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Serotonergic dysfunction: Brain imaging and behavioral correlates

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Identification of gene–environment and gene–gene interactions has become increasingly important in understanding psychiatric disorders. Dysfunction of central serotonergic neurotransmission has been implicated in alcoholism, depression, and anxiety. We review the literature on nonhuman primates that assesses the interaction between the genetic constitution of the regulatory region of the serotonin transporter (5-HTT) and environmental factors. Prospective studies in nonhuman primates that underwent social stress found a reduction of the serotonin turnover rate among carriers of one or two short alleles in a functional polymorphism of the 5-HTT promoter. In these primates, brain imaging studies showed a relative increase in the availability of raphe serotonin transporters. A low serotonin turnover rate and a high availability of serotonin transporters were associated with reduced response to excessive alcohol intake, anxiety, and impulsive aggression. Animal experiments point to a relationship between serotonergic dysfunction, negative mood states, and excessive alcohol intake, which may in part be mediated by reduced alcohol-induced sedation.

Serotonergic pathways arise from the brain-stem raphe nuclei and innervate a multitude of brain areas, which may explain the variety of psychiatric disorders in which dysfunction of serotonergic neurotransmission has been implicated (Baumgarten & Grozdanovic, 1997; Cloninger, 1987; Grove, Coplan, & Hollander, 1997; Meltzer, Maes, & Elkis, 1994; Owens & Nemeroff, 1994). Once serotonin is released into the synaptic cleft, its reuptake is regulated by the availability and function of serotonin transporters. A functional polymorphism in the regulatory region of the serotonin transporter (5-HTT) gene has been associated with a twofold difference in serotonin reuptake rates and the risk to develop negative mood states (Caspi et al., 2003; Lesch et al., 1996). Besides negative mood states such as anxiety and depression (Artigas, 1995; L. C. Barr et al., 1994; Mann et al., 1996; Praag, 1977; Träskman-Bendz, Åsberg, Bertilsson, & Thorén, 1984), serotonergic dysfunction may also contribute to the pathogenesis and maintenance of excessive alcohol consumption and to impulsive behavior (Fils-Aime et al., 1996; Lemarquand, Pihl, & Benkelfat, 1994). The acute response to alcohol is modulated both by the structure of the 5-HTT gene and by stress factors that affect the serotonin turnover rate and the in vivo availability of serotonin transporters (C. S. Barr et al., 2003; Doudet et al., 1995; Heinz et al., 1998; Hu et al., 2005; Schuckit et al., 1999). These observations may be relevant for the development of excessive alcohol intake and alcohol dependence, since a low level of response to acute alcohol intake is more common in the relatively alcohol-naive offspring of alcoholics and is predictive of subsequent alcohol abuse and dependence (Rodriguez, Wilson, & Nagoshi, 1993; Schuckit et al., 1999; Schuckit & Smith, 1996; Volavka et al., 1996). In this review, we will trace these lines of evidence and examine whether studies in nonhuman primates offer a coherent view of the behavioral correlates of serotonergic dysfunction.

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Genetic and Environmental Effects on Serotonergic Neurotransmission

In humans and nonhuman primates, both genetic and environmental factors contribute to the serotonin turnover rate, as assessed by the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF; Clarke et al., 1996; Higley, Suomi, & Linnoila, 1991; Higley et al., 1993; Oxenstierna et al., 1986; for a summary of the results from nonhuman primates, see Table 1). The central serotonin turnover rate and reuptake capacity can be assessed in vivo in nonhuman primates. Among adult primates, heritability of serotonin turnover accounted for 42% of the variance in CSF 5-HIAA concentrations (Kaplan et al., 2000). Among

Table 1
Associations Between 5-HTT Promoter Polymorphism, CSF 5-HIAA Concentrations, and Clinical Variables in the Reviewed Primate Studies

