Evolutionary underpinnings of excessive alcohol consumption

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ABSTRACT

Given our close phylogenetic relatedness, non-human primates, in principle, could serve as an ideal model for alcoholism. Indeed, many studies in both humans and rhesus macaques show relationships between excessive alcohol consumption, aggression and serotonergic function, as measured by concentrations of the principal metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF). An important behavioral predictor of excessive alcohol consumption in both humans and rhesus monkeys is the propensity toward impulsivity. Integrating behavioral and neuroendocrine data from captive and semi-free-ranging rhesus macaques, we posit that benefits derived from impulsive and aggressive behaviors in some contexts might contribute indirectly to the maintenance of traits involved in alcoholism and excessive alcohol intake.

KEYWORDS 5-HIAA, alcoholism, Darwinian medicine, evolution, primate behavior.

INTRODUCTION

In the past decade, interest has grown in seeking evolutionary explanations for the susceptibility to disease. This approach, referred to as Darwinian medicine, has not only offered insights into the occurrence of cancer and the transmission of infectious diseases, but has also provided researchers with clues as to why some people are vulnerable to diseases such as depression, alcohol dependence and alcoholism. In this chapter we use the terms alcoholism and alcohol dependence interchangeably, and excessive alcohol use refers to heavy drinking in the absence of physical dependence. Alcohol dependence and alcoholism seem to present an evolutionary paradox. While alcoholism appears to reduce fitness, it persists as a phenotype in the human population. Surprisingly, few examinations have used an evolutionary approach to explain why some individuals are more susceptible to alcohol dependence than others. Understanding the evolutionary basis of excessive alcohol consumption may allow researchers to understand better etiological mechanisms and develop potential treatments for alcoholism. In this paper, we apply principles of evolutionary biology to developmental, behavioral and neuroendocrinological investigations of captive and free-ranging non-human primates to further understand excessive alcohol consumption and alcoholism. Because alcohol consumption in non-human primates does not occur spontaneously in nature, it is unlikely that a propensity to consume alcohol was selected for directly. However, alcoholics exhibit multiple traits. Some of these traits may have selective benefits in certain specific environments. We advance the hypothesis that natural selection may maintain genes for traits that lead to excessive alcohol consumption and dependence because these same traits may enhance fitness in other contexts.

RHESUS MACAQUES AS A HUMAN MODEL FOR EXCESSIVE ALCOHOL CONSUMPTION AND ALCOHOLISM

It is generally accepted that numerous neurological, developmental and psychological variables place individ-

uals at risk for alcohol dependence and alcoholism. While no single heritable trait is common to all individuals who suffer from alcohol dependence or alcoholism, over the past few years a number of variables have become accepted as heritable risk factors. Emotional responses to fearful stimuli and a drive to seek reinforcement, for example, are both adaptive responses. These same traits are also widely accepted as motivating factors in excessive alcohol consumption and alcoholism. A major theme of the paper is that heritable traits that provide adaptive advantages in one context may contribute indirectly to the maintenance of traits deleteriously involved in alcoholism and excessive alcohol intake.

Many traits that predict excessive alcohol consumption and dependence in humans have also been studied in non-human primates. Non-human primates are ideally suited to investigate evolutionary mechanisms of human traits. They are our closest phylogenetic relatives and resemble humans in their behavior, development, neuroanatomy and neurophysiology. Like humans, rhesus macaques (*Macaca mulatta*) exhibit individual temperaments and personalities. Similar to human societies, rhesus macaques live in large social groups and develop complex, life-long social bonds with both related and unrelated conspecifics; thus, rhesus macaques are good subjects for researchers to model the role of social variables in alcohol-related problems.

