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Perspectives on Reward Circuitry, Neurobiology, Genetics and Pathology: Dopamine and Addiction

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A conference on the neurobiology, genetics and pathology of reward systems was held at the Ritz Carlton hotel in San Francisco November 12-13th 2000. The conference chairpersons were Kenneth Blum, Ph.D. and Ernest Noble, Ph.D., M.D., scientific chairpersons were George Uhl, M.D., PhD and Nora Volkow, M.D, clinical chairpersons were: Eric Braverman, M.D. and David Smith, M.D. Nick Nolte served as spokesperson.

At this meeting, a large body of convergent data showed how scientists have now identified many psychological and psychopathological elements of reward. They have mapped many brain anatomic and neurochemical components that play large roles in reward processes. Recent studies document substantial genetic components for the substance abuse disorders that represent some of the best-studied pathological variants in reward system function. Several of these findings converge on the idea that many normal and pathological components of reward involve dopamine circuitry in the brain, making dopamine-influenced brain circuits and dopaminergic gene variants likely candidates to contribute to individual differences in reward system function. Although the meeting focused on these features, participants clearly outlined roles for serotonin, opiate, acetylcholine, amino acids and other brain neurotransmitters acting independently of or in even quite intimate inactions with dopaminergic systems.

Studies in animals focus attention on the A_{10} dopamine system whose cell bodies lie in the ventral tegmental area and whose axons project to forebrain areas including the nucleus accumbens and prefrontal cerebral cortex. This system's activation by abused substances, by novelty, and by natural rewards such as food and sexual behavior points toward its possible role as a common link for diverse rewards. Such a common link, in turn, provides a ready substrate for possible common pathological diatheses that could manifest themselves in several, plieotrophic, dysrewarded phenotypes. Blum and others have used the term "reward deficiency syndrome" to discuss parts of this concept.

Animal models have clearly demonstrated the roles that genetics can play. Studies of the natural strain variation and quantitative trait locus (QTL) studies have included studies of the Fisher and Lewis rat strains that differ in dopaminergic functions and in drug-reward related phenotypes including drug self administration. Transgenic mice with experimentally-induced alterations in several dopaminergic genes also display substantial differences in rewarded phenotypes. Such differences are especially well-documented for drug reward from psychostimulants. Rats whose DA DRD2 receptor levels are transiently enhanced by gene transfer techniques reduce alcohol consumption, suggesting a relative protective effect of higher DA D2 receptor density against drug self-administration.

Several lines of human evidence also point to roles for dopaminergic systems in reward. The ability of drugs of abuse to alter regional brain metabolism and to change the levels of dopamine available for occupying DRD2 receptors in limbic brain regions and nucleus accumbens can be studied *in vivo* with positron emission tomographic (PET). PET studies in pathological obesity and in cocaine, alcohol, heroin, marijuana, and methamphetamine- dependent individuals find low DA D2 receptors and low levels of frontal cortical and cingulate glucose utilization. These results support the idea that a deficit in available DA D2 receptors and low levels of reward circuit activities could facilitate addictive behaviors. Nonaddicted subjects with high DRD2 receptor levels often report unpleasant responses to psychostimulants, while subjects with low levels report pleasant responses. Addictive behaviors could thus be seen as homeostatic "attempts" to restore activities in these circuits toward more normal activities.

Additional human evidence for roles for variants in dopaminergic systems comes from studies of allelic variants at different dopaminergic gene loci in individuals with different patterns of reward system function. Alcoholics and polysubstance abusers have been especially studied, since classical genetic studies demonstrate relatively large, ca 50% overall genetic influences in these disorders. Consensus was strong that the genetic architectures underlying substance abuse, alcohol, and even other reward systems problems is likely to be polygenic; perhaps with no individual allele that contributes as much as 10% to overall vulnerability in the population. Although several scientific viewpoints on the roles of dopaminergic gene variants in human addictions now exist, meeting participants provided data that documented modest contributions of human DRD2 gene variants to addictions, consistent with a "polygene" role for DRD2 variants. Data from association with alcoholism, linkage with alcoholism, association with drug abuse, and preliminary evidence for correlation with PET and drug response data all supported such positive and limited roles for DRD2 allelic variation. Current data also suggests that many effects of such single loci, in members of the general population, are also likely to be pieotrophic. Allelic variants could be manifest in altered substance abuse vulnerability and also in a variety of other reward system problems and normal human variations, including personality and perhaps features that manifest as EEG/evoked potential variants. Initial DRD2 polymorphism data indicate tentative associations with aggression, anti-social personality, conduct disorder, social alienation/schizoid personality, social phobia/avoidant personality, attention deficit hyperactivity disorder, carbohydrate bingeing behavior, stress reactions, and visual evoked response and P300 amplitudes and latency. COMT and DRD4 human allelic variants have now been described in replicated studies to play polygenic roles, with models suggesting that each could contribute ca 4% to the genetic component of drug abuse. Initial data supports a DRD4 link with stress reactivity. The meeting's striking areas of convergent information, as documented above and in the accompanying abstracts, contrasted with several areas in which little current substantial data exists. Little evidence documented the large likely roles that environment and environment/gene interactions provide. Interactions between gene variation and susceptibility to neurotoxic exposures to abused drugs experienced *in utero* or during childhood and adolescence are of especial concern. Uncertainty is also raised by the modest and variable efficacies of current candidate treatment modalities, including antidrug vaccines or antisera, and even chiropractic or acupuncture approaches that suggests the need for more study of these modalities. Despite these gaps in information, however, the meeting highlighted the possibility that the current progress in studying the anatomy, neurobiology and genetics of dopaminergic systems in addictions may well provide models for studies of other neurotransmission systems in reward function and dysfunctions. All of these data are likely to provide us with clearer and more effective approaches to addictive and other pathologies of these circuits.