Study	Stress	Genotype	Clinical Variables	Animals	*N**	Results
Higley et al., 1991	PR vs. MR Acute stress: 4-day social separations at 6, 18, or 50 months of age	None	CSF 5-HIAA concentration	Rhesus macaques	28	Age-related decline in 5-HIAA levels was greater in MR animals; PR males showed increased 5-HIAA concentration relative to females and to MR males.
Doudet et al., 1995	None	None	Ratings of aggressive behavior made by a primatologist; CSF 5-HIAA concentrations; PET [^{18}F]fluorodeoxyglucose	Adult male rhesus macaques	9	Negative correlation between aggressive behavior and CSF 5-HIAA concentrations; negative correlations between CSF 5-HIAA levels and both whole brain and orbitofrontal cortex glucose utilization
Higley et al., 1996	PR vs. MR Acute stress: 4-day social separations at 6 and 50 months of age	None	Consumed alcohol before, during, and after the social separation; social behavior; CSF 5-HIAA concentration	Rhesus macaques	29	MR animals consumed less alcohol than did PR animals during baseline, but not during separation condition; PR animals showed decreased 5-HIAA levels in infancy and adulthood; 5-HIAA levels did not change from infancy to adulthood within rearing conditions; high rates of alcohol were consumed by young animals with low 5-HIAA levels during separation and by those with infrequent social interactions and less competent social behaviors. No gender differences were found.
Clarke et al., 1996	PR vs. MR	None	CSF 5-HIAA concentration at 6–8 months of age	Infant rhesus macaques	26/22	PR animals showed a greater developmental decline in 5-HIAA levels.
Heinz et al., 1998	PR (n = 10) vs. MR (n = 1)	5-HTT promoter *l*/*l* and *l*/*s*	PET [I123]β-CIT; ratings of aggression; CSF 5-HIAA concentration	5-year-old male rhesus macaques	11	Negative correlation between β-CIT binding to serotonin transporters in the brain stem and 5-HIAA concentrations; greater β-CIT binding and low CSF 5-HIAA concentrations were accompanied by greater aggressiveness and less sensitivity to alcohol-induced intoxication; β-CIT binding did not differ between *l*/*l* and *l*/*s* carriers.
Bennett et al., 2002	PR vs. MR	5-HTT promoter *l*/*l* and *l*/*s*	CSF 5-HIAA concentrations	Rhesus macaques ranging in age from 2 years to adult	132	Decreased CSF 5-HIAA concentrations in PR *l*/*s* animals
C. S. Barr et al., 2003	PR vs. MR	5-HTT promoter *l*/*l* and *l*/*s*	Initial sensitivity to alcohol	Adolescent, alcohol-naive rhesus macaques	52/71	*l*/*l* carriers showed decreased sensitivity to the ataxic and sedating effects of alcohol; PR animals with the *l*/*l* genotype showed less sensitivity than did PR *l*/*s* animals.
Westergaard et al., 2003	None	None	Observations of aggression and impulsive risk-taking behavior; CSF 5-HIAA	Adolescent free-ranging female rhesus macaques	44	Correlation between 5-HIAA and aggressive behavior
C. S. Barr, Newman, Shannon, et al., 2004	PR vs. MR Acute stress: 4-day-long separations	5-HTT promoter *l*/*l* and *l*/*s*	ACTH and cortisol levels	6-month-old rhesus macaques	106/102	Increased cortisol level during separation and decreased level among PR animals; increased ACTH levels during separation; *l*/*s* carriers had higher ACTH levels than did *l*/*l* carriers; PR *l*/*s* animals had higher ACTH levels during separation than did other animals.
C. S. Barr, Newman, Schwandt, et al., 2004	PR vs. MR Acute stress: 30-min separations	5-HTT promoter *l*/*l* and *l*/*s*	ACTH and cortisol levels	Infant rhesus macaques	100/90	ACTH levels during separation were higher in *l*/*s* than in *l*/*l* males. In females, only PR *s* carriers showed increased ACTH and decreased cortisol responses to stress.

Note—PR, peer reared; MR, mother reared; CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid; ACTH, adrenocorticotropic hormone. *Total *N* is broken down by males/females, where appropriate.

humans, heritability accounts for about 35% of this variance, and environmental factors play a very important role in the regulation of the serotonin turnover rate (Beck et al., 1984; Oxenstierna et al., 1986). Environmental factors are of special interest if they have long-lasting effects on serotonergic neurotransmission, as has been shown following early social separation stress (Clarke et al., 1996; Higley et al., 1991; G. H. Jones, Hernandez, Kendall, Marsden, & Robbins, 1992).