While free-ranging non-human primates do not naturally have access to alcohol as do humans, when it is available, most rhesus macaques consume alcohol at levels that produce pharmacological effects (i.e. Higley & Linnoila 1997). To investigate alcoholism and alcohol dependence with a non-human primate model, we have typically trained subjects to drink a sweetened solution and then added sufficient alcohol to produce a wine-like 8.5% solution (Higley & Linnoila 1997). During experiments, subjects are simultaneously offered free choice of water, an aspartame sweetened water vehicle, and an aspartame sweetened alcohol solution. This procedure ensures that the motivation for alcohol consumption is for its pharmacological properties rather than for its sweetened taste. Most monkeys readily consume this flavored alcohol at comparable rates to the typical human (about one to three drinks over the course of an hour). This rate of consumption produces blood alcohol levels between 0.05% and 0.08%. Fewer than 10% of the subjects are teetotalers, failing to drink appreciable quantities of alcohol over the course of a study. By contrast, similar to humans, a few (15–20%) drink at rates that routinely exceed the limits for intoxication, showing behaviors indicative of intoxication such as stumbling or stupor. When subjects are allowed daily 1-hour access to this alcohol solution, during each session they show an initial 'binge-like' high rate of consumption. Like humans, on average male rhesus macaques consume more alcohol per kilogram body weight than females (Higley 1996). Taken together, rhesus macaques can serve as an ideal model for investigating the pathogenesis of alcohol dependence and alcoholism from an evolutionary perspective.

SELECTIVE FACTORS IN TYPE I ALCOHOL DEPENDENCE AND ALCOHOLISM

Parallels between humans and non-human primates in alcohol-related psychopathology suggest that similar mechanisms act to maintain traits underlying alcoholism. By examining similarities between the physiology and behaviors underlying excessive alcohol consumption we can identify variables which contribute to, and which are predictive of, alcoholism in humans. As physiological mechanisms can be more readily studied in non-human primates than in humans, non-human primates have been particularly useful in studies investigating the biological basis of alcoholism. One of the most influential theories that has guided our study of the biological variables affecting alcoholism is Cloninger's neurogenetic, tridimensional personality model of alcoholism (Higley & Bennett 1999). This model identifies two subtypes of alcoholism, Type 1 and Type 2 (Cloninger 1987).

Type 1 alcoholism is believed to result from anxiety-mediated alcohol consumption and is influenced by both genetics and environmental experiences. Type 1 alcoholics are thought to consume alcohol primarily to alleviate anxiety. They are characterized by an exaggerated avoidance of harm and excessive dependence on rewards. Anxiety avoidance can have both beneficial and detrimental consequences for fitness. An example derives from the primate mother–infant relationship. Natural selection has given rise to a primate infant who develops a strong dependence on her or his mother. This dependence involves close physical proximity to the mother who regulates infant arousal. The maternal–infant bond ensures that the infant receives not only physical nourishment and protection, it also facilitates information transmission and support for the development of future independence and emotional stability. Anxiety and arousal are proximate influences that motivate the young infant to stay close to its mother (Harlow & Harlow 1965). By contrast, an excess of anxiety can elicit chronic physical contact between mother and infant, which can prevent infants from pursuing social relationships and from forming social bonds with peers (Dolhinow & Murphy 1983; Higley & Suomi 1989).

Experimental manipulation of the early mother–infant social bond in rhesus macaques can lead adoles-

cent macaques to exhibit a profile of high anxiety, which is positively related to rates of alcohol consumption, compatible with predictions of Type 1 alcoholism (Higley *et al.* 1991). Under experimental conditions, where infants are reared with mothers who are less sensitive to their infants' needs, and in conditions where infants are reared in peer groups without mothers, studies show that infant-like anxiety and arousal are maintained into adolescence and adulthood (Capitanio *et al.* 1986; Higley *et al.* 1996d,e). As adolescents, these maternally deprived, peer-reared subjects exhibit high levels of anxiety, cortisol and central corticotropin-releasing hormone (CRH) (Higley *et al.* 1996d, e). Perhaps as a consequence of heightened anxiety, peer-reared subjects are likely to consume alcohol to excess, and rates of consumption are positively correlated with behavioral indices of fear and anxiety (Higley *et al.* 1991; Fahlke *et al.* 2000).

Further support of the postulate that anxiety in one environment elicits positive mother–infant responses but alcohol problems in other environments comes from conditions where mother-reared subjects are separated from their mothers as adolescents. Their anxiety increases and they consume alcohol at levels comparable to those consumed by the alcohol-preferring peer-reared monkeys (Higley *et al.* 1991). In both the peer-reared and separated mother-reared monkeys, anxiety under different environmental conditions elicits excessive alcohol consumption (Higley *et al.* 1991; Fahlke *et al.* 2000). In short, a trait in one environment can be adaptive, as anxiety promotes the mother–infant bond. Under a different environmental condition, this same trait can reduce fitness, as in the case when anxiety prevents the formation of social bonds, mating opportunities, or induces alcohol dependence or leads to alcoholism.

