Reward Deficiency Syndrome

Addictive, impulsive and compulsive disorders—including alcoholism, attention-deficit disorder, drug abuse and food bingeing—may have a common genetic basis

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In 1990 one of us published with his colleagues a paper suggesting that a specific genetic anomaly was linked to alcoholism (Blum et al. 1990). Unfortunately it was often erroneously reported that they had found the "alcoholism gene," implying that there is a one-to-one relation between a gene and a specific behavior. Such misinterpretations are common—readers may recall accounts of an "obesity gene," or a "personality gene." Needless to say, there is no such thing as a specific gene for alcoholism, obesity or a particular type of personality. However, it would be naive to assert the opposite, that these aspects of human behavior are not associated with any particular genes. Rather the issue at hand is to understand how certain genes and behavioral traits are connected.

In the past five years we have pursued the association between certain genes and various behavioral disorders. In molecular genetics, an association refers to a statistically significant incidence of a genetic variant (an allele) among genetically unrelated individuals with a particular disease or condition, compared to a control population. In the course of our work we discovered that the genetic anomaly previously found to be associated with alcoholism is also found with increased frequency among people with other addictive, compulsive or impulsive disorders. The list is long and remarkable—it comprises alcoholism, substance abuse, smoking, compulsive overeating and obesity, attention-deficit disorder, Tourette's syndrome and pathological gambling.

We believe that these disorders are linked by a common biological substrate, a "hard-wired" system in the brain (consisting of cells and signaling molecules) that provides pleasure in the process of rewarding certain behavior. Consider how people respond positively to safety, warmth and a full stomach. If these needs are threatened or are not being met, we experience discomfort and anxiety. An inborn chemical imbalance that alters the intercellular signaling in the brain's reward process could supplant an individual's feeling of well being with anxiety, anger or a craving for a substance that can alleviate the negative emotions. This chemical imbalance manifests itself as one or more behavioral disorders for which one of us (Blum) has coined the term "reward deficiency syndrome."

This syndrome involves a form of sensory deprivation of the brain's pleasure mechanisms. It can be manifested in relatively mild or severe forms that follow as a consequence of an individual's biochemical inability to derive reward from ordinary, everyday activities. We believe that we have discovered at least one genetic variant that leads to an alteration in the reward pathways of the brain. It is a variant form of the gene for the dopamine D2 receptor, called the A1 allele. This is the same genetic variant that we previously found to be associated with alcoholism. In this review we shall look at evidence suggesting that the A1 allele is also associated with a spectrum of impulsive, compulsive and addictive behaviors. The concept of a reward deficiency syndrome unites these disorders and may explain how simple genetic anomalies give rise to complex aberrant behavior.

The Biology of Reward

The pleasure and reward system in the brain was discovered by accident in 1954. The American psychologist James Olds was studying the rat brain's alerting process, when he mistakenly placed the electrodes in a part of the limbic system, a group of structures deep within the brain that are generally believed to play a role in emotions. When the brain was wired so that the animal could stimulate this area by pressing a lever, Olds found that the rats would press the lever almost nonstop, as many as 5,000 times an hour. The animals would stimulate themselves to the exclusion of everything else except sleep. They would even endure tremendous pain and hardship for an opportunity to press the lever. Olds had clearly found an area in the limbic system that provided a powerful reward for these animals.

Research on human subjects revealed that the electrical stimulation of some areas of the brain (the medial hypothalamus) produced a feeling of quasi-or-
Figure 1. Alcoholism is partly a consequence of a genetically based deficiency that affects the pleasure and reward areas of the brain, according to the authors. The deficient genes code for receptors and transporters for the neurotransmitter dopamine. Recent studies suggest that the same genetic variants are associated with a spectrum of disorders involving compulsive, impulsive and addictive behavior, which comprise a reward deficiency syndrome. The authors propose a neurobiological mechanism to account for the manifestation of the syndrome and suggest possibilities for treatment.

gasmic sexual arousal (Olds and Olds 1969). If certain other areas of the brain were stimulated, an individual experienced a type of light-headedness that banished negative thoughts. These discoveries demonstrated that pleasure is a distinct neurological function that is linked to a complex reward and reinforcement system (Hall, Bloom and Olds 1977).

During the past several decades research on the biological basis of chemical dependency has been able to establish some of the brain regions and neurotransmitters involved in reward. In particular it appears that the dependence on alcohol, opiates and cocaine relies on a common set of biochemical mechanisms (Cloninger 1983, Blum et al. 1989). A neuronal circuit deep in the brain involving the limbic system and two regions called the nucleus accumbens and the globus pallidus appears to be critical in the expression of reward for people taking these drugs (Wise and Bozarth 1984). Although each substance of abuse appears to act on different parts of this circuit, the end result is the same: Dopamine is released in the nucleus accumbens and the hippocampus (Koob and Bloom 1988). Dopamine appears to be the primary neurotransmitter of reward at these reinforcement sites.