Central serotonergic neurotransmission is also modulated by the functional capacity of serotonin transporters, which regulate reuptake of extracellular serotonin. Serotonin transporter expression and functional capacity are influenced by a variable number of tandem repeat polymorphic sites in the regulatory unit of the serotonin transporter gene (SLC6A4). Homozygous carriers of a long allele (*l*/*l* genotype) express about twice as many serotonin transporters as do carriers of one or two short alleles (*s* carriers; Heinz et al., 2000; Lesch et al., 1996; Little et al., 1998).

One environmental factor that has been examined in the context of gene–environment interaction and serotonin function is stress (see Table 1). A brain imaging study with SPECT and the radioligand β-CIT measured the availability of serotonin transporters in relation to CSF 5-HIAA concentrations. The study was performed with adult rhesus macaques who experienced social separation stress during their early development (Heinz et al., 1998; see Figure 1). Concentrations of the serotonin metabolite 5-HIAA in the CSF have been found to be reduced in primates that had been separated from their mothers after birth and peer-reared, in comparison with concentrations in mother-reared animals (Clarke et al., 1996; Higley, Suomi, & Linnoila, 1996). CSF 5-HIAA levels decreased further when the primates were completely isolated from their peers within their early development (during the first 6 months of life). The reductions in CSF 5-HIAA concentrations were trait-like and persisted during adulthood (Heinz et al., 1998; Higley et al., 1996). During early social separation stress, rhesus macaques displayed increased anxiety-like behaviors (Higley et al., 1991), and during adulthood the male animals showed an increase in impulsive aggressiveness (Higley et al., 1996). In these primates, low CSF 5-HIAA concentrations were correlated with an increased availability of serotonin transporters in the brain stem (raphe) area (Heinz et al., 1998). Low CSF 5-HIAA concentrations and a high availability of brain-stem 5-HTT correlated with reduced time spent in social contacts and an increased frequency of self-initiated aggressive acts (Heinz et al., 1998). In female rhesus monkeys, low CSF 5-HIAA was associated with low-intensity, restrained aggression, which is typically observed in matrilineal defense of social status (Westergaard et al., 2003). Interestingly, the effects of early social isolation stress on CSF 5-HIAA concentrations seem to be modulated by the structure of the 5-HTT regulatory region. It has been observed that social isolation is followed by a reduction in the serotonin turnover rate in carriers of a short allele of the promoter of the 5-HTT gene, but not in homozygote carriers of two long alleles (Bennett et al., 2002). When these primates were exposed to complete social isolation during their early development (first 6 months of life), carriers of one short allele of the 5-HTT promoter showed higher concentrations of cortisol and adrenocorticotropine hormone (ACTH) than did homozygote carriers of the long allele (C. S. Barr, Newman, Schwandt, et al., 2004). Increased stress-associated activation of the hypothalamic–pituitary–adrenal (HPA) axis may downregulate serotonin transporters (Slotkin, McCook, Ritchie, Carroll, & Seidler, 1997). In accordance with this hypothesis, plasma cortisol concentrations were inversely correlated with the availability of brain-stem 5-HTT in healthy control subjects and male alcoholics, in whom stress may precipitate relapse to alcohol seeking (Heinz et al., 2002; see Figure 2).

The high availability of raphe serotonin transporters that was found in primates with low CSF 5-HIAA concentrations may be due to a real increase in serotonin transporter

