Findings of other studies, however, indicate an increase in 24 hour serum cortisol in both depressed and manic phases (Linkowski et al., 1994; Cervantes et al., 2001). There are conflicting reports on cerebrospinal fluid (CSF) cortisol and corticotrophin-releasing hormone (CRF) levels in the depressed and manic phases of bipolar disorder. Gerner and Wilkins (1983) found that CSF cortisol values in manic patients were significantly lower than in any subgroups of depressed patients. Swann and colleagues (1992) found that in a group of drug-free manic subjects, CSF and urinary free cortisol excretion levels were elevated in manic and mixed phases compared with healthy subjects, but did not differ from those of depressed patients in any cortisol measures (Swann et al., 1992). CRF levels in CSF are elevated in some patients with depression; however, normal levels have been reported in euthymic bipolar subjects, as well as during mania (Berrettini et al., 1987; Banki et al., 1992).

The Role of the Thyroid Axis

The hypothalamic-pituitary-thyroid (HPT) axis, sleep, and wakefulness are intimately linked. While the normal circadian thyroid-stimulating hormone (TSH) peak is in the early morning hours and falls to a nadir during the day, sleep actually suppresses TSH levels. An increase in TSH and triiodothyronine (T_3) during sleep deprivation has been reliably documented.¹ Previous studies have also found a phase effect in that TSH and T_3 rise during sleep deprivation and return to normal or below normal immediately after the sleep deprivation ends (David et al., 2000). For unclear reasons, the normal nocturnal TSH surge is blunted in bipolar (Souetre et al., 1988) and in unipolar depression (Loosen et al., 1987). An increase in TSH has been seen over baseline after sleep deprivation in unipolar and bipolar responders.² In a study of serial sleep deprivation procedures, TSH and T_3 were found to rise post-procedure, with TSH falling to baseline after a night's sleep, while T_3 remained elevated (Kuhs et al., 1996). Parekh and colleagues (1998) report a robust correlation between the degrees of TSH changes and the antidepressant effects of sleep deprivation; however, those relationships are unknown during the switch process.

The Role of the Serotonergic System

The safety and tolerability of selective serotonin reuptake inhibitors (SSRIs) have made these drugs the standard first-line treatment for depression. However, studies have assessed the efficacy of SSRIs in bipolar depression and the risk of switching associated with their use. A recent study (Rousseva et al., 2003) assessed the response and switch rates in 44 patients with bipolar disorder treated with SSRIs for 6 weeks in an observational study. It was found that switches to hypomania or mania occurred in 24 percent of patients treated with SSRIs. There was no difference in the incidence of switches for fluvoxamine (33 percent), fluoxetine (25 percent), or paroxetine (20 percent).

Pathophysiological studies of the serotonin system in bipolar subjects have had variable findings. CSF 5-HIAA measures in bipolar patients have led to conflicting findings (for a thorough review of the CSF studies, see *Manic-Depressive Illness 2E*, Chapter 14).

Using a drug challenge paradigm, studies examining the sensitivity of the serotonergic system as measured by changes in plasmatic levels of prolactin and cortisol after administration of d-fenfluramine in manic patients have had contradictory results (Thakore et al., 1996; Yatham, 1996). More consistent results have been found after administration of sumatriptan (a 5-HT_{1D} agonist): no growth hormone (GH) response was induced in manic compared with depressed patients (Yatham et al., 1997), as well bipolar patients who also suffered migraine (Mahmood et al., 2002), revealing a subsensitivity of 5-HT function in these subgroups of patients.

The Role of the Dopaminergic System

In a placebo-controlled study of 25 healthy volunteers, the group receiving d-amphetamine 20 mg showed manic-like behavior, with the symptoms peaking 2.5 hr after the drug was administered (Jacobs and Silverstone, 1986). A similar effect was observed when a megadose of d-amphetamine, 1 mg/kg, was used in 10 healthy volunteers, with the peak of hypomanic/manic-like symptoms occurring after 1–1.5 hr; the effect lasted for 12 hr (Vollenweider et al., 1998). A third series of 25 healthy volunteers received a dose of 25 mg of d-amphetamine versus placebo. Hypomanic-like symptoms were observed 1 hr after the drug's administration (Asghar et al., 2003). In medically ill and depressed patients, a chart review demonstrated cases of hypomania 1 to 5 days after d-amphetamine was initiated at doses as low as 5–10 mg/day (Mesand et al., 1995).