Although the system of neurotransmitters involved in the biology of reward is complex, at least three other neurotransmitters are known to be involved at several sites in the brain: serotonin in the hypothalamus, the enkephalins (opioid peptides) in the ventral tegmental area and the nucleus accumbens, and the inhibitory neurotransmitter GABA in the ventral tegmental area and the nucleus accumbens (Stein and Belluzzi 1986, Blum 1989). Interestingly, the glucose receptor is an important link between the serotonergic system and the opioid peptides in the hypothalamus. An alternative reward pathway involves the release of norepinephrine in the hippocampus from neuronal fibers that originate in the locus coeruleus.

In a normal person, these neurotransmitters work together in a cascade of excitation or inhibition—between complex stimuli and complex responses—leading to a feeling of well being, the ultimate reward (Cloninger 1983, Stein and Belluzzi 1986, Blum and Koslowski 1990). In the
cascade theory of reward, a disruption of these intercellular interactions results in anxiety, anger and other “bad feelings” or in a craving for a substance that alleviates these negative emotions. Alcohol, for example, is known to activate the norepinephrine system in the limbic circuitry through an intercellular cascade that includes serotonin, opioid peptides and dopamine. Alcohol may also act directly through the production of neurotransmitters that interact with opioid receptors or with dopaminergic systems (Alvaksinen et al. 1984; Blum and Kozlowski 1990). In the cascade theory of reward, genetic anomalies, prolonged stress or long-term abuse of alcohol can lead to a self-sustaining pattern of abnormal cravings in both animals and human beings.

Support for the cascade theory can be derived from a series of experiments on strains of rats that prefer alcohol to water. Compared to normal rats, the alcohol-preferring rats have fewer serotonin neurons in the hypothalamus, higher levels of enkephalin in the hypothalamus (because less is released), more GABA neurons in the nucleus accumbens (which inhibit the release of dopamine), a reduced supply of dopamine in the nucleus accumbens and a lower density of dopamine D2 receptors in certain areas of the limbic system (Russell, Linan and Taljaard 1988; McBride et al. 1990; Zhou et al. 1990; McBride et al. 1993).

These studies suggest a four-part cascade in which there is a reduction in the amount of dopamine released in a key reward area in the alcohol-prefering rats. The administration of substances that increase the supply of serotonin at the synapse or that directly stimulate dopamine D2 receptors reduce craving for alcohol (McBride et al. 1993). For example, D2 receptor agonists reduce the intake of alcohol among rats that prefer alcohol, whereas D2 dopamine-receptor antagonist increase the drinking of alcohol in these inbred animals (Dyr et al. 1993).

Support for the cascade theory of alcoholism in human beings is found in a series of clinical trials. When amino-acid precursors of certain neurotransmitters (serotonin and dopamine) and a drug that promotes enkephalin activity were given to alcoholic subjects, the individuals experienced fewer cravings for alcohol, a reduced incidence of stress, an increased likelihood of recovery and a reduction in relapse rates (Brown et al. 1990; Blum and Trachtenberg 1988; Blum,
Furthermore, the notion that dopamine is the "final common pathway" for drugs such as cocaine, morphine and alcohol is supported by recent studies by Jordi Ortiz and his associates at Yale University School of Medicine and the University of Connecticut Health Services Center. These authors demonstrated that the chronic use of cocaine, morphine or alcohol results in several biochemical adaptations in the limbic dopamine system. They suggest that these adaptations may result in changes in the structural and functional properties of the dopaminergic system.

We believe that the biological substrates of reward that underlie the addiction to alcohol and other drugs are also the basis for impulsive, compulsive and addictive disorders comprising the reward deficiency syndrome.

**Alcoholism and Genes**

An alteration in any of the genes that are involved in the expression of the molecules in the reward cascade might predispose an individual to alcoholism. Indeed, the evidence for a genetic basis to alcoholism has accumulated steadily over the past five decades. The earliest report comes from studies of laboratory mice by the American psychologist L. Mirone in 1952. Mirone found that, given a choice, certain mice preferred alcohol to water. Gerald McLearn at the University of California at Berkeley took this a step farther by producing an inbred mouse (the C57 strain) that had a marked preference for alcohol. The alcohol-preferring C57 strain bred true through successive generations—it was the first clear indication that alcoholism has a genetic basis (McLearn and Rodgers 1959).

