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The Neurobiology and Genetics of Suicide and Attempted Suicide:

A Focus on the Serotonergic System

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Numerous abnormalities have been found in the serotonergic system in suicide attempters and completers. There is considerable evidence that the serotonergic system is partly under genetic control and that as yet unknown genetic factors mediate the risk for suicidal behavior independently of the genetic factors responsible for the heritability of major psychiatric conditions associated with suicide. An argument is made that there is a relationship of genetic variants to intermediate phenotypes, such as impulsivity, psychomotor change, pathological aggression and biological abnormalities including specific gene products. A variety of biological indices have been generated by new approaches using postmortem tissue and in vivo imaging that will provide a rich substrate for further genetic studies. ***[Neuropsychopharmacology 24:467–477, 2001]*** *© 2001 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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Major depression and suicidal behavior are independently related to altered serotonergic function (Mann and Stanley 1986). See Table 1 for a summary (Malone and Mann 1993; Owens and Nemeroff 1994; Stoff and Mann 1997; Mann 1998). In major depression there are fewer platelet serotonin transporters (5-HTT), lower CSF 5-HIAA (Mendels et al. 1972; Sjöström and Roos 1972; Ashcroft et al. 1973a, 1973b; Post and Goodwin 1974; Bowers 1974; Goodwin and Post 1977; van Praag and de Haan 1979; Koslow et al. 1983; Åsberg et al. 1984; Gerner et al. 1984; Roy et al. 1985; Redmond et al. 1986), as well as a reduced growth hormone (GH) response to 5-hydroxytryptophan (5-HTP) (Upadhyaya et al. 1991) and a blunted prolactin (PRL) response to oral fenfluramine (Siever et al. 1984; Coccaro et al. 1989; O'Keane and Dinan 1991; Mann et al. 1992) and to intravenous L-tryptophan (Heninger et al. 1984; Cowen et al. 1990; Price et al. 1991; Upadhyaya et al. 1991). The antidepressant efficacy of selective serotonin reuptake inhibitors (SSRIs) suggests the abnormality in depression probably includes impaired serotonergic function, because selective enhancement of serotonergic activity is therapeutic (Åsberg et al. 1986a). Depletion of serotonin by parachlorophenylalanine (PCPA) (Shopsin et al. 1976) or by reduction of brain tryptophan (Delgado et al. 1990), quickly reverses the antidepressant effect of serotonergic medication in patients (Åsberg et al. 1986a), suggesting that sustained enhancement of serotonergic function is a necessary requirement to sustain this SSRI-mediated antidepressant effect. It seems that the abnormality in serotonergic function may be a biochemical trait, because a blunted prolactin response to fenfluramine and a vulnerability to depression in response to tryptophan depletion are present during the

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Table 1. Evidence for Independent Serotonergic Abnormalities in Association with Major Depression and Suicidal Acts

Presynaptic Indices	Major Depression	Suicide/Suicide Attempts
CSF 5-HIAA	↓	↓
Serotonin transporter		
Platelets	↓	NC
Brainstem	↓	↓[a]
	↓	↓
Prefrontal cortex	(Dorsal and ventral)	(Only ventral?)
Postsynaptic receptors		
5-HT_{2A}	↓	↑
Transmission		
Prolactin response to serotonin		
Fenfluramine	↓[a]	↓
Tryptophan	↓	—
Growth hormone		
5-HTP	↓	↓
Antidepressants		
	SSRIs effective	Lithium effective
	Reversal by 5-HT depletion[b]	—

Relapse induced long after remission by tryptophan depletion.
[a]Depressed suicides.
[b]Prolactin response to fenfluramine is blunted long after remission and off medication.

period of remission between episodes (Flory et al. 1998). An intermorbid biological abnormality or trait implies a genetic or developmental origin, although enduring illness or treatment effects cannot be ruled out.