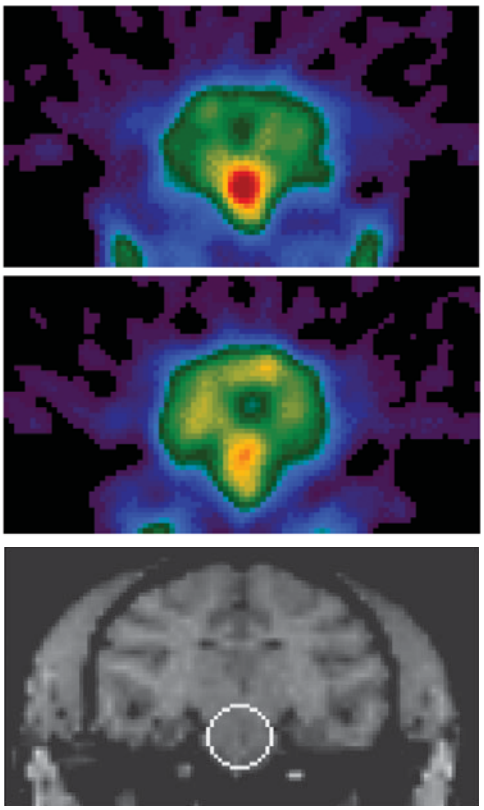

Figure 1. Serotonin transporter availability measured with β-CIT and SPECT in rhesus monkeys with and without early social isolation stress (coronal images). (Top) High serotonin transporter availability in an adult rhesus monkey who grew up without his mother (peer-reared). (Middle) Low serotonin transporter availability in an adult monkey who grew up with his mother (mother-reared). (Bottom) Placement of region of interest in the coregistered MRI in the brain-stem (raphe) area. From "In Vivo Association Between Alcohol Intoxication, Aggression, and Serotonin Transporter Availability in Nonhuman Primates" by A. Heinz, J. D. Higley, J. G. Gorey, R. C. Saunders, D. W. Jones, D. Hommer, et al., 1998, *American Journal of Psychiatry*, *155*, p. 1025. Copyright 1998 by the American Psychiatric Association. Adapted with permission.

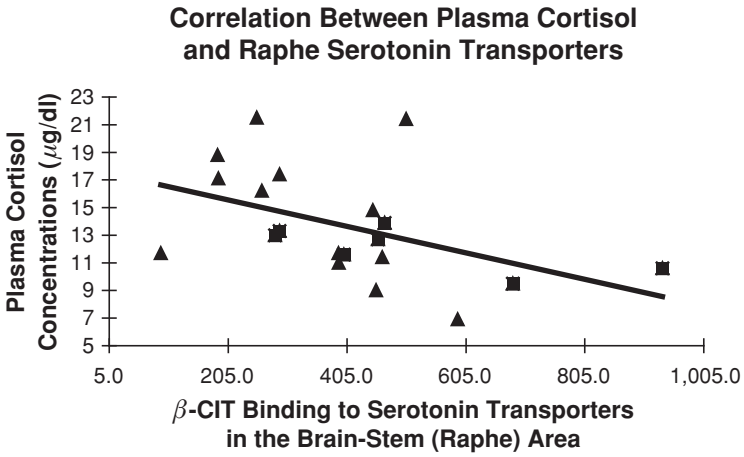

Figure 2. High cortisol concentrations (as found, e.g., during withdrawal stress) were correlated with low availability of brain-stem (raphe) serotonin transporters in male alcoholics (triangles) and healthy controls (squares). From "Relationship Between Cortisol and Serotonin Metabolites and Transporters in Alcoholism [Correction of Alcoholism]" by A. Heinz, D. W. Jones, G. Bissette, D. Hommer, P. Ragan, M. Knable, et al., 2002, *Pharmacopsychiatry*, *35*, p. 131. Copyright 2002 by Georg Thieme Verlag. Adapted with permission.

density. An increase in functional reuptake capacity may be associated with reduced extracellular concentrations of monoamine neurotransmitters and their metabolites. Indeed, a postmortem study in nonhuman primates observed an increase in striatal dopamine transporter density in association with low concentrations of the dopamine metabolite homovanillic acid (Mash et al., 1996). Moreover, a combined microdialysis and β-CIT SPECT study revealed that the availability of monoamine uptake sites was inversely correlated with extracellular neurotransmitter concentrations (Heinz, 1999). Conversely, blockade or loss of dopamine or serotonin transporters induced an increase in extracellular neurotransmitter concentrations in animal models (Giros, Jaber, Jones, Wightman, & Caron, 1996; Kreiss & Lucki, 1995), confirming the hypothesis that the availability of monoamine transporters regulates extracellular monoamine concentrations. Alternatively, low extracellular 5-HIAA concentrations may be correlated with increased binding of β-CIT to serotonin transporters because of decreased competition of the radioligand with endogenous serotonin (D. W. Jones et al., 1998). In line with this hypothesis, restoration of synaptic serotonin concentrations to normal levels after depletion was associated with a significant reduction in β-CIT binding to raphe 5-HTT in nonhuman primates (Heinz et al., 2004). In any event, an increased availability of serotonin transporters, as assessed with β-CIT SPECT, was associated with low CSF 5-HIAA concentrations in humans and nonhuman primates (Heinz et al., 1998; Heinz et al., 2002; see Table 1).