With regard to bipolar disorder, 3 patients received a 2-day oral administration of d-amphetamine 30 mg versus l-amphetamine 30 mg versus placebo. Two of them (66 percent) developed hypomanic behavior exclusively 1.5–3 hr after d-amphetamine administration (Van Kammen and Murphy, 1975). Recently, a quantitative analysis of symptoms was performed

using the Young Mania Rating Scale (YMRS) in 13 bipolar patients receiving IV d-amphetamine 0.3 mg/kg compared with a group of healthy volunteers. Transient hypomania was found to occur in bipolar euthymic patients, with significantly higher YMRS scores: The scores were 14 ± 10 in bipolar patients versus 4.6 ± 7 in the group of healthy volunteers. The effects did not last longer than 24 hr.

Pharmacological evidence supports the notion that manipulation of the dopaminergic system is capable of modulating bipolar illness. Dopamine (DA) agonists appear to be effective antidepressants and are able to precipitate mania in some bipolar patients (Goodwin and Jamison, 1990; Manji and Potter, 1997). Most recently, investigators have used a catecholamine depletion strategy (employing the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine, or AMPT) in lithium-treated, euthymic bipolar patients (Anand et al., 1999). Intriguingly, they did not observe any mood-lowering effects of AMPT, but did observe a “rebound hypomania” in a significant percentage of the patients. Although preliminary, these results are compatible with a dysregulated signaling system wherein the compensatory adaptation to catecholamine depletion results in an “overshoot” due to impaired homeostatic mechanisms. Most recently, McTavish and colleagues (2001) found that a tyrosine-free mixture lowered both subjective and objective measures of the psychostimulant effects of methamphetamine, as well as manic scores. These preliminary findings suggest that tyrosine availability to the brain attenuates pathological increases in DA neurotransmission following methamphetamine administration and putatively in mania.

The Role of the Noradrenergic System and Related Neuropeptides

Despite methodological difficulties in assessing CNS noradrenergic functions in humans, extensive investigation supports the presence of noradrenergic system abnormalities in bipolar disorder.³ Postmortem studies have shown increased NE turnover in the cortical and thalamic areas of bipolar subjects (Young et al., 1994b; Vawter et al., 2000), whereas in vivo studies have found plasma levels of NE and its major metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), to be lower in bipolar than unipolar depressed patients, and higher in bipolar patients when manic than when depressed (Goodwin and Jamison, 1990; Manji and Potter, 1997). The same occurs with urinary MHPG levels, which are lower in bipolar depressed patients, while longitudinal studies show that MHPG excretion is higher in the manic than in the depressed state.⁴ Finally, in a consistent mode, CSF NE and MHPG are also reported to be higher in mania than in depression (Gerner et al., 1984); however, the effects of diverse antidepressants cannot be ruled out.

Other paradigms for NE receptor function tend to suggest the possibility of an altered sensitivity of α_2 - and β_2 -adrenergic receptors in mood disorders (Schatzberg and Schildkraut, 1995; Manji and Potter, 1997). Genetics studies have also been conducted, showing that polymorphic variation of enzymes involved in amine metabolism (i.e., tyrosine hydroxylase, catechol-O-methyltransferase) can confer different susceptibility to developing bipolar symptoms.⁵ Although promising, however, these findings need to be replicated, and subgroups of bipolar patients to whom these alterations may apply need to be identified.