Lower serotonergic activity is also independently associated with suicidal behavior. We have hypothesized that there is a serotonergic abnormality contributing to the diathesis or vulnerability for suicidal acts (Mann 1998). Lower levels of CSF 5-HIAA (Åsberg et al. 1986b) and a blunted prolactin response to fenfluramine (Mann et al. 1992) correlate with the presence and lethality of past suicide attempts in patients with major depression and can predict future suicide or suicide attempts (Roy et al. 1989; Träskman-Bendz et al. 1992; Nordström et al. 1994). The association between suicide attempts and low CSF 5-HIAA has also been reported in schizophrenia and personality disorders, indicating that this association is independent of diagnosis. Lower brainstem serotonin (5-HT) and/or 5-hydroxyindoleacetic acid (5-HIAA) levels, and alterations in binding kinetics of a number of serotonin receptor subtypes are reported postmortem in the brain of suicide victims compared with nonsuicides (see Arango and Mann 1992; Arango and Underwood 1997 for a review), including the 5-HTT (Stanley et al. 1982; Meyerson et al. 1982; Crow et al. 1984; Paul et al. 1984; Owen et al. 1986; Arató et al. 1987; Arora and Meltzer 1989; Lawrence et al. 1990a, 1990b; Arora and Meltzer 1991; Arató et al. 1991; Laruelle et al. 1993; Mann et al. 1996), and these findings seem to be independent of psychiatric diagnosis (Mann et al. 1989; Arango and Mann 1992). Changes in 5-HTT and 5-HT_{1A} binding in suicide victims are most pronounced in the ventral prefrontal cortex (Arango et al. 1995a), an area involved in behavioral inhibition. Impulsive, aggressive behaviors are more common in suicide attempters (Barratt 1965; Weissman et al. 1973; Mann 1995; Fulwiler et al. 1997), and also correlate with lower serotonergic activity, consistent with a common, underlying, disorder of inhibition or restraint. In rodents and primates, aggressiveness is increased after inhibition of serotonin synthesis or in association with lower serotonergic activity (Vergnes et al. 1986; Molina et al. 1987; Higley et al. 1992). Ventral PFC dysfunction, including impaired serotonergic input, may form part of the diathesis for both impulsive aggression and suicide (Mann 1995).

Independently transmitted genetic factors partly explain the risks for major depression (Gershon 1990) and for suicide (Roy 1993; Roy et al. 1995). Adoption and family studies indicate that suicidal acts have a genetic contribution in terms of cause or diathesis that is independent of the heritability of major psychiatric disorders (Schulsinger et al. 1979; Egeland and Sussex 1985; Roy 1986; Roy et al. 1991; Brent et al. 1996). The data from twin studies (Roy 1993) show a much higher concordance rate for monozygotic (MZ) than for dizygotic (DZ) twins (13.2% vs. 0.7%), strongly supportive of a genetic component in suicidal behavior. The rate of suicide in DZ twins, although lower than for MZ twins, is over threefold higher than the expected rate of 0.2%. Roy and colleagues (Roy et al. 1995) also found a higher rate of concordance for suicide attempts in MZ as compared to DZ twins surviving the co-twin's suicide. The rate of concordance for attempted suicide (38%) was higher than for completed suicide (13.2%), indicating attempted and completed suicide are both heritable components of the phenotype of suicidal behavior. The

largest published twin study (Statham et al. 1998) found a concordance rate for a serious suicide attempt in MZ twins (23.1%), to be over 17-fold greater than the risk compared to the total sample. The heritability for serious suicide attempts was 55%.

Identification of the responsible genes can involve a general survey of the entire human genome. An alternative approach is to identify such candidate genes as those related to the serotonergic system. Genetic factors affecting psychopathology, including suicide risk may operate through effects on serotonergic activity, because of the heritability of serotonin function (Higley et al. 1996) (see Ishikawa et al. 1989; Higley et al. 1992 for a review). Preliminary results are promising. Suicidal acts and serotonergic indices, such as CSF 5-HIAA and the prolactin response to fenfluramine, are associated with an intronic polymorphism (a genetic variant in a noncoding part of the gene) in the gene for tryptophan hydroxylase (Mann et al. 1997; Jönsson et al. 1997; Nielsen et al. 1998; Manuck et al. 1999), the rate limiting biosynthetic enzyme for serotonin. Other candidate genes, such as for the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{1B} serotonin receptors, and the serotonin transporter (5-HTT), are suggested by the specific serotonergic abnormalities observed in major depression and in individuals with a history of serious suicidal acts or suicide (see Malone and Mann 1993; Mann 1998 for review).