SELECTIVE FACTORS IN TYPE 2 ALCOHOL DEPENDENCE AND ALCOHOLISM

As noted earlier, Cloninger proposes a second kind of alcoholism: Type 2 alcoholism. Type 2 alcoholism includes among its central components an early age onset of alcohol problems, antisocial behavior and problems of impaired social functioning, such as reduced social affiliation and less competent social skills, impaired impulse control, excessive aggression and high novelty seeking, with low avoidance of harm. Cloninger proposed that central nervous system (CNS) deficits of serotonin and norepinephrine contribute to the risk of Type 2 alcoholism. In Cloninger's original formulation (Cloninger 1987; Cloninger *et al.* 1988), alcohol was thought to increase CNS serotonergic activity temporarily, leading to gratification as a direct result of its effects on serotonin or dopamine and, in turn, on the reward system in the CNS (LeMarquand *et al.* 1994). Studies have shown that one of the most frequent correlates of Type 2 alcoholism is antisocial personality traits (Cloninger 1986; Helzer & Pryzbeck 1988; Windle 1990). For example, impaired social functioning beginning early in life is predictive of excessive alcohol use in adolescence (Andersson & Magnusson 1989). Adolescents who rate themselves as socially isolated are more likely to *abuse* substances, including alcohol (Windle *et al.* 1991). Also likely to perceive themselves as having problems with alcohol are young and elderly men with few friends (Meyers *et al.* 1982) and adult children of alcoholics who rate themselves as more socially isolated, with few friends (Domenico & Windle 1993).

Paralleling studies in humans (Kruesi *et al.* 1992), in a series of studies we found that naturally occurring reduced serotonin functioning is correlated with reduced sociality. For example, in a sample of free-ranging adolescent male monkeys, subjects with low CSF 5-HIAA concentrations interacted affiliatively less often and were found in a social context less often than males of higher CSF 5-HIAA concentrations (Mehlman *et al.* 1995). In a laboratory study, we also found that low rates of affiliative interactions are positively correlated with low CSF 5-HIAA concentrations among juveniles of both sexes and adult females (Higley *et al.* 1994, 1996a). Hence, the phenotypic expression of low CSF 5-HIAA concentrations includes low rates of social interactions and perhaps few social companions. Given that non-human primates with infrequent social interactions and few social companions often display low CSF 5-HIAA concentrations, one might predict that reduced sociality would be related to high rates of alcohol consumption. These predictions were tested by measuring sociality prior to alcohol consumption and correlating it with alcohol consumption. We predicted that subjects who spent the least amount of time in a social context would consume more alcohol than subjects spending more time interacting socially. Consistent with our predictions, infrequent social interactions were predictive of high alcohol consumption, and when the subjects that were prone to consume high volumes of alcohol interacted socially their interactions were brief and appeared furtive (Higley *et al.* 1996e).

Banding together as a social group is conducive to defense from predators. In times of plenty, there is little nutritional cost to monkeys living in social groups. There are conditions, however, where solitary living can be beneficial. For example, in times of scarcity, large social groups may rapidly consume the limited resources. One possible advantage of being solitary under conditions of scarce resources is that a monkey who forages by itself can avoid competing with other group members and may

thereby be more likely to continue to obtain sufficient calories to survive.

As stated previously, Cloninger's formulation predicts impaired levels of CNS serotonin in Type 2 alcoholics. Indeed, in humans and other primates, individual subjects who consume alcohol in excess are likely to have low CSF 5-HIAA concentrations (reviewed in LeMarquand *et al.* 1994). For example, relative to healthy volunteers, young alcoholic men and women exhibit lower concentrations of CSF 5-HIAA (Ballenger *et al.* 1979; Banki 1981; Borg *et al.* 1985), even during periods of abstinence. (Limson *et al.* 1991; Sher *et al.* 1991; Giancola *et al.* 1993).