Secondary Behavioral Manifestations of Central Serotonergic Dysfunction

Aggressive behavior may be a secondary or even primary correlate of reduced central serotonin turnover. It has been suggested that the experience of punishment is associated with a serotonergic activation of the septohippocampal behavior inhibition system, which is subjectively unpleasant and induces subsequent passive avoidance (Gray, 1982). Serotonergic dysfunction may thus be associated with a failure to activate the behavior inhibition system, which manifests as impulsiveness and uncontrolled aggressive behavior. An alternative hypothesis has been suggested, that impulsive aggressiveness is not a specific correlate of central serotonergic dysfunction and that a dysfunction of serotonergic neurotransmission is more credibly related to negative mood states such as anxiety or depression (Artigas, 1995; Knutson et al., 1998; Owens & Nemeroff, 1994; Young, Warsh, Kish, Shannak, & Hornykeiwicz, 1994). In accordance with this view, the pleasant psychopathological effects of "ecstasy" (methylenedioxymethamphetamine) have been associated with acute serotonin release (Huether, Zhou, & Ruther, 1997). Moreover, improvement of negative mood states during medication with selective serotonin reuptake inhibitors (SSRIs) has been attributed to an *increase* rather than a decrease in synaptic serotonin concentrations, an observation that is difficult to reconcile with the notion of serotonergic neurotransmission stimulating a punishment system (Artigas, 1995; Kreiss & Lucki, 1995; Limberger, Starke, & Singer, 1990; Muck-Seler, Jevric-Causevic, & Diksic, 1996). Furthermore, several studies have indicated that serotonin depletion induces negative mood states among patients with obsessive-compulsive disorder and in patients with major depression who previously responded to SSRI medication with a reduction in the severity of clinical depression (L. C. Barr et al., 1994; Delgado et al., 1990). These observations are in line with older human CSF studies, in which a significant association was observed between an increase in a primarily low CSF

5-HIAA concentration and clinical remission of depressive symptoms (Praag, 1977; Träskman-Bendz et al., 1984). Together, these observations indicate that an increase in synaptic serotonin concentrations may not represent the neurobiological correlate of punishment but, rather, may induce a *reduction* in anxiety and depressiveness.

The associations between central serotonergic dysfunction and both negative mood states and impulsive aggression may derive from a common ground. Specifically, it has been argued that the association between a low serotonin turnover rate and aggressive behavior may be mediated by negative emotions such as feeling insecure and threatened (Heinz, Mann, Weinberger, & Goldman, 2001). This hypothesis was based on a study by Knutson et al. (1998) in humans who engaged in a competitive game and received SSRI medication to induce an acute increase in synaptic serotonin concentrations. Knutson et al. (1998) found that the primary correlate of SSRI intake was a decrease in insecurity and anxiety, and the reduction in aggressive behavior was statistically explained by the decrease in negative emotions. The reduction in aggressiveness may thus be due to a decrease in perceptions of threat and insecurity. This interpretation is supported by animal experiments showing that serotonin depletion induces anxious and insecure behavior patterns (Knutson, Panksepp, Narayanan, & Rossi, 1996), and increased serotonin turnover is associated with higher social competence in competitive games (Knutson, Panksepp, & Pruitt, 1996).

A high serotonin turnover rate may protect against the impact of threat-related environmental cues: McCormick (1992) and Baumgarten and Grozdanovic (1995) have suggested that serotonergic neurotransmission supports a "protective filter effect" by modulating thalamo-cortical circuits, thus reducing the impact of sensory inputs. In light of this hypothesis, it is remarkable but counterintuitive that in humans, a genetic disposition for low serotonin transporter expression has been associated with an increased amygdala response to fearful faces and aversive stimuli (Hariri et al., 2002; Heinz et al., 2005). The exact interactions between human 5-HTT polymorphism, serotonin turnover rate, and anxiety require further examination.