Substance abuse or alcoholism have been associated with high rates of suicide, suicide attempts, and aggression as well as with dysfunction of the central serotonergic system (Ballenger et al. 1979; Virkkunen et al. 1994). Genetic factors play a role in alcoholism (Schuckit et al. 1985) and major depression (Gershon et al. 1989) but their precise identity is unknown. Again the serotonergic system may play a role. It has been suggested that the risk for suicidal behavior, aggressive acts, alcoholism, and substance abuse have, in part, a common underlying genetic or biological predisposition mediated by serotonergic activity (Mann 1998). It should be noted that if a considerable amount of the variance in serotonergic activity is attributable to genetic factors (heritable paternal variance is 37% and heritable maternal variance is 22%; see (Higley et al. 1993). Thus, there remains considerable potential for such environmental factors as diet and early rearing experiences to influence serotonergic activity.

The 5-HT_{1B} GENE AND RECEPTOR IN SUICIDAL BEHAVIOR

Aggressive behavior and increased alcohol and cocaine intake have been reported in 5-HT_{1B} receptor gene knockout mice (Saudou et al. 1994; Crabbe et al. 1996; Ramboz et al. 1996; Rocha et al. 1998). In a more recent study (Crabbe et al. 1999), the increased alcoholism in the 5-HT_{1B} knockout could not be confirmed in different laboratories using standardized methods, either because the original finding was incorrect, attributable to genetic drift in the mice, or for other technical reasons. Nevertheless, this mouse model suggests that functional variants in the 5-HT_{1B} receptor gene may contribute to such human psychopathologies as suicide, aggression, major depression, alcoholism, or substance abuse. There are two human 5-HT_{1B} receptor subtypes: 5-HT_{1B} (5-$HT_{1D\beta}$) and 5-HT_{1D} (5-$HT_{1D\alpha}$) (Hamblin and Metcalf 1991; Levy et al. 1992; Weinshank et al. 1992; Demchyshyn et al. 1992). The 5-HT_{1D} and 5-HT_{1B} receptors inhibit transmitter release from nerve terminals (Hoyer and Middlemiss 1989; Martin and Humphrey 1994) and inhibit neuronal firing as somato-dendritic autoreceptors, respectively.

A common polymorphism at the human 5-HT_{1B} receptor locus (G861C) has been identified (Sidenberg et al. 1993; Lappalainen et al. 1995). An uncommon molecular variant with the substitution of a cysteine for a phenylalanine residue (F124C) has also been detected in the human 5-HT_{1B} receptor gene (Nöthen et al. 1994).

In genomic DNA samples from 178 unrelated subjects, two polymorphisms of the 5-HT_{1B} receptor gene were identified in our laboratory (Huang et al. 1999). One is at nucleotide 861 ((Lappalainen et al. 1995). The other we have identified as a new polymorphism at nucleotide 129 of the coding region. This polymorphism was in absolute linkage disequilibrium with the polymorphism at nucleotide 861, meaning they always occur together. Across our entire study population, we found similar allelic frequencies (83 and 17%) to those reported by Lappalainen (72 and 28%). These two polymorphic sites are silent and do not change primary amino acid structure composition of the receptor.

We found no association of suicide, major depression, alcoholism, or a history of pathological aggression, with 5-HT_{1B} genotypes or allelic frequency for the two polymorphisms in a post-mortem study of 5-HT_{1B} binding (Huang et al. 1999). However, our study population was small and could have missed an uncommon association. Lappalainen and colleagues (Lappalainen et al. 1998) reported an association of alcoholism with the G861C locus. Alcoholics had a higher 861C allele frequency. In a separate group of Southwestern Native Americans, a condition described as antisocial alcoholism (implies a combination of aggressive traits and alcoholism) was also linked to G861C (Lappalainen et al. 1998). Our post-mortem sample included only 64 alcoholics, and we have now conducted further study of this possible association in a larger sample in vivo and found evidence of an association of alcoholism to the 861C allele.