As we discuss later, diminished serotonergic activity is one of the biological variables underlying specific types of impulse-control deficits implicated in aggression, as well as alcohol abuse and alcoholism (Cloninger 1987; reviewed in Higley *et al.* 1996a). Principal among the studies that have investigated serotonin function and alcoholism is the finding that individuals with low CSF 5-HIAA concentrations exhibit high levels of impulsive behavior (Limson *et al.* 1991; Sher *et al.* 1991; Giancola *et al.* 1993). Type 2 alcoholics, sons of alcoholic fathers (Giancola *et al.* 1993; Limson *et al.* 1991; Sher *et al.* 1991) and in some studies, daughters of alcoholic fathers (Sher *et al.* 1991) have been rated highly in impulsivity and other measures of behavioral dyscontrol. Impulsivity in individuals with impaired CNS serotonin functioning is thought to contribute to alcoholism, because once individuals begin drinking, deficits in their impulse control fuel excessive alcohol consumption. As impaired CNS serotonin appears to be a heritable mechanism underlying alcoholism, it is important to characterize the phenotypic expression of this trait and to consider what factors contribute to variability in serotonergic function.

GENETIC AND ENVIRONMENTAL INTERACTIONS THAT CONTRIBUTE TO ALCOHOL CONSUMPTION AND ALCOHOLISM

Phylogenetically, serotonin is one of the oldest neurotransmitters. It is involved in a variety of motivational conditions ranging from emotional states such as depression, anger and aggression to eating and eating disorders, sleep and impulse control. Heritable influences provide a major impact in developing some forms of alcoholism and in a parallel fashion are critical in CNS serotonin functioning. Heritability accounts for approximately 40% of the variance in alcoholism (Merikangas 1990). One study of humans, with a limited sample size of monozygotic and dizygotic twins, investigated genetic contributions to CSF monoamine metabolite concentrations. In that study, CSF 5-HIAA concentrations were not found to be heritable (Oxenstierna *et al.* 1986); however, in an investigation which included a large number of non-human primate research subjects tested under closely controlled conditions, clear genetic and environmental influences of CNS serotonin activity were revealed (Higley *et al.* 1994). This study, which controlled for rearing (environmental) effects, revealed significant heritable effects ($h^2 > 0.5$) for both sons and daughters in concentrations of CSF 5-HIAA when the results were pooled statistically according to the biological father. In addition, there were substantial maternal genetic influences on the young offspring's 5-HIAA ($h^2 > 0.5$). A subsequent study replicated this earlier study, demonstrating a paternal genetic contribution to CSF 5-HIAA (Clarke *et al.* 1994).

As one might predict of a genetically mediated trait, interindividual differences in CSF 5-HIAA concentrations are relatively stable over time and context (Kraemer *et al.* 1989; Higley *et al.* 1992; Higley *et al.* 1993). If a stable personality trait is maintained by a central neurotransmitter system, one would expect similar interindividual stability in the central response of the system, controlling the personality trait or behavior. Indeed, in rhesus macaques, once rates of alcohol consumption stabilize, interindividual differences in alcohol consumption are thereafter stable over time, and CSF 5-HIAA concentrations and alcohol consumption are negatively correlated (Higley *et al.* 1991; Kraemer & McKinney 1985).

More recently, molecular genetics have been applied as tools to investigate how genotypic variation affects the phenotypic variation in CNS serotonin functioning. Length variation in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) in the serotonin transporter promoter appears to increase serotonin-associated traits (Lesch *et al.* 1996). Recent studies in non-human primates have shown that the phenotypic expression of this genotype is dependent on the early rearing background of subjects. (Bennett *et al.* 2002). More specifically, monkeys who were raised in the absence of adults but in the company of age-related peers and who carry the short 5-HTTLPR allele are significantly more likely to exhibit lower CSF 5-HIAA concentrations than either other peer-reared animals or mother-reared animals, who are homozygous for the long allele. Indeed, genotypic differences do not affect serotonin turnover in monkeys reared by their mothers.