The first evidence that alcoholism has a genetic basis in human beings came in 1972 when scientists at the Washington University School of Medicine in St. Louis found that adopted children whose biological parents were alcoholics were more likely to have a drinking problem than those born to nonalcoholic parents (Schuckit, Goodwin and Winokur 1972). In 1973 Goodwin and Winokur, working at the Psykologisk Institut in Copenhagen, studied 5,483 men in Denmark who had been adopted in early childhood. They found that the sons born to alcoholic fathers were three times more likely to become alcoholic than the sons of nonalcoholic fathers.

![Figure 4. Reward cascade in the limbic system consists of excitatory (blue) and inhibitory (red) connections between neurons that are modulated by neurotransmitters. The activation of the dopamine D2 receptor (green) by dopamine on the cell membranes of neurons in the nucleus accumbens and the hippocampus is hypothesized by the authors to be the "final common pathway" of the reward cascade. If the activity of the dopamine D2 receptor is deficient, the activity of neurons in the nucleus accumbens and the hippocampus is decreased, and the individual experiences unpleasant emotions or cravings for substances that can provide temporary relief by releasing dopamine. Alcohol, cocaine and nicotine are known to promote the release of dopamine in the brain. A simplified version of the cascade is presented here. Disorders of the cells and molecules in the "upstream" part of the cascade may also disrupt the normal activity of the reward system. The cascade begins with the excitatory activity of serotonin-releasing neurons in the hypothalamus. This causes the release of the opioid peptide met-enkephalin in the ventral tegmental area, which inhibits the activity of neurons that release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The disinhibition of dopamine-containing neurons in the ventral tegmental area allows them to release dopamine in the nucleus accumbens and in certain parts of the hippocampus, permitting the completion of the cascade. (Illustration by Robert L. Brown.)](image-url)
two years we compared eight genetic markers associated with various neurotransmitters (including serotonin, endogenous opioids, GABA, transferrin, acetylcholine, alcohol dehydrogenase and aldehyde dehydrogenase). In each instance we failed to find a direct association between the genetic markers and alcoholism.

The opportunity to investigate a ninth genetic marker arose after Olivier Civelli of the Vollum Institute at Oregon University cloned and sequenced the gene for one form of the dopamine D₃ receptor. The D₂ receptor is one of at least five physiologically distinct dopamine receptors (D₁, D₂, D₃, D₄ and D₅) found on the synaptic membranes of neurons in the brain (Sibley and Monsma 1992). Previous studies had established that D₂ receptors are expressed in neurons within the cerebral cortex and the limbic system, including the nucleus accumbens, the amygdala and the hippocampus. Because these are the same areas of the brain (with the exception of the cortex) that are believed to be involved in the reward cascade, Civelli's work provided the opportunity to investigate an important molecular candidate for genetic aberrations among alcoholics.

The technique we used to distinguish between the D₂ receptor genes of alcoholics and those of nonalcoholics relies on the detection of restriction-fragment-length polymorphisms (RFLPs). This approach involves the use of DNA-cutting enzymes (restriction endonucleases) that cleave the DNA molecule at specific nucleotide sequences. If there are genetic differences between two individuals such that a restriction enzyme cuts their DNA along different points in (or near) a gene, the resulting fragments of their genes will be of different lengths. These differing fragments, or polymorphisms, are recognized by the use of a radiactively labeled DNA probe—in this case a short sequence of the D₂ receptor gene—that binds to a complementary DNA sequence on the fragments. Radiolabeled fragments of different lengths signify a difference in the cleavage sequence recognized by the restriction enzyme (Grandy et al. 1989).

The restriction enzyme (Tag 1) cuts the nucleotide sequence at a site just outside the coding region for the D₂ receptor gene. This produces the Tag 1A polymorphisms. To date there are four Tag 1A alleles known, the A₁, A₂, A₃ and A₄ alleles. The A₁ and A₂ alleles are rare, whereas the A₃ allele is found in nearly 75 percent of the general population and the A₁ allele in about 25 percent of the population.

In 1990 we used the Tag 1 enzyme to search for Tag 1A polymorphisms in the DNA extracted from the brains of deceased alcoholics and a control population of nonalcoholics. The results were striking: in our sample of 35 alcoholics we found that 69 percent had the A₁ allele and 31 percent had the A₃ allele. In 35 nonalcoholics we found that 20 percent had the A₁ allele and 80 percent had the A₃ allele.