We also found no difference in 5-HT_{1B} binding parameters in our post-mortem study between suicide, major depression, or individuals with pathological ag-

gression and nonsuicides. Arranz and colleagues (Arranz et al. 1994) also found no difference in B_{max} and K_D between the suicide and nonsuicide groups for the 5-HT_{1B} receptor in post-mortem frontal cortex samples. However, they found a significant decrease in the number of 5-HT_{1B} binding sites and in the K_D in nondepressed suicides. We found the presence or absence of major depression made no difference to the results. Lowther and colleagues (Lowther et al. 1997) reported that there were significantly more 5-HT_{1B} receptor binding sites in globus pallidus but not in the frontal or parietal cortices from the antidepressant-free suicides who died by violent means. Thus, further study of the globus pallidus of suicides would be of interest. The absence of altered binding in prefrontal cortex in their study is in agreement with our results.

The 5-HT_{1B} receptor seems to play a role in the modulation of aggressive behavior and alcohol or cocaine consumption in animal models (Saudou et al. 1994). We found no group differences in 5-HT_{1B} binding kinetics in association with alcoholism or pathological aggression. However, we did find a decrease in 5-HT_{1B} binding in the alcoholic group when using a matched pairs design (Arango et al. 1995b). Further such studies are needed in larger samples of pathologically aggressive patients as well as alcoholics.

THE TRYPTOPHAN HYDROXYLASE GENE

There are now seven positive candidate gene studies showing an association between a polymorphism of the tryptophan hydroxylase (TPH) gene and suicidal behavior and one positive linkage study. Linkage studies require knowledge of the relationship between subjects and usually involve members of the same family, such as an extended pedigree or pairs of siblings or parents and children. Because association studies involve unrelated larger populations, the results are often less reliable and subject to more confounds, such as differences in the frequency of the polymorphism in different populations, independent of disease. The associations with suicidal behavior are in opposite directions for impulsive criminal alcoholic attempters as compared to depressed attempters. Nielsen and colleagues (Nielsen et al. 1994) first reported an association between a polymorphism in the tryptophan hydroxylase (TPH) gene in intron 7, A779C, and suicidal behavior. Among a sample of 56 impulsive, alcoholic offenders, the L allele (equivalent to the C allele) was associated with lower CSF 5-HIAA and a higher rate of attempted suicide (0.68 vs. 0.46, $p < .02$). These results were replicated and extended by Nielsen and colleagues (Nielsen et al. 1998), in a sample of 804 Finnish alcoholic offenders, controls, and their relatives. In an association study, the L allele was shown to be more common in the impulsive offenders who attempted suicide (LL 72%, UL, 59%, and UU 31%). This finding was even more striking if restricted to serious suicide attempts. In the nonimpulsive group, a significant association between suicidal behavior and TPH alleles was weaker, similar to that reported below by Mann and colleagues (Mann et al. 1997).

We (Mann et al. 1997) examined the prevalence of the same polymorphism in 29 depressed attempters and 22 depressed nonattempters. The rarer U allele was found in higher frequency (41 vs. 20%) in attempters, compared to nonattempters with major depression, and a dose response relationship between odds of suicide attempt and the U allele was found. Buresi and colleagues (Buresi et al. 1997) compared the prevalence of the A218C TPH polymorphism in 236 suicide attempters and 161 controls. The A218C polymorphism is in tight disequilibrium with the above noted A779C polymorphism, meaning they usually coexist in the same subject. The rarer A allele was more common among the suicide attempters (46.4 vs. 35.7%, $p = .003$). The frequency of the A allele was even greater in those with serious ("violent") suicide attempts. These results were recently replicated in a Swedish sample (44.5 vs. 37% in controls) (Persson 1999), and are similar to those reported by Mann and colleagues (Mann et al. 1997).