Exacerbation of central serotonergic dysfunction during clinical disorders such as major depression may then lead to overactivation of the amygdala by aversive environmental stimuli, and indeed, increased glucose turnover rates were observed in depressed patients (Drevets, 2000). These observations suggest that serotonergic neurotransmission promotes a feeling of security and tranquility (Knutson, Panksepp, & Pruitt, 1996; Raleigh, McGuire, & Brammer, 1988), and that subjects with a deficit in serotonergic neurotransmission may feel insecure, anxious, and threatened (Clarke et al., 1996; Higley et al., 1991; Jones et al., 1992). In this view, the manifestation of aggressiveness or clinical depression after serotonin depletion is a secondary consequence from general feelings of tension and insecurity that manifest as negative mood states (Heinz et al., 2001; Knutson et al., 1998), which may depend upon the manifestation of other causal factors such as learned behavior in social contexts (Kraemer & McKinney, 1979; Raleigh & McGuire, 1991). Further animal experiments and human studies in clinical populations will have to assess the interactions between serotonergic dysfunction, amygdala activation, and specific negative mood states.

Serotonergic Neurotransmission and the Response to Acute Alcohol Intake

Dysfunction of central serotonergic neurotransmission has long been suggested to characterize early-onset alcoholism with increased aggressiveness (Fils-Aime et al., 1996). Therefore, animal models were studied to elucidate the potential connection between serotonergic dysfunction, excessive alcohol intake, and aggressive behavior. In humans and nonhuman primates, subjects who show a low response to the effects of acute alcohol intake may lack a "warning signal" and tend to excessively consume alcohol, and indeed, a low alcohol response was associated in prospective human studies with excessive alcohol intake and increased risk to develop alcohol dependence (Schuckit et al., 1999; Schuckit & Smith, 1996). Nonhuman primates that carried two long alleles of the 5-HTT promoter gene showed a low response to alcohol in comparison with carriers of one or two short alleles (C. S. Barr et al., 2003). An increase in serotonin transporter availability may also result from early social isolation stress: In nonhuman primates separated from their mothers after birth, a low serotonin turnover rate and high availability of raphe serotonin transporters were associated with a low response to the acute effects of alcohol intake (Heinz et al., 1998; see Figure 3). A dysfunction of central serotonergic neurotransmission may contribute to low alcohol response by reducing the sedative, GABAergic effects of alcohol in-

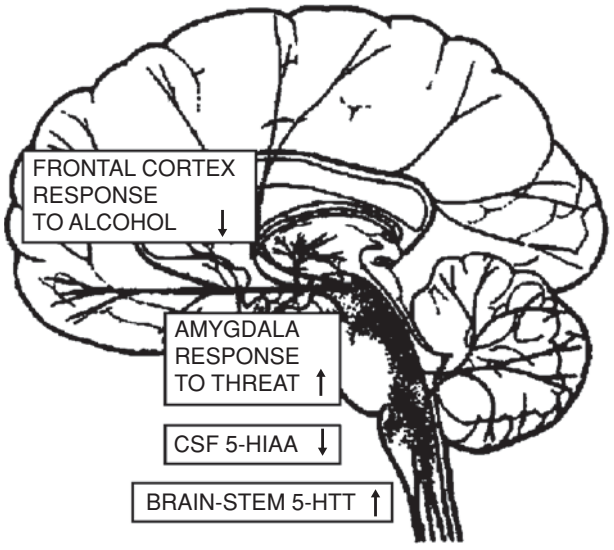

Figure 3. Alterations in serotonergic neurotransmission following early social separation stress. 5-HTT *s* carriers may be specifically vulnerable to social isolation stress (Hartka et al., 1991) and may respond with an increase in serotonin transporter availability, a low serotonin turnover, an increased amygdala response to threat, and a low response to the acute effects of alcohol intake.