Since our 1990 study, some laboratories have failed to find a connection between the A₁ allele and alcoholism. However, a review of their work shows that their samples were not limited to severe forms of alcoholism, which we believe to be an important distinguishing criterion. In our original study, over 70 percent of the alcoholics had cirrhosis of the liver, a disease suggestive of severe and chronic alcoholism. Moreover, the negative studies failed to adequately assess controls to eliminate alcoholism, drug abuse and other related “reward behaviors.” In this regard, Katherine Neiswanger and Shirley Hill of the University of Pittsburgh recently found a strong association of the A₁ allele and alcoholism and suggested that early failures were the result of poor assessment of a true phenotype in the controls (Neiswanger, Kaplan and Hill 1995). To date, 14 independent laboratories have supported the finding that the A₁ allele
is a causative factor in severe forms of alcoholism, though perhaps not in milder forms (Blum and Noble 1994). These findings do not prove that the A1 allele of the dopamine D2 receptor gene is the only cause of severe alcoholism, but they are a powerful indication that the A1 allele is involved with alcoholism.

Further evidence for the role of biology in alcoholism comes from efforts to find electrophysiological markers that might indicate a predisposition to the addictive disorder. One such marker is the latency and the magnitude of the positive 300-millisecond (P300) wave, an indicator of the general electrical activity of the brain that is evoked by a specific stimulus such as a tone. It turns out that abnormalities in the electrical activity of the brain are evident in the young sons of alcoholic fathers. Their P300 waves are markedly reduced in amplitude compared to the P300 waves of the sons of nonalcoholic fathers. These results raised the question as to whether this deficit had been transferred from father to son and whether this deficit would predispose the son to substance abuse in the future (Begleiter, Porjesz, Bihari and Kissin 1984).

Experiments carried out since then have answered both questions. The alcoholic fathers had the same P300wave deficit seen in their sons, and the sons showed increased drug-seeking behaviors (including alcohol and nicotine) compared to the sons of nonalcoholic fathers. Moreover, the sons of alcoholic fathers had an atypical neurocognitive profile (Whipple, Parker and Noble 1988). It now appears that children with P300 abnormalities are more likely to abuse drugs and tobacco in later years (Berman, Whipple, Fitch and Noble 1993).

Remarkably, Noble and his colleagues found an association between the A1 allele and a prolonged latency of the P300 wave in children of alcoholics (Noble et al. 1994). Two of us (Blum and Braverman) extended this work and observed a similar correlation between the A1 allele and a prolonged P300 latency in a neuropsychiatric population. Subjects who are homozygous for the A1 allele showed significantly prolonged P300 latency compared to A1/A2 and A2/A2 carriers.

Drug Addiction and Smoking
Cocaine can bring intense, but temporary, pleasure to the user. The aftermath is addiction and severe psychological and physiological harm. Various psycho-
Although there is little known about the genetics of cocaine dependence, extensive scientific data are available on the effects of cocaine on brain chemistry. The current view is that the system that uses dopamine in the brain plays an important role in the pleasurable effects of cocaine. In animals, for example, the principal location where cocaine takes effect is the dopamine D<sub>2</sub> receptor gene on chromosome 11 (Koob and Bloom 1988). Recently George Koob and his colleagues of the Scripps Research Institute in La Jolla, California, found evidence suggesting that the dopamine D<sub>3</sub> receptor gene is a primary site of cocaine effects. The exact effect of cocaine on gene expression is unknown. However, we do know that D<sub>3</sub> receptors are decreased by chronic cocaine administration, and this may induce severe craving for cocaine and possibly cocaine dreams (Volkow et al. 1993).

A recent study by Ernest Noble of the University of California at Los Angeles and Blum found that about 52 percent of cocaine addicts have the A<sub>1</sub> allele of the dopamine D<sub>2</sub> receptor gene, compared to only 21 percent of nonaddicts. The prevalence of the A<sub>1</sub> allele increases significantly with three risk factors: parental alcoholism and drug abuse; the potency of the cocaine used by the addict (intranasal versus "crack" cocaine); and early-childhood deviant behavior, such as conduct disorder. In fact, if the cocaine addict has three of these risk factors, the prevalence of the A<sub>1</sub> allele rises to 87 percent. These findings suggest that childhood behavioral disorders may signal a genetic predisposition to drug or alcohol addiction (Noble et al. 1993).

A recent survey by the National Institute of Drug Abuse of five independent studies showed that the A<sub>1</sub> allele is also associated with polysubstance dependence (Uhl, Blum, Noble and Smith 1993). The A<sub>1</sub> allele is also associated with an increase in the amount of money spent for drugs by polysubstance-dependent people (Comings et al. 1994).