Abbar and colleagues (Abbar et al. 1995) failed to find an association between an unspecified polymorphism of the TPH gene and suicide attempt. It is unclear if this polymorphism is in linkage disequilibrium with the above noted A218C and A779C polymorphisms. However, more recently, this group also found an association between the A218C TPH polymorphism and suicide attempt in a clinical sample.

The U allele of the A218C polymorphism of the TPH gene is associated with aggressive behavior in community volunteers and to a blunted prolactin response to the serotonin-releasing agent fenfluramine (Manuck et al. 1999). The U allele is also associated with low CSF 5-HIAA (Jönsson et al. 1997). Thus, two different indices of serotonergic function indicate lower activity to be associated with the U allele, the same allele associated with suicidal behavior in most studies. Lower serotonergic function could be a consequence of lower tryptophan hydroxylase activity resulting in less serotonin being synthesized. The intronic polymorphism may affect transcription rates or may be in linkage disequilibrium with another polymorphism of functional importance in the gene or its promoter region that, in turn, results in altered or reduced enzyme activity.

SEROTONIN TRANSPORTER GENE

Fewer platelet serotonin transporter sites and reduced platelet serotonin uptake have been reported in major

depression (Malone and Mann 1993; Owens and Nemeroff 1994). Functional imaging and post-mortem brain studies conducted in depressed patients suggest that there may also be less 5-HTT binding in the brain (Perry et al. 1983; Arango et al. 1995a; Malison et al. 1998). Platelet 5-HTT binding seems to be unrelated to levels of brain 5-HTT binding (Owens and Nemeroff 1994; Malison et al. 1998). Thus, direct studies of the brain are necessary to determine the state of 5-HTT binding in major depression.

The serotonin transporter (5-HTT) binding site is found on serotonin nerve terminals and platelets (Langer et al. 1980; Laruelle et al. 1988), and as such it is regarded as an index of serotonin nerve terminal number or integrity (Paul et al. 1984; Laruelle et al. 1988; Arango and Mann 1992; Soucy et al. 1994). The human 5-HTT gene is located on chromosome 17q11.1-q12. A 44 base pair deletion/insertion polymorphism (5-HTTLPR) is present in the 5′ flanking regulatory region that results in differential expression of 5-HTT and V_{max} for serotonin reuptake in transformed lymphoblastoid cell lines (Lesch et al. 1996). In these cell lines (Lesch et al. 1996), the short form of the 5-HTTLPR locus is associated with 40% fewer binding sites in the homozygote (SS) and the heterozygote (SL), compared with the long form (LL). Therefore, the presence of fewer 5-HTT sites on the platelets of depressed patients, and fewer 5-HTT sites in the prefrontal cortex of suicide victims, may be attributable to an association of the short form of the 5-HTTLPR locus with major depression or suicide.

However, it seems there is no association of the 5-HTTLPR genotype with a mood disorder. There are 14 studies examining linkage or association between the 5-HTTLPR locus and mood disorders in a variety of unipolar and bipolar samples from several ethnic groups. Only 4/14 studies are positive, and one of the positive studies (Du et al. 1999) found an association between depressed suicides and the long form of the 5-HTTLPR polymorphism, which is the opposite of the hypothesized relationship. Aggression, impulsivity, alcoholism, and substance abuse all carry an elevated risk of suicide and are also associated with serotonergic abnormalities (Whitaker-Azmitia and Peroutka 1990; Mann et al. 1999). Unfortunately, the 5-HTTLPR genotype is not clearly associated with alcoholism (Gelernter et al. 1997; Sander et al. 1997; Schuckit et al. 1999), or impulsive traits (Lesch et al. 1996; Ball et al. 1997; Ebstein et al. 1997).