THE RELATIONSHIP BETWEEN SEROTONERGIC FUNCTION AND BEHAVIOR

It is generally thought that serotonin plays a role in some forms of violent behavior. Men who exhibit a life-long pattern of aggression and violence tend to exhibit low

CSF 5-HIAA concentrations (Brown *et al.* 1982; Linnoila *et al.* 1983; Virkkunen *et al.* 1994a; Virkkunen *et al.* 1994b). More specifically, adolescents who exhibit inappropriate or excessive aggression (Kruesi *et al.* 1992), and men who initiate unplanned violence or display higher than average life-time rates of aggression (Brown *et al.* 1982; Linnoila *et al.* 1983) all tend to exhibit lower than average baseline CSF 5-HIAA concentrations.

The existence of an inverse relationship between serotonergic function and aggression has also been revealed in a variety of mammalian taxa, including golden hamsters (Ferris *et al.* 1997), Norway rats (Popova *et al.* 1991a), silver foxes (Popova *et al.* 1991b), dogs (Reisner *et al.* 1996), vervet monkeys (reviewed in McGuire, Raleigh & Brammer 1984) and rhesus macaques (Higley *et al.* 1996c). Furthermore, studies investigating aggression in rhesus macaques show that low concentrations of CSF 5-HIAA are associated with aggression that is impulsive and unrestrained (Higley *et al.* 1996c). In this same study, high rates of impulsive behavior were positively correlated with severe, unrestrained aggression but not with competitive, restrained aggression that seldom escalates out of control (Higley *et al.* 1996c). Experimental research provides further evidence that serotonergic function may play an etiological role in disorders of impulse control and aggression. In selective breeding programs which have produced animals with less aggressive temperaments, animals show a concomitant increase in CNS 5-HT and 5-HIAA concentrations as each generation becomes increasingly docile (Naumenko *et al.* 1989; Popova *et al.* 1991a, 1991b). Moreover, agents pharmacologically increasing serotonergic activity decrease aggression, while decreasing serotonergic activity increases aggression in rodents (Miczek & Donat 1990; Olivier & Mos 1990; Nikulina *et al.* 1992) and monkeys (Higley *et al.* 1998).

Given the relationships between low serotonin functioning and aggression, and its costly physical and social consequences across animal taxa, the conservation of this trait (low CSF 5-HIAA) is enigmatic. Determining the mechanisms that maintain this trait remains an intriguing issue, which we discuss later. We now focus on findings derived from studies of rhesus macaques to evaluate the fitness consequences for individuals varying in concentrations of CSF 5-HIAA and to consider potential mechanisms which may act to maintain this trait.

SEROTONIN PHENOTYPES AND SELECTIVE PRESSURES

In male rhesus macaques, mating success results from a combination of male–male competition for sexual access to females, and from female choice of males (Manson 1992). Unlike humans who mate and reproduce throughout the year, the timing of reproduction in rhesus macaques is mostly concentrated to a given period of time. During the mating season males experience many hormonal and neuro-endocrine changes, including increases in average levels of CSF 5-HIAA (Zajicek *et al.* 2000), and concentrations of CSF and plasma free-testosterone (Mehlman *et al.* 1997). Males and females may form consortships: a period of time where heterosexual pairs devote exclusive mating access to one another. In a recent study, we found that free-ranging males with above average concentrations of CSF 5-HIAA were significantly more likely to engage in consortships. By contrast, males with below average concentrations of CSF 5-HIAA failed to elicit consort relationships during the breeding season and produced fewer sperm plugs than males with higher concentrations of CSF 5-HIAA.