Although not viewed in the same light as the use of cocaine and other illicit drugs, cigarette smoking is another form of chemical addiction. Most attempts to stop smoking are associated with withdrawal symptoms typical of other chemical addictions. Although environmental factors may be important determinants of cigarette use, there is strong evidence that the acquisition of the smoking habit and its persistence are strongly influenced by hereditary factors. Of particular significance are studies of identical twins, which show that when one twin smokes, the other tends to smoke. This is not the case in nonidentical twins. In one twin study, Dorit Carmelli of the Stanford Research Insti-
tute and her associates examined a national sample of male twins who were veterans of World War II. A unique aspect of this study was that the twins were surveyed twice, once in 1967–68 and again 16 years later. This allowed an examination of genetic factors in all aspects of smoking—initiation, maintenance, and quitting. In general, whatever happened to one identical twin happened to the other—including the long-term pattern of not smoking, smoking and then quitting smoking. The absence of these similarities in a control population of nonidentical twins suggests a strong biogenetic component in smoking behavior (Swan et al. 1990).

Animal studies have suggested that the dopaminergic pathways of the brain may be involved. For example, the administration of nicotine to rodents disturbs dopamine metabolism in the reward centers of the brain to a greater extent than does the administration of alcohol.

With this in mind, one of us (Comings) and his colleagues investigated the incidence of the A1 allele in a population of Caucasian smokers. These smokers did not abuse alcohol or other drugs, but had made at least one unsuccessful attempt to stop smoking. It turned out that 48 percent of the smokers carried the A1 allele. The higher the prevalence of the A1 allele, the earlier had been the age of onset of smoking, the greater the amount of smoking and the greater the difficulty experienced in attempting to stop smoking. In another sample of Caucasian smokers and non-smokers, Noble and his colleagues found that the prevalence of the A1 allele was highest in current smokers, lower in those who had stopped smoking and lowest in those who had never smoked (Noble et al. 1994).

**Compulsive Bingeing and Gambling**

Obesity is a disease that comes in many forms. Once thought to be primarily environmental, it is now considered to have both genetic and environmental components. In a Swedish adoption study, for example, the weight of the adult adoptees was strongly related to the body-mass index of the biological parents and to the body-mass index of the adoptive parents. The links to both genetic and environmental factors were dramatic. Other studies of adoptees and twins suggest that heredity is an important contributor to the development of obesity, whereas childhood environ-
ment has little or no influence. Moreover, the distribution of fat around the body has also been found to have heritable elements. The inheritance of subcutaneous fat distribution is genetically separable from body fat stored in other compartments (among the visera in the abdomen, for example). It has been suggested that there is evidence for both single and multiple gene anomalies (Bouchard 1995).

Given the complex array of metabolic systems that contribute to overeating and obesity, it is not surprising that a number of neurochemical defects have been implicated. Indeed at least three such genes have been found: one associated with cholesterol production, one with fat transport and one related to insulin production (Bouchard 1995). The ob gene and its product the leptin protein have also been implicated in regulating long-term eating behavior (Zhang et al. 1994). Most recently another protein, glucagon-like peptide 1 (GLP-1) has been found to be involved in the regulation of short-term eating behavior (Turtun et al. 1996). The relationship between leptin and GLP-1 is not known. The ob gene may be involved in the animal’s selection of fat, but perhaps not in the ingestion of carbohydrates, which appears to be regulated by the dopaminergic system. It may be that the ob gene is functionally linked to the opioid peptidergic systems involved in reward.

Whatever the relation between these systems, the complexity of compulsive eating disorders suggests that more than one defective gene is involved. Indeed, the relation between compulsive overeating and drug and alcohol addiction is well documented (Krahn 1991, Newman and Gold 1992). Neurochemical studies show that pleasure-seeking behavior is a common denominator of addiction to alcohol, drugs and carbohydrates (Blum et al. 1990). Alcohol, drugs and carbohydrates all cause the release of dopamine in the primary reward area of the brain, the nucleus accumbens. Although the precise localization and specificity of the pleasure-inducing properties of alcohol, drugs and food are still debated, there is general agreement that they work through the dopaminergic pathways of the brain. Other studies suggest the involvement of at least three other neurotransmitters: serotonin, GABA and the opioid peptides.

Variants of the dopamine D2 receptor gene appear to be risk factors in obesity. The A1 allele was present in 45 percent of obese subjects as compared to 19 percent of nonobese subjects (Noble, Noble and Ritchie 1994). Furthermore, the A1 allele was not associated with a number of other metabolic and cardiovascular risks, including elevated levels of cholesterol and high blood pressure. In contrast, when the subject’s profile included factors such as parental obesity, a later onset of obesity and carbohydrate preference, the prevalence of the A1 allele rose to 85 percent. More recently another study found a significant association between genetic variants of the D2 receptor and obese subjects (Comings et al. 1993).