The NIMH longitudinal study was one of the first to examine factors associated with switch to mania (Bunney et al., 1972a,b,c). The authors report on the switch process for 10 switches in 8 inpatient subjects—6 into mania and 4 into hypomania—over a period of 5 years, none of which were associated with medication. In these patients, 24 hr urine collection revealed a significant increase in urine NE and cyclic adenosine monophosphate (cAMP) on the switch day, which remained high for the period of mania. There was no significant change in epinephrine, DA, MHPG, or 5-HIAA prior to switching. Some subjects had an increase in urinary DA during the manic phase (Bunney et al., 1970).

In studies of depressed patients, an increase in plasma NE and in NE metabolites (Ebert and Ebmeier, 1996) has been found in responders to sleep deprivation therapy. Decreased MHPG levels have been found in CSF of sleep deprivation responders versus nonresponders (Post, et al., 1976; Gerner et al., 1979). It has been suggested that the increase in NE and its metabolites seen with sleep deprivation may be secondary to the higher levels of locomotor activity seen in responders (Szuba et al., 1991) and is irrelevant to the antidepressant effect of sleep deprivation. No conclusive data exist for comparing these measurements during sleep deprivation and the switch process. (For more information on sleep in affective disorders, see Chapter 16 of *Manic-Depressive Illness 2E*; see also online Appendix A16.)

The neuropeptides galanin and neuropeptide Y (NPY) are found in discrete neuronal systems, where they coexist with classic transmitters and that may exert trophic effects in the CNS. Galanin, a 29-amino acid peptide, can be synthesized in several ascending systems, including cholinergic forebrain neurons, serotonergic dorsal raphe neurons, and the noradrenergic locus coeruleus (LC) system. In the CNS, galanin alters the release of several neurotransmitters and has also been shown to increase the levels of GH, prolactin, and luteinizing hormone; to inhibit glucose-induced insulin release; and to affect gastrointestinal motility (Vrontakis, 2002). Lesioning studies of the anterior noradrenergic bundle comparably reduced cerebral cortical galanin and NE concentrations (Gabriel et al., 1995), whereas acute treatments with physostigmine (which inhibit cerebral acetylcholinesterase, or AchE) had no effect on galanin

concentrations. Weiss and colleagues (1998) suggest that galanin may have a role in depressive states. They hypothesize that increased activity of the LC neurons causes release of galanin in the ventral tegmentum. The galanin in turn inhibits the activity of dopaminergic cell bodies in this region whose axons project to forebrain, thereby resulting in two of the principal symptoms seen in bipolar depression—decreased motor activation and decreased appreciation of pleasurable stimuli (anhedonia).

NPY is a 36 amino-acid peptide neuropeptide that is widely distributed in the central⁶ and peripheral nervous systems. NPY is found in brain structures such as the amygdala, cortex, hippocampus, periaqueductal gray matter, and LC, where it is collocated with NE (Heilig and Widerlov, 1990). NPY has been shown to decrease NE release and increase postsynaptic noradrenergic signal transduction (Pernow et al., 1988; Rasmusson et al., 1998).

The Role of Antidepressant- or Sleep Deprivation-Induced Increases in the Expression of Brain-Derived Neurotrophic Factor (BDNF)

As discussed in Chapter 16 of *Manic-Depressive Illness 2E*, sleep deprivation is the only known therapeutic maneuver that appears to alter mood in a majority of both bipolar and unipolar patients in a matter of hours (see also online Appendix A16). Important for the present discussion, sleep deprivation is also capable of triggering switches into mania/hypomania. Thus study of the potential cellular mechanisms by which sleep deprivation may bring about these rapid behavioral changes in patients with mood disorders may be particularly informative.

Temporal Regulation of the Activity of the Locus Coeruleus

Biological rhythms regulate precisely the timing of discrete events, as well as their temporal sequence and duration, and thereby play important roles in controlling critical organismic functions ranging from cell cycle events to circadian rhythms. Such rhythms usually reflect a complex interaction between endogenous rhythmic and other (e.g., homeostatic, adaptive, pathological) mechanisms. The temporal dissociation between the firing of the LC noradrenergic neurons and the sensitivity of postsynaptic targets in the cortex may have considerable relevance for the antidepressant effects of sleep deprivation.