Given the potential loss of mating opportunities associated with diminished serotonergic functioning, this would seem to place such individuals at risk for a loss of reproductive success. To address this question, we examined in a recent study whether rhesus macaque males differing in concentrations of CSF 5-HIAA also differed in reproductive outcome using our captive facilities at the National Institutes of Health, Primate Unit in Poolesville, MD, USA (M. Gerald *et al.*, pers. comm.). Our analyses revealed variable reproductive consequences for males differing in concentrations of CSF 5-HIAA. Males that sired offspring were more likely to exhibit higher concentrations of CSF 5-HIAA than non-successful males. Thus, just as serotonergic function is correlated with Type 2 alcohol problems and affects many aspects of behavior and survivorship, adult male rhesus macaques exhibiting low concentrations of CSF 5-HIAA apparently lose reproductive benefits when compared to those males with higher CSF 5-HIAA concentrations. It is even more puzzling that this trait (low CSF 5-HIAA concentrations) has been maintained in the overall population because it also places young monkeys at risk for premature death. In rhesus macaque society, there is an association between the length of a male's tenure in a social group and the number of relationships a male forms and maintains, especially with the adult females of the troop, and the social dominance ranking he attains (Drickamer & Vessey 1973). This association has important consequences for the adolescent male monkey who migrates between social groups. Following puberty, male rhesus macaques transfer from their natal social groups to novel social groups (Berard 1990). Mehlman *et al.* (1995) found that males with lower concentrations of CSF 5-HIAA were more likely to transfer from their natal groups at a younger age, often when they have not fully reached maturity. Replicating these findings, another study found that males with high CSF 5-HIAA concentrations were

more likely to remain in their natal social groups until they were older and mature (Kaplan *et al.* 1995). Social skills develop with age, which may aid males when entering a new social group. Migration to a new social group is dangerous and highly stressful for young males and often results in wounding and sometimes even in death (i.e. Packer 1979; van Noordwijk & van Schaik 1985; Pusey & Packer 1987). Young males could potentially benefit from delaying migration until they are older, as older brothers and other familiar conspecifics may have transferred to nearby groups, facilitating an immigrant's integration into a new social group (Drickamer & Vessey 1973).

Based on these findings of early migration in males with low CSF 5-HIAA concentrations, we predicted premature mortality in these subjects. Paralleling studies in humans (Faustman *et al.* 1993), we found a relationship between early mortality and low CSF 5-HIAA in nonhuman primates. In this study there were relatively high rates of mortality among subjects with low concentrations of CSF 5-HIAA during the time when most males leave their natal groups (Higley *et al.* 1996b). Direct observations of aggressive behavior showed that dead or missing subjects initiated violent behavior, as measured by escalated aggression, a measure of potentially injurious aggression, at a higher rate than that of living subjects. Subjects who died because of violence also exhibited CSF 5-HIAA concentrations in the lowest quartile of the sample and had been rated previously as more aggressive. No subjects exhibiting concentrations of CSF 5-HIAA from the highest quartile were found dead or missing.

POSSIBLE EVOLUTIONARY EXPLANATIONS FOR EXCESSIVE ALCOHOL CONSUMPTION AND ALCOHOLISM

We have identified other costs associated with serotonin-related traits that are associated with excessive alcohol consumption and dependence. We have described their central role in alcohol dependence and alcoholism. We suggest that one of the mediating factors which place subjects with low CNS serotonin functioning at risk for alcohol dependence and alcoholism is impulsivity. Indeed, in primate societies, low central serotonin activity has also been linked to behavioral measures of impulsivity such as spontaneous and potentially dangerous leaps between tree-tops, repeated entrance in baited traps (Mehlman *et al.* 1995; Higley *et al.* 1996b; Fairbanks *et al.* 2001) and high rates of alcohol consumption once a drinking bout starts (Higley *et al.* 1996a,b). Impulsivity is generally considered deleterious to normative functioning. Nevertheless, genes for impulsivity can be maintained in the overall population in so far as they bestow fitness gains. Despite the apparent fitness costs associated with impulsivity, we assert that the benefits derived from impulsivity in various contexts may play a role to maintain the phenotypic expression of low CNS serotonin turnover.

One possible explanation to account for the heritable maintenance of low CSF 5-HIAA concentrations and its potential influence on alcohol consumption in the overall population derives from the male migration data, which revealed that males with relatively low concentrations of CSF 5-HIAA transfer from their natal groups at a young age (Mehlman *et al.* 1995). While these males tend to be less mature it is possible that, with the motivating influence of sexually active females, these impulsive males with low CSF 5-HIAA concentrations migrate early to seek sexual opportunities. While impulsivity may lead an animal to stepping in danger's way, 'nothing ventured, nothing gained' may be the plight of the excessively inhibited. In this context, inhibited males may be at a disadvantage when it comes to reproducing. Since inhibited males may be less likely to leave their natal group and to enter a new group, they may lose reproductive opportunities, as males who remain in their natal group are less likely to reproduce (Berard *et al.* 1993).