We have replicated our previous report of lower 5-HTT binding localized to the ventral prefrontal cortex of suicide victims (Arango et al. 1995a). Most, but not all, studies of the serotonin transporter binding site in the brain of suicide victims (Stanley et al. 1982; Crow et al. 1984; Paul et al. 1984; Arató et al. 1987; Lawrence et al. 1990a, 1990b; Arató et al. 1991; Hrdina et al. 1993; Laruelle et al. 1993; Arango et al. 1995a; Mann et al. 1996; Du et al. 1999) report a reduction in 5-HTT binding, although one found an increase (Meyerson et al. 1982) and four found no change in the prefrontal cortex (Owen et al. 1986; Gross-Isseroff et al. 1989; Arora and Meltzer 1989, 1991). One of the latter studies (Gross-Isseroff et al. 1989) found increases and decreases in binding in an autoradiographic study of a variety of brain regions. The regionally restricted reduction in 5-HTT binding in suicide may partly explain the inconsistencies in the literature, because negative findings regarding 5-HTT binding and suicide may be a consequence of looking at the "wrong" brain region.

A limitation of most previous studies is the lack of information as to which cases of suicide or nonsuicides had a history of major depression. If there is a more widespread reduction in 5-HTT binding in major depression, that would mean that the choice of brain region would be less critical in studies that included a preponderance of cases with major depression. Of course, studies that included suicide victims who also had major depression could not distinguish effects of the two disorders separately.

Alterations in 5-HTT binding specifically related to suicide risk, seem to be concentrated in the ventral prefrontal cortex (PFC) (Arango et al. 1995a). This area plays a role in mediating inhibition or restraint. Acquired injuries of the ventral PFC are associated with disinhibition and an increase in impulsive behaviors including aggression and suicide attempts (Damasio et al. 1994; Shallice and Burgess 1996). Hence, we hypothesized that reduced serotonergic input into ventral prefrontal cortex, or lesions of the ventral prefrontal cortex, may underlie an impairment of behavioral inhibition or restraint, and an increased propensity for suicidal acts in patients who feel depressed or hopeless.

Increased corticosteroid secretion is associated with more severe depression (Sachar et al. 1970; Carroll et al. 1976; Brown et al. 1987), but preliminary animal studies do not suggest an effect on 5-HTT gene expression or binding (Kuroda et al. 1994). Thus, the cause of less 5-HTT binding in major depression remains unknown. There is less binding of ^{123}I-beta-CIT in the midbrain of depressed patients using SPECT imaging (Malison et al. 1998). Studies of platelet serotonin transporter binding generally report fewer 5-HTT sites (Owens and Nemeroff 1994), suggesting a systemic reduction in 5-HTT sites in major depression. If so, that would also be consistent with a yet to be identified genetic cause or a systemic effect on gene expression.

5-HT_{2A} RECEPTOR AND GENE IN SUICIDAL BEHAVIOR

Many, but not all, studies have found an increase in prefrontal cortical 5-HT_{2A} receptor binding in the brain of suicide victims (see Arango et al. 1997 for a review).

Moreover, platelet 5-HT_{2A} receptor binding also seems to be increased in suicidal patients (Pandey 1997). This possible systemic effect raises the possibility of a genetic mechanism. A polymorphism has been reported at position 102 (102 T/C) in the 5-HT_{2A} receptor gene (Zhang et al. 1997). Although 4/17 studies found an association of the CC genotype or the C allele with schizophrenia, there are few studies involving mood disorders (two negative results in bipolar disorder, one report of an association of the C allele with major depression (Du et al. 2000), and one report of an association of the T allele with unipolar depression). Zhang and colleagues (Zhang et al. 1997) found a weak association of the TT genotype with suicide attempts in patients with mood disorders. Turecki and colleagues (Turecki et al. 1999), in a subsequent study of suicide victims, found no association with the same allele. Moreover, they also reported greater 5-HT_{2A} binding in the PFC of suicide victims and that the T allele was associated with higher 5-HT_{2A} binding. The increase in 5-HT_{2A} binding in the suicide victims seemed to be independent of this locus. Inconsistent with these two studies, Du and colleagues (Du et al. 2000) reported more suicidal ideation in association with the CC genotype. More work in this area would be of interest. Because there seem to be more 5-HT_{2A} receptors in suicide, functional polymorphisms involving the promoter region that affect gene expression may explain this finding. There are also suggestions that signal transduction via the 5-HT_{2A} receptor may be impaired in suicide attempters (Mann et al. 1992) and perhaps these protein variants are attributable to alternative splicing or in the case of the related 5-HT_{2C} receptor, RNA editing, alter coupling efficiency to second messenger transducers.

