

Appendix A14.2

Neurotransmitter-Related Enzymes

To supplement the discussion of the neurobiology of bipolar disorder in Chapter 14, here we provide a survey of investigations of neurotransmitter-related enzymes, including monoamine oxidase (MAO), catechol-O-methyltransferase (COMT), and dopamine- β -hydroxylase (DBH).

Three major enzymes acting on amines have been under investigation for their relationship to manic-depressive illness: monoamine oxidase (MAO), catechol-o-methyltransferase (COMT), and DA- β -hydroxylase (DBH). MAO oxidatively deaminates norepinephrine (NE), serotonin, dopamine (DA), and other monoamines, and is the principal degradational enzyme for these compounds. In neurons, MAO is located within the presynaptic terminal, and it is also found in glial mitochondria in the central nervous system (CNS). In this system, COMT is extraneuronal with respect to the presynaptic terminal—that is, it is located either on or in the postsynaptic membrane or associated gland elements. DBH is the final enzyme in the synthetic chain for NE, converting DA to NE. It is so highly localized in the storage vesicles of NE nerve terminals, both central and peripheral, that it has been used as a noradrenergic neuronal marker. When nerves in the peripheral CNS are stimulated, DBH is released along with NE (Smith and Winkler, 1972).

MAO and DBH are by far the most extensively studied enzymes in bipolar disorder. Both are relatively stable within a given individual but are widely variable across individuals (especially DBH). DBH is a soluble enzyme in plasma, and its level partially reflects the peripheral sympathetic tone. Family and twin studies indicate that the activity of both enzymes is highly heritable (for more information on these studies, see *Manic-Depressive Illness 2E*, Chapter 13). The very large genetically determined variation among individuals has complicated attempts to examine relationships between enzyme levels and illness groups.

In clinical studies, MAO is obtained from blood platelets, which have a number of important similarities to nerve endings (Murphy et al., 1982b). The two species of MAO (A and B) have different substrate specificities: MAO-A, the principal subtype in neurons, metabolizes NE, serotonin, and DA, while MAO-B metabolizes phenylethylamine and DA. Since platelet MAO is of the B type, some questions arise about the interpretation of changes in the platelet enzymes in bipolar disorder (Murphy et al., 1979).

Peripheral COMT is found in association with red blood cell (RBC) membranes and is under genetic control. The relationship between RBC and neuronal COMT is not clear.

Monoamine Oxidase

The numerous MAO studies in affective illness (reviewed by Murphy et al., 1982a) vary considerably not only in the clinical groups studied, but also in the assay methods employed. Most of the studies in bipolar depression, including those with the largest patient samples, have demonstrated significantly lower enzyme activity compared with controls, a pattern not reflected in the studies with unipolar patients. The lower activity seen in bipolar patients appears to be restricted to bipolar-I patients, since the four studies that identified bipolar-II patients did not show difference from controls. Longitudinal studies of bipolar patients indicate that platelet MAO is state-independent.

MAO-A is an important target of a number of antidepressant drugs that inhibit its activity. Based on this pharmacological action and other evidence, a number of researchers have reasoned that depression may have its biological basis in disruption of central MAO systems. A number of investigators have measured MAO activity in brains from suicide victims; no change in MAO-A activity was found in the frontal cortex of suicide victims compared to that of controls.¹ Ordway and colleagues (1999) also failed to find any differences in MAO-A distribution at any level of the locus coeruleus (LC) or raphe nuclei between subjects with major depression and psychiatrically normal controls.

A large number of studies have investigated the possible involvement of MAO-A gene variations in bipolar disorder and as possible determinants of lithium responsiveness, but data are inconclusive (for more information on genetics in bipolar disorder, see Chapter 13 of *Manic-Depressive Illness 2E*). Both acute and chronic lithium have been reported to increase or not to change the turnover of NE in some but not all regions of the brain (see the Chapter 14, *Manic-Depressive Illness 2E* discussion of the noradrenergic system). Although these results suggest that lithium may increase the activity of the MAO enzyme, subsequent data remain conflicting (discussed in Lenox and Manji, 1998).