Furthermore, while an impulsive phenotype may appear deleterious, to the extent that it offers young migrating males quick and aggressive tendencies, low CSF 5-HIAA concentrations may serve an important function in survival. When they are not in social groups, adult male rhesus macaques often live and travel alone. Without the potential benefit of safety in numbers from group living, solitary males must fend for themselves. A tendency to act aggressively, driven by serotonergic activity, may offer a competitive advantage when faced with other solitary males. Thus, under some conditions, low CSF 5-HIAA concentrations may serve an important survivorship function.

Despite the reproductive advantage of males with relatively high concentrations of CSF 5-HIAA, by examining the ages of sires differing in concentrations of CSF 5-HIAA an interesting result emerged (Gerald *et al.* 2001). Independent of serotonin functioning, older males were on average more likely to reproduce. Males with higher CSF 5-HIAA who reproduced successfully were also more likely to be older than their competing group mates who did not successfully reproduce. By contrast, among males reproducing with diminished serotonergic function, younger males were more likely to reproduce. This age difference between sires differing in serotonin turnover may be interpreted as a life-history strategy for males with a low CSF 5-HIAA phenotype. A

male with relatively high concentrations of CSF 5-HIAA may have the skills and opportunities to cultivate relationships with females which can translate to higher reproductive success (Mehlman *et al.* 1997; but see Manson 1994a). Furthermore, as these males also live longer than males with lower CSF 5-HIAA concentrations they may have, on average, more reproductive years to live, to enhance their relative reproductive success even further. Impulsivity can increase the risk of premature mortality, thereby curtailing the reproductive career of a male with low CSF 5-HIAA concentrations. However, early transfers may provide males with low concentrations of CSF 5-HIAA with reproductive opportunities at a younger age. This finding that males with lower CSF 5-HIAA reproduce at a younger age suggests an interesting reproductive strategy. They may live a *live fast, die young* strategy. Reduced serotonergic activity may offer fitness gains to individuals who impulsively seek furtive mating opportunities. While 'sneaky' copulations can lead individuals to risk retaliation from high social ranking individuals (Manson 1994b), this strategy may prove adaptive in so far as these individuals reproduce successfully, especially if they reproduce at a high rate earlier in life, a possibility that we are currently testing.

Borrowing from antagonistic pleiotropy theory (Williams 1957), while placing individuals at a disadvantage later in life, natural selection may favor relatively low concentrations of CSF 5-HIAA because of the early beneficial effects that it confers. Selection can maintain such genes because by the time the gene exerts its damage, its bearers will already have reproduced more than other individuals. Population genetic models of evolution in age-structured populations demonstrate that the force of natural selection declines with age. Specifically, alleles, which act late in life, affect reproductive success less strongly and thereby experience a weaker selective pressure than alleles acting early in life. Thus, it is possible that under some conditions, selection may favor genes for impulsivity, which can act to increase early fertility at the expense of later survival.

Newlin (1999) postulates that an individual may seek acute benefits of alcohol, which act to boost a 'self perceived survival ability and reproductive fitness', as alcohol falsely offers individuals feelings related to enhanced survivorship and reproductive success (Nesse & Berridge 1997). Cloninger predicted that on average Type 2 alcoholics would be more motivated than the norm to seek reward and reinforcement. In addition to inhibiting aggressive impulses, several studies suggest that boosted serotonergic function may act to inhibit a variety of urges, including seeking reinforcement. Indeed, serotonin-acting drugs are well known to inhibit food intake and sexual activity (Gorzalka *et al.* 1990; Hull & Lorrain 1999; Leibowitz & Alexander 1998). Data from animal studies indicate that 5HT may control impulses related to obtaining reinforcement. For example, pharmacologically reducing CNS 5HT activity in rodents increases the frequency of performing a response for a reward despite the threat of punishment for responding (Gleeson *et al.* 1989; Miczek *et al.* 1989; reviewed in: Soubrié 1986). Based on such postulates, it could be hypothesized that pharmacological agents that boost serotonergic activity would decrease alcohol consumption. Studies show this is true in both rodents and non-human primates (Gill & Amit 1989; McBride *et al.* 1989; Higley *et al.* 1998). Some clinical studies show that selective serotonin reuptake inhibitors (SSRIs) decrease alcohol preference and consumption (Gorelick 1989; Gorelick & Paredes 1992; Naranjo & Kadlec 1990).