5-HT_{1A} RECEPTOR AND GENE

Although membrane binding studies have generated conflicting results, autoradiographic studies of 5-HT_{1A} binding in suicide victims reported increased binding (see Arango et al. 1997 for a review). Moreover, one group reports that, as with the reduction in 5-HTT binding, the increase in 5-HT_{1A} binding is localized to the orbital PFC. Both increased and decreased binding have been reported to the 5-HT_{1A} autoreceptor in the raphe nucleus of suicide victims (Kassir et al. 1998; Stockmeier et al. 1998). A role for the 5-HT_{1A} receptor in anxiety is suggested by inferences of increased anxiety in the 5-HT_{1A} knockout mouse model (Ramboz et al. 1998) and the anxiolytic effect of 5-HT_{1A} agonists.

A common polymorphism (C-1018G) has been reported in the human 5-HT_{1A} gene (Wu and Comings 1999). Nakhai and Nielsen (Nakhai et al. 1995) reported two amino acid substitutions in the 5-HT_{1A} receptor (glycine22serine; isoleucine 28valine). Xie and Deng (Xie et al. 1995) report an amino acid substitution and insertion at positions 454–459 but no association with mood disorders. Studies of these polymorphisms in suicide, mood disorders, and anxiety disorders are awaited. What we seek are relevant functional polymorphisms that alter gene expression, receptor affinity, or receptor coupling to second messenger components.

MONOAMINE OXIDASE A GENE

Monoamine oxidase (MAO) A preferentially deaminates norepinephrine and serotonin. Deletion of the x-chromosomal MAOA gene in mice results in a more aggressive phenotype (Cases et al. 1995). A chain termination mutation in the eighth axon in a Dutch kindred (Brunner et al. 1993a, 1993b) is linked to mental retardation and pathological aggression, including arson, in males only. A variable repeat (VNTR) is found in the 5′ flanking promoter region and results in differences in gene expression in vitro ((Sabol et al. 1998). Alleles 1 and 4 showed less transcriptional activity than alleles 2 and 3 in MAOA promoter constructs (Sabol et al. 1998). We have found that in comparison to the 2/3 allele group (males), the 1/4 allele group in males was less aggressive and impulsive and had greater serotonergic activity as measured by the prolactin response to fenfluramine ((Manuck et al. in press). A dinucleotide repeat in intron 2 (MAOA-CA_n), in linkage disequilibrium with the uVNTR MAOA polymorphism, was not associated with behavior or serotonergic function (Manuck et al. in press). Further study of the relationship between possible less MAOA gene expression and serotonergic activity in humans is needed. The absence of MAOA and increased aggression is understandable as a consequence of more norepinephrine or potential developmental abnormalities and not attributable to more serotonin.

CONCLUSIONS

Many significant abnormalities have been found in the serotonergic system in suicide attempters and completers. Studies of candidate genes are in an early phase, but promising results are emerging that suggest that genetic factors influencing suicide risk may operate, at least in part, through the serotonergic system. Future approaches should examine the relationship of genetic variants to intermediate phenotypes such as impulsivity, psychomotor change, components of altered sleep architecture, substance abuse, pathological aggression, and biological abnormalities, including specific gene products. Terwilliger has advocated this approach, because the relationship of intermediate phenotypes to causal or vulnerability genes is closer and easier to

demonstrate than to complex syndromes or diseases (Terwilliger and Göring 2000). Post-mortem studies can examine gene expression as well as protein products. In vivo studies can quantify receptors and transmitter turnover or synthesis. These neurobiological indices offer a growing array of intermediate phenotypes.

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