take. GABA activation potentiates the sedative effects of ethanol, and GABAergic dysfunction has been associated with decreased sedative effects of alcohol (Liljequist & Engel, 1982; Silveri & Spear, 2002). Moreover, high doses of alcohol sedate via blockade of glutamatergic NMDA receptors (Krystal et al., 1998; Tsai, Gastfriend, & Coyle, 1995). Reduced prefrontal serotonergic neurotransmission can interfere with both GABAergic and glutamatergic neurotransmission via 5-HT_{1A} and 5-HT_4 receptors (Cai, Flores-Hernandez, Feng, & Yan, 2002; Cai, Gu, Zhong, Ren, & Yan, 2002; Feng, Cai, Zhao, & Yan, 2001; Krystal, Abi-Dargham, Laruelle, & Moghaddam, 1999). In support of this hypothesis, Doudet et al. (1995) observed a significant correlation between CSF 5-HIAA concentrations and central effects of GABAergic drugs in nonhuman primates, so that prefrontal glucose utilization rates during GABAergic sedation were least affected in rhesus monkeys with the lowest CSF 5-HIAA concentrations. In a free choice paradigm, low CSF 5-HIAA concentrations and a high availability of serotonin transporters correlated with increased alcohol intake by nonhuman primates (Heinz, Schäfer, Higley, Krystal, & Goldman, 2003).

Disposition to Excessive Alcohol Intake: Gene–Environment Interactions As Mimicking Gene–Gene Interactions

The predisposition for excessive alcohol intake is modulated by gene–environment interactions. In the nonhuman primate model of Higley et al. (1996), early social isolation stress was followed by (1) low levels of CSF 5-HIAA concentration, (2) a high availability of brain-stem serotonin transporters, and (3) reduced drug-elicited GABAergic sedation (Doudet et al., 1995; Heinz et al., 1998). The constitution of serotonin transporters and $GABA_A$ receptors may result in a similar interaction between a high availability of central serotonin transporters and a low response of $GABA_A$ receptors: In two human studies, researchers observed that a low response to acute alcohol intake was associated with the 5-HTT *l*//*l* genotype (Hu et al., 2005; Schuckit et al., 1999). Moreover, in humans, a low response to alcohol was associated with an allelic variant, Ser385, of the $GABA_{A\alpha6}$ receptor polymorphism Pro385Ser (Schuckit et al., 1999). In rodents, a single-nucleotide mutation in the $GABA_{A\alpha6}$ receptor subunit was also associated with a sensitivity to acute motor-impairing effects of moderate alcohol and benzodiazepine intake (Korpi, Kleingoor, Kettenmann, & Seeburg, 1993). In a pilot study by Schuckit et al. (1999), all human subjects who carried the *l*//*l* genotype of the 5-HTT promoter and the Pro/Ser genotype of the $GABA_{A\alpha6}$ receptor subunit later became alcohol dependent. Together, these observations indicate that both genetic and environmental (stress) factors may interact with central serotonin turnover rates and the availability of serotonin transporters, interfere with the balance between glutamatergic excitation and GABAergic inhibition, and reduce the ataxic and sedative effects of acute alcohol intake (Heinz et al., 1998; Higley et al., 1996; Schuckit et al., 1999).

Inconsistent results were found in studies that assessed the potential association of serotonin transporter genotype with the risk to develop alcoholism (Edenberg et al., 1998; Gelernter, Kranzler, & Cubells, 1997; Sander et al., 1998). Nonhuman primate studies suggest that environmental stress factors result in an interaction between serotonergic dysfunction and the alcohol response of $GABA_A$ receptors that mimics genetic effects on serotonin transporters and GABAergic neurotransmission. In Bennett et al. (2002), exposure to early social isolation stress reduced CSF 5-HIAA concentrations in nonhuman primates that had one or two short alleles of the 5-HTT regulatory unit, but it did not interact with CSF 5-HIAA concentrations in the *l*//*l* genotype. The primates examined in Heinz et al. (1998) were mostly carriers of the "stress-vulnerable" genotype with one or two short alleles of the 5-HTT regulatory unit. In this genotype, a high availability of brain-stem serotonin transporters may result from stress-induced decreases in central serotonin turnover (Bennett et al., 2002; Heinz et al., 1998), but in the *l*//*l* genotype, a high availability of central serotonin transporters is due mainly to genetic factors (Lesch et al., 1996). Independent of its genetic or environmental causation, the resulting high availability of brain-stem serotonin transporters may contribute to a low response to alcohol intake and to excessive alcohol consumption (C. S. Barr et al., 2003; Heinz et al., 1998).