There is also an increased prevalence of the A1 allele in obese subjects who have severe alcohol and drug dependence (Blum et al. 1996a). When obesity, alcoholism and drug addiction were found in a patient, the incidence of the A1 allele rose to 82 percent. In contrast, the allele had an incidence of zero percent in nonobese patients who were also not substance abusers and did not have a family history of substance abuse. The presence of the dopamine D2 receptor gene variants increases the risk of obesity and related behaviors.

Pathological gambling—in which an individual becomes obsessed with the act of risking money or possessions for greater “payoffs”—occurs at a rate of less than two percent in the general population. Although it is the most socially acceptable of the behavioral addictions, pathological gambling has many affinities to alcohol and drug abuse. Clinicians have remarked on the similarity between the aroused euphoric state of the gambler and the “high” of the cocaine addict or substance abuser. Pathological gamblers express a distinct craving for the “feel” of gambling; they develop tolerance in that they need to take greater risks and make larger bets to reach a desired level of excitement, and they experience withdrawal-like symptoms (anxiety and irritability) when no “action” is available (Volberg and Steadman 1988). Indeed, there is a typical course of progression through four stages of the compulsive-gambling syndrome: winning, losing, desperation and hopelessness—a series not uncommon to other addictive behaviors.

Might the dopamine pathways in the brain be involved with pathological gambling? A recent study of Caucasian pathological gamblers found that 50.9 percent carried the A1 allele of the dopamine D2 receptor (Comings et al. 1996b). The more severe the gambling problem, the more likely it was that the individual was a carrier of the A1 allele. Finally, in a population of males with drug problems who were also pathological gamblers the incidence of the A1 allele rose to 76 percent.

Attention-Deficit Disorder
This disorder is most commonly found among school-age boys, who are at least four times more likely to express the

![Figure 11](image-url) Likelihood of carrying the A1 allele increases as the number of risk factors increases among cocaine-dependent people. Three risk factors are especially significant: parental alcoholism and drug abuse, the potency of the cocaine used by the addict (intranasal versus “crack” cocaine), and early childhood deviant behavior, such as conduct disorder. The study included 49 subjects (Noble, Blum and Khalsa 1993).
Figure 12. Differences in the density of dopamine D₂ receptors in the brain of a normal subject (top row) and the brain of a cocaine abuser one month (middle row) and 4 months (bottom row) after withdrawal are revealed by the binding of a radioactive tracer in these positron-emission-tomography (PET) scans. The long-term decrease of dopamine D₂ receptors in the cocaine abuser suggests that the lower activity of these receptors is a chronic condition. The decrease in the dopamine D₂ receptors may contribute to the individual’s craving for cocaine. Here the density of the dopamine D₂ receptors is shown at four different levels in the basal ganglia. (Photograph courtesy of Nora Volkow, Brookhaven National Laboratory. Used with permission from Synapse © 1993, Wiley-Liss, Inc.)

These children have difficulty applying themselves to tasks that require a sustained mental effort; they can be easily distracted, they may have difficulty remaining seated without fidgeting and they may impulsively blurt out answers in the classroom or fail to wait their turn. Although normal children occasionally display these symptoms, attention-deficit disorder is diagnosed when the behavior’s persistence and severity impedes the child’s social development and education.

Early speculation about the causes of attention-deficit disorder focused on potential sources of stress within the child’s family, including marital discord, poor parenting, psychiatric illness, alcoholism or drug abuse. It has become progressively clear, however, that stress within the family cannot explain the incidence of the disorder. There is now little doubt that the disorder has a genetic basis.

Evidence in support of this notion comes from patterns of inheritance in the families of children with the disorder and from studies of identical twins. For example, consider instances in which full siblings and half-siblings (who have only half of the genetic identity of full siblings) are both raised in the same family environment. If the behavioral symptoms of attention-deficit disorder were “learned” in the family, then the incidence of the disorder should be the same for full siblings as it is for half-siblings. In fact, half-siblings of children with attention-deficit disorder have a significantly lower frequency of the disorder than full siblings (Lopez 1965). In another study, investigators found that if one identical twin had attention-deficit disorder, there was a 100 percent probability that the other also had the disorder. In contrast, the incidence of concordance among non-identical twins was only 17 percent. This result has been supported by two other independent studies of identical twins (Willerman 1973). Finally, one of us (Comings) and his coworkers found that the A₁ allele of the dopamine D₂ receptor gene was present in 49 percent of the children with attention-deficit disorder compared to only 27 percent of the controls (Comings et al. 1991).