The LC comprises more than 70 percent of the forebrain noradrenergic innervations. It projects to cortical, subcortical, and limbic structures, including the hippocampus, hypothalamus, and amygdala, as well as the cerebellum, medulla, and spinal cord. Electrophysiological studies

have now confirmed that the LC produces a relatively constant tonic firing throughout all behavioral states except REM sleep, when there is an absence of noradrenergic discharge from LC. Importantly, it is during this period of noradrenergic quiescence that the target tissues may display their greatest sensitivity. This scenario suggests that activating the quiescent LC noradrenergic projections during the period of normal REM would result in an increase of NE interacting with a “primed, sensitized” postsynaptic milieu, thereby producing robust molecular and cellular changes. As discussed in the next section, this is precisely what recent gene expression studies have revealed.

Temporal Regulation of Noradrenergically-Mediated Gene Expression in Critical Neuronal Circuits

Although perhaps intuitively obvious, there is now incontrovertible evidence that the expression of selected critical genes varies dramatically during sleep and waking—which likely plays a major role in regulating various long-term neuroplastic events. A number of mRNA differential display, microarray, and biochemical studies have shown that short-term sleep deprivation is associated with an immediate increase in levels of pCREB (the active form of this transcription factor); increase in expression of BDNF; and increase in expression of BDNF’s receptor, TrkB. As discussed above, these are precisely the plasticity-related molecules whose expression is increased by chronic antidepressant treatment.

In an extension of these gene expression studies, Cirelli and Tononi (2000a) hypothesized that a key factor responsible for the induction of the plasticity genes was the level of activity of the neuromodulatory noradrenergic and serotonergic systems. Both of these systems project diffusely to most of the brain, where they regulate gene expression, and are quiescent only during REM sleep. To delineate the putative roles of the NE and 5-HT projections in regulating the expression of the aforementioned plasticity genes, a series of lesioning studies was undertaken. These studies showed that the expression of these molecules was regulated by the noradrenergic system and that lesions of the noradrenergic system, specifically of the LC, abolished the upregulation of their expression. By contrast, these investigators found that lesions of the serotonergic system had no effect on the level of expression of these genes.

Thus, it is quite plausible that sleep deprivation may bring about its rapid antidepressant effects by activating the LC noradrenergic system at a time when it would normally be quiescent (i.e., during periods of REM sleep at night). This may then allow the interaction of released NE with a primed, sensitized postsynaptic milieu in critical circuits, resulting in the rapid and robust

expression of plasticity genes such as CREB, BDNF, and TrkB, and consequently a rapid antidepressant response, as well as a switch into mania/hypomania.

There is thus a striking similarity between the effects of chronic antidepressants and short-term sleep deprivation on the BDNF signaling cascade. Do these effects play a role in the treatments' ability to induce switches in susceptible individuals? As discussed in Chapter 13 of *Manic-Depressive Illness 2E*, some studies have found excess transmission of the valine allele of amino acid 66 of BDNF in those with bipolar disorder. Interestingly, this is the form of BDNF that has been associated with enhanced stimulated release in vitro (Egan et al., 2003) and with younger age of onset of the disorder (Rybakowski et al., 2003). Thus while quite preliminary, the data raise the intriguing possibility that bipolar individuals with the val/val BDNF genotype may be at greater risk for antidepressant- or sleep deprivation-induced switches into mania. Studies are currently underway at NIMH to address this possibility.

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¹ Kasper et al., 1988; Baumgartner et al., 1990a,b; Parekh et al., 1998

² Kuhs et al., 1996; Parry et al., 1996; Parekh et al., 1998

³ Goodwin and Jamison, 1990; Schatzberg and Schildkraut, 1995; Manji and Potter, 1997

⁴ Goodwin and Jamison, 1990; Schatzberg and Schildkraut, 1995; Bowden et al., 1997a; Manji and Potter, 1997.

⁵ Kirov et al., 1998; Serretti et al., 1998; Rotondo et al., 2002

⁶ Hokfelt et al., 1983; Everitt et al., 1984; Chronwall et al., 2004; Gray and Morley, 1986.