Catechol-o-Methyltransferase

RBC COMT was initially reported to be significantly lower in a group of women with primary affective disorders than in controls (Cohn et al., 1970). In a later study by the same group, the enzyme was reported to differentiate bipolar and unipolar depressed patients (Dunner et al., 1977). However, several subsequent attempts to replicate these findings have failed to

produce a consensus (Fähndrich et al., 1980). Many factors might explain the discrepancies, including gender differences (Gershon and Jonas, 1975), assay differences, and genetic subgroups (Karege et al., 1987).

As with MAO-A, a large number of studies have investigated the possible involvement of COMT gene variations in bipolar disorder and as possible determinants of lithium responsiveness, but the data to date are inconclusive (for further discussion, see Chapter 13 of *Manic-Depressive Illness 2E*). Most recently, the Weinberger and Egan groups (Weinberger et al., 2001; Egan et al., 2001) have investigated COMT variants as mediators of the prefrontal cortical abnormalities (both neuropsychological and functional neuroimaging of prefrontal information processing) in schizophrenia. The investigators examined the relationship of a common functional polymorphism (Val(108/158) Met) in the COMT gene, which accounts for a four-fold variation in enzyme activity and DA catabolism, to both prefrontally mediated cognition and prefrontal cortical physiology. In 175 patients with schizophrenia, 219 unaffected siblings, and 55 controls, COMT genotype was found to be significantly related in allele dosage fashion to performance on the Wisconsin Card Sorting Test of executive cognition frequency of perseverative errors (Egan et al., 2001; Weinberger et al., 2001). Consistent with other evidence that DA enhances prefrontal neuronal function, the load of the low-activity Met allele was found to predict enhanced cognitive performance. Functional MRI confirmed that COMT genotype affects prefrontal physiology during working memory. Finally, family-based association studies have revealed excessive transmission to schizophrenic offspring of the allele (val) related to poorer prefrontal function (Egan et al., 2001; Weinberger et al., 2001). In view of the likely involvement of the dopaminergic system in bipolar disorder and the evidence for prefrontal cortical abnormalities, similar studies in bipolar disorder are clearly warranted (see Chapter 9 of *Manic-Depressive Illness 2E*).

Dopamine- β -Hydroxylase

As noted above, it is difficult to evaluate diagnostic group differences in plasma DBH levels because of very large variation among individuals. DBH differs from MAO and COMT in that its level in plasma is determined partly by a dynamic process—the rate of transmitter release from sympathetic nerve endings. Most studies of plasma DBH in depressive illness (few of which have applied the bipolar-unipolar distinction) have been negative or inconclusive. Relatively lower levels of plasma DBH in bipolar depressed patients compared with unipolar patients or controls would be consistent with the previously reviewed data on NE and its metabolite, which suggest a lower noradrenergic tone in bipolar depressed patients. Thus when

Strandman and colleagues (1978) studied 89 affectively ill patients, some in the depressed and others in the recovered phase, they noted that DBH levels were somewhat lower in bipolar than in unipolar patients, a difference that just achieved statistical significance. Several other studies have found DBH levels lower in bipolar depressed patients than in controls.² In a group of 25 bipolar patients, Puzynski and colleagues (1983) noted that the mean DBH level was 25 percent lower than in unipolar patients or controls, but the very large variance precluded statistical evaluations. Among these depressed patients, the lowest DBH level—nearly 50 percent lower than in the controls ($p < 0.05$)—was in the group with a family history of affective illness. Ikeda and colleagues (1982) report on a longitudinal study of four cycling manic-depressive patients in which DBH was consistently higher in the manic than in the depressive phase. However, the extent to which DBH (released from sympathetic nerves and adrenal medulla into plasma) can reflect noradrenergic tone is unknown based on a large genetically determined variation among individuals. Fewer studies have investigated the possible involvement of DBH gene variations in bipolar disorder and as possible determinants of lithium responsiveness; once again, the data obtained thus far are inconclusive (see Chapter 13 of *Manic-Depressive Illness 2E*).

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¹ Mann and Stanley, 1984; Sherif et al., 1991; Galva et al., 1995.

² Levitt et al., 1976; Rihmer et al., 1983; Kjellman et al., 1986