Somewhat surprisingly, however, in one clinical study assessing the effects of the SSRI sertraline on alcohol consumption, sertraline reduced alcohol consumption more in the anxiety-laden Type 1 alcoholics than in Type 2 alcoholics (Pettinati *et al.* 2000). This may be in part because sertraline reduces both anxiety aggression. In our study of alcohol-consuming non-human primates, alcohol consumption was correlated with individual subjects' anxiety levels (Higley *et al.* 1998), and it reduced both aggression and anxiety-like behaviors. Nevertheless, consistent with its action on impulsivity, sertraline only reduced consumption in the monkeys who showed binge-like high alcohol consumption patterns.

In a recent study, drinking outcomes that were associated with Type 2 alcoholism were differentially improved by the selective serotonin receptor (5HT 3 receptor) antagonist ondansetron (Johnson *et al.* 2000). Thus there is parallel evidence that serotonin acts on urges that bring reinforcement and that when alcohol is available, subjects with low CSF 5-HIAA concentrations are more likely to use alcohol to excess. It should be noted, however, that not all novelty seekers are impulsive and many novelty seekers never have problems with alcohol. Similarly, impaired CNS serotonin functioning is not a biological guarantee that a subject will develop novelty seeking traits, act impulsively and ultimately develop alcohol problems. In his latest review of Type 1 and Type 2 alcoholism, Cloninger (1999) indicates that novelty seeking is not the same thing as antisocial personality, and that other traits must be present for a personality disorder to occur. For example, many novelty seekers develop a fully mature personality and novelty seeking is one aspect in the richness of their lives. In such cases, novelty seeking may perhaps represent an adaptive trait. Explorers may represent a group of individuals high in novelty seeking who benefited from the risks that they take.

If alcohol produces a false sense of enhanced fitness and if individuals with diminished serotonergic function are less likely to inhibit their urges when seeking reinforcement, together, this may account for why individuals who consume alcohol in excess possess relatively low concentrations of CSF 5-HIAA. This also may explain, in part, what mechanisms can maintain low CNS serotonin functioning in a population. During times of resource scarcity, where there is intense local resource competition, impulsivity, with a highly motivated desire for reinforcers such as food, could offer an individual with impaired serotonergic function an edge in competing for resources, because they are more likely to take risks which have an adaptive pay-off. In industrialized societies where alcohol is widely available, this same trait in individuals has deleterious effects, producing high alcohol consumption and increasing the probability of relapse.

CONCLUSION

In this paper, we have emphasized the significance of phenotypic traits of low CNS serotonin activity such as impulsivity in predicting excessive alcohol consumption and alcohol dependence. Both humans and non-human primates with diminished concentrations of CSF 5-HIAA appear to display dramatic behavioral differences from individuals with higher concentrations of CSF 5-HIAA. This variability in behavior also appears to lead to different fitness consequences. Given that the range of concentrations of CSF 5-HIAA varies across populations, it is important to stress that this phenotypic dichotomy is a heuristic to reflect relative measures. Furthermore, while we have focused on serotonin there are other neurotransmitters and factors that contribute to alcohol dependence and alcoholism.

Connecting the findings from non-human primates to patterns of excessive alcohol dependence and alcoholism in humans begs the question: what can we learn from these studies of non-human primates? Both continuous pursuit and the unflagging inhibition of impulsive and aggressive behaviors may present negative fitness consequences in some environments and situations, but it may have a reproductive pay-off in other conditions. In other words, while impulsivity may ultimately lead individuals to their untimely death in some environments, impulsivity may offer individuals selective advantages such as food access and mating opportunities to reproduce in other conditions. However, in environments where alcohol is accessible, impulsivity may at the same time render individuals vulnerable to abusing alcohol. Applying a Darwinian medicine approach to identify the specific behavioral and neuroendocrine underpinnings of alcohol dependence may reveal clues regarding the evolution and etiology of alcoholism.

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