Some other recent work has linked attention-deficit disorder with another impulsive disorder: Tourette syndrome. More than 100 years ago the French neurologist Gilles de la Tourette described a condition that was characterized by compulsive swearing, multiple muscle tics and loud noises. He found that the disorder usually appeared in children between 7 to 10 years old, with boys more likely to be affected than
Figure 13. Effectiveness of dopamine agonists (brown) in the treatment of certain forms of alcoholism may depend on the individual’s genotype for the dopamine D₃ receptor gene. The authors propose that alcoholics who carry the A₁ allele are more likely to respond positively to treatment with a dopamine agonist (such as bromocriptine). However, if such individuals are treated with a placebo (beige) they are more likely to relapse into alcoholism. Alcoholics with the A₁/A₁ genotype do not respond to dopamine agonists (or to a placebo) because their alcoholism is not associated with the dopamine D₃ receptor. The authors suggest that the use of dopamine agonists to treat alcoholics with the A₁ allele initiates a feedback system that produces more dopamine receptors after a period of about six weeks.

girls. Tourette suggested that the condition might be inherited.

In the early 1980s one of us (Comings) and his colleagues studied 246 families in which at least one member of the family had Tourette disorder. The study indicated that virtually all cases of Tourette syndrome are genetic (Comings et al. 1991). Subsequent studies also found that there was a high incidence of impulsive, compulsive, addictive, mood and anxiety disorders on both sides of the affected individual’s family (Comings and Comings 1987). The A₁ allele was implicated in a recent report showing that nearly 45 percent of the people diagnosed with Tourette disorder carried the aberrant gene (Comings et al. 1991). Moreover, the A₁ allele had the highest incidence among people who had the severest manifestations of the disorder.

As mentioned earlier, Tourette syndrome appears to be tightly coupled to attention-deficit disorder. In studies of the two disorders, it was found that 50 to 80 percent of the people with Tourette syndrome also had attention-deficit disorder. Furthermore, an increased number of relatives of individuals with Tourette disorder also had attention-deficit/hyperactivity disorder (Knell and Comings 1993). It now appears that Tourette syndrome is a complex illness that may include attention-deficit disorder, conduct disorder, obsessive, compulsive and addictive disorders and other related disorders. The close coupling between these disorders has led one of us (Comings) to propose that Tourette syndrome is a severe form of attention-deficit disorder (Comings and Comings 1989; Comings 1995).

The high frequency of the A₁ allele among people with Tourette syndrome and attention-deficit disorder raises the question of whether other genes affecting dopaminergic function might also be involved in these disorders. Two others that have been considered are the gene for the enzyme dopamine B-hydroxylase, which converts dopamine to norepinephrine, and the gene for the dopamine transporter, which takes dopamine back into the presynaptic terminal after it is released into the synapse. In both cases, variant forms of these genes are associated with Tourette syndrome (Comings et al. 1996c). The abnormal dopamine B-hydroxylase gene (the “DBH Taj B1” allele) was further associated with learning disabilities, conduct disorder and substance abuse, whereas the variant of the dopamine transporter (the “10 repeat” allele) was also associated with alcohol abuse, depression and obsessive-compulsive disorder. This observation was supported by other work showing that the 10 repeat allele for the dopamine transporter gene was associated with attention-deficit/hyperactivity disorder (Cook et al. 1995). Moreover, elevated levels of the dopamine transporter mol-
we do not yet understand, carrying the A1 allele reduces the expression of the D2 gene compared to carrying the A2 allele. Perhaps a regulatory site for the D2 receptor gene is affected in A1 carriers.

Fewer numbers of dopamine D2 receptors in the brains of A1 allele carriers may translate into lower levels of dopaminergic activity in those parts of the brain involved in reward. A1 carriers may not be sufficiently rewarded by stimuli that A2 carriers find satisfying. This may translate into the persistent cravings or stimulus-seeking behavior of A1 carriers. Moreover, because dopamine is known to reduce stress, individuals who carry the A1 allele may have difficulty coping with the normal pressures of life. In response to stress or cravings, A1 carriers may turn to other substances or activities that release additional quantities of dopamine in an attempt to gain temporary relief. Alcohol, cocaine, marijuana, nicotine and carbohydrates (like chocolate) all cause the release of dopamine in the brain and bring about a temporary relief of craving. These substances can be used singly, in combination or to some extent interchangeably.