Moreover, 5-HTT *s* carriers may be specifically vulnerable to social isolation stress and may react with increased HPA-axis activation and negative mood states such as clinical depression or anxiety, factors that may also contribute to excessive alcohol intake in humans (Hartka et al., 1991). Although anxiety was only slightly increased in healthy human volunteers who carried one or two short alleles of the 5-HTT regulatory unit (Lesch et al., 1996), subjects with this genotype displayed increased amygdala activation when confronted with fearful faces (Hariri et al., 2002; Heinz et al., 2005) and showed increased occurrence of clinical depression when they had been exposed to abuse during early childhood (Caspi et al., 2003). Interestingly, nonhuman primates showed a gender-specific interaction between early social isolation stress and HPA-axis activation during further stress exposure in a study by C. S. Barr, Newman, Schwandt, et al. (2004). In this study, female and male rhesus monkeys were exposed to early social separation stress and either were peer-reared (PR) or grew up with their mothers (MR). When subjected to complete social isolation, male carriers of one short allele of the 5-HTT gene displayed increased ACTH concentrations compared with *l* homozygotes, and this increase was independent of whether they were PR or MR. In female primates, an increase in cortisol concentrations in *s* carriers compared with *l* homozygotes was only found in PR monkeys—that is, in those who had experienced early adversity in the form of social separation stress. Further studies will have to examine the interaction between gender, 5-HTT genotype, and the behavioral correlates of stress-associated changes in serotonin turnover and HPA-axis activation.

Conclusion

Current studies suggest that 5-HTT genotype mediates the impact of early social separation stress on the central serotonin turnover rate and the activation of the stress hormone axis in nonhuman primates, and potentially also in humans (C. S. Barr, Newman, Schwandt, et al., 2004; Bennett et al., 2002). In nonhuman primates, social separation stress has been associated with a low serotonin turnover rate and associated changes in the availability of central serotonin transporters (Heinz et al., 1998; Higley et al., 1996). Among these subjects, a low serotonin turnover rate and high availability of brain-stem serotonin transporters correlated with increased anxiety, impulsive aggression, and low response to alcohol (Heinz et al., 1998; Higley et al., 1991). A low response to ethanol and increased aggressiveness was also found in mice lacking the 5-HT_{1B} receptor (Coccaro et al., 1989; Saudou et al., 1994). In a series of human studies, a low serotonin turnover rate was associated with anxious behavior and perceptions of threat, which may secondarily have contributed to impulsive aggression (Knutson et al., 1998; Meltzer et al., 1994; Praag, 1977). Conversely, in healthy human volunteers, increased amygdala activation elicited by aversive stimuli was found in carriers of a short allele of the promoter of the serotonin transporter gene. These subjects also displayed increased activation of the medial prefrontal cortex, an area that may contribute to emotion regulation (Heinz et al., 2005; Pezawas et al., 2005). In nonhuman primate studies, *s* carriers were specifically vulnerable to social isolation stress and displayed significant reductions in the central serotonin turnover rate (Bennett et al., 2002). In a human study, *s* carriers who had experienced a high number of traumatizing events displayed a higher risk to develop negative mood states such as major depression (Caspi et al., 2003). It is possible that in these subjects, a stress-related reduction in central serotonin turnover may have interfered with the 5-HTT-genotype-driven interaction between the amygdala and the medial prefrontal cortex, thus impairing prefrontal emotional control, but this hypothesis has so far not been tested in humans. On the basis of the available primate studies, gender effects may also play a role in humans and influence whether serotonin dysfunction results in negative mood states or impulsive aggression (C. S. Barr, Newman, Schwandt, et al., 2004; Heinz et al., 1998).

Further studies are required in order to examine the relationship between these behavioral phenotypes, serotonergic dysfunction and genotype, and the pathogenesis and maintenance of clinical disorders such as major depression and alcoholism.

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