Although we believe that the gene for the D2 receptor plays a critical role in reward deficiency syndrome, other genes (such as the dopamine transporter gene) are undoubtedly involved in the different manifestations of the syndrome. Scientists from Israel and the National Institute of Mental Health recently showed that a genetic variation of the dopamine D2 receptor gene is associated with people who are novelty (or sensation) seekers (Ebstein et al. 1996 and Benjamin et al. 1996). Both studies set out to test the hypothesis advanced by Robert Cloninger of Washington University that novelty-seeking behavior is modulated by the way brain cells process dopamine. Richard Ebstein and his colleagues at the Herzog Memorial Hospital in Jerusalem found that novelty seekers—who tended to be compulsive, exploratory, fickle, excitable, quick-tempered and extravagant—were much more likely to have a longer version of the receptor gene than individuals who were not novelty seekers. Subjects with the shorter version of the gene scored lower on test of novelty seeking and tended to be reflective, rigid, loyal, stoic, slow-tempered and frugal. Jonathan Benjamin and his colleagues found similar results in their sample of 315 American subjects.

The work from the laboratories of Benjamin and Ebstein provide support of the earlier work of Susan George and associates at the University of Toronto who found a strong association between variants of the D3 gene and alcoholism and nicotine dependence. The D2 receptor gene and the D4 receptor gene have fairly similar nucleotide sequences and may have similar physiological functions. In this respect, it is intriguing that investigators at the University of California, Los Angeles found an association between the A1 allele and individuals who were classified as “sensation seekers” and were characterized by agitation, impulsivity, excitability and a “hot temper” (Compton et al. unpublished). All of these studies further support a connection between the reward deficiency syndrome and the dopaminergic system.

Treatment

In the United States alone there are 18 million alcoholics, 28 million children of alcoholics, 6 million cocaine addicts, 14.9 million people who abuse other substances, 25 million people addicted to nicotine, 54 million people who are at least 20 percent overweight, 3.5 million school-age children with attention-deficit disorder or Tourette syndrome, and about 448,000 compulsive gamblers. We believe that recognizing the role of dopamine and the D2 receptor in the manifestation of these addictions and disorders is the first step toward rational treatment for a devastating problem in our society.

There is reason to believe that a pharmacological approach could help people with reward deficiency syndrome. It is tempting to speculate that the pharmacological sensitivity of alcoholics to dopamine agonists (bromocriptine, bupropion and n-propyl-nor-apomorphine) may be partly determined by the individual’s D2 genotype. We predict that A1 carriers should be pharmacologically more responsive to D2 agonists, especially in the treatment of alcoholics or stimulant-dependent people. At least one study has already shown that the

Figure 14. Reward deficiency syndrome comprises a spectrum of impulsive, compulsive, addictive and personality disorders that are based on a common genetic deficiency in the dopamine D2 receptor, according to the authors. A predictive model based on Bayes’s Theorem suggests that an individual who carries the A1 allele for the dopamine D2 receptor has a 74 percent chance of developing one of the disorders of the reward deficiency syndrome (Blum et al. 1996b). The type of disorder that is manifested by any particular individual is determined by other genetic and environmental factors, which are not yet fully understood.
direct microinjection of the D₂ agonist n-propylnor-apomorphine into the rat nucleus accumbens significantly suppresses the animal’s symptoms after the withdrawal of opiates (Harris and Aston-Jones, 1994).

A recent double-blind study demonstrates the utility of this approach in human subjects (Lawford et al. 1995). The D₂ agonist bromocriptine or a placebo was administered to alcoholics who were carriers of the A₁ allele (A₁/A₁ and A₁/A₂ genotypes) or who only carried the A₂ allele (A₂/A₂). The greatest improvement in the reduction of craving and anxiety was found among the A₁ carriers who were treated with bromocriptine. The attrition rate was highest among the A₁ carriers who were treated with the placebo.

These findings provide an important rationale for DNA testing to detect genetic variants for the D₂ receptor or other dopamine-related genetic variants in the tertiary treatment of alcoholism. Unlike certain other complex disorders, such as Alzheimer’s disease, the early identification and treatment of alcohol and drug abuse can occasionally alter the devastating course of these addictions. Consider the successes of self-help programs such as Alcoholics Anonymous and Narcotics Anonymous, psychopharmacological adjunctive therapy, neuroregulation or brain-wave training and electrophysiological stimulation. Identifying individuals with the A₁ allele offers the possibility of helping individuals before alcoholism or substance abuse affect their lives. We foresee the possibility for better treatment, new forms of prevention and the removal of the social stigma attached not only to alcoholism but also to related “reward-seeking” behaviors comprising the reward deficiency syndrome.

Bibliography


