Neuro-chemical activation of brain reward meso-limbic circuitry is associated with relapse prevention and drug hunger: A hypothesis

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Abstract

Background: It is no surprise that it has taken over four decades to confirm and extend the crucial role of dopamine and related genes and gene deficits in the etiology of risk for drug dependence. Hundreds of studies, enabled by neuroscience neuroimaging and genetic advances, have been reported. While dopamine theories have been reported, confirmed, replicated and replicated again, changes have been slow to move from the bench to the bedside. Unlike penicillin used to target certain infections, addiction requires the consent, motivation and enthusiastic participation of the patient. Clearly, current treatment has not caught up with advances in the science. In-patient and out-patient treatment still relies on detoxification, abstinence and 12 step programs. Addiction is a chronic and relapsing disease. Addiction treatment can be reported as cures at 3 or 6 weeks, only to be clearly failures at 1 or 5 years. The logical standard of care should focus on detoxifying, stabilizing and returning the patient to the pre-loss of control or pre-addiction neurochemical state.

Method: Pre-clinical and clinical data on neurochemistry and neurogenetics of Substance Use Disorder (SUD) as it relates to both relapse and drug hunger has been reviewed.

Results: We are proposing herein that efforts to physiologically integrate known neural mechanisms with other psychotherapeutic treatment options to combat relapse should be encouraged. It is well known that after prolonged abstinence, recovered addicts are particularly vulnerable to relapse. Individuals who use their drug of choice after abstinence experience a powerful euphoria that can quickly precipitate a full-blown relapse. While a biological explanation for this conundrum has remained elusive, we hypothesize that this clinically observed “supersensitivity” might be the result of pre-morbid or state genetic hypodopaminergic polymorphisms.

Hypothesis: We are proposing that recent studies have indicated that genetic, personality and environmental factors are predictors of drug use in adolescents. Exploration of various treatment approaches for the most part reveal poor outcomes in terms of relapse prevention and continued drug hunger. The authors are proposing a new paradigm shift in residential, non-residential and aftercare involving the incorporation of genetic testing to identify risk alleles coupled with D2 receptor stimulation using neurodatogen amino acid precursor enkephalinase – catecholamine-methyltransferase (COMT) inhibition therapy. A natural but therapeutic nutraceutical formulation potentially induces DA release could cause the induction of D2-directed mRNA and proliferation of D2 receptors in the human. We further hypothesize that this proliferation of D2 receptors in turn will induce the attenuation of drug-like craving behavior. Finally, pharmacological therapies have had limited success because these powerful agents have focused on maintenance or interference with drug euphoria rather than correcting or compensating for pre-morbid dopamine system deficits These concepts await further confirmation via required neuroimaging studies.
Neuroscience and psychiatric genetics of addiction: comprehensive supporting overview

While the theories of a role of DA imbalances in the reward circuit have been proposed for several decades [2] we thought it was parsimonious to not only reiterate these ideas but expand these concepts especially coupled to treatment approaches. The brain reward circuitry, in particular, the dopaminergic system and the dopamine D2 receptor, has been implicated in reward mechanisms [3] especially as it related to drug-seeking behavior. The net effect of neurotransmitter interaction at the meso-limbic brain region induces “reward” when dopamine (DA) is released from the neuron at the nucleus accumbens (NAc) due to a drug like ethanol and interacts with a dopamine D2 receptor [4,5]. The “reward cascade” [5] involves the release of serotonin, which in turn, (at the hypothalamus) stimulates enkephalin, which in turn inhibits GABA at the substantia nigra, which in turn fine tunes the amount of DA released at the NAc or “reward site” [5–7] [see Fig. 1].

It is well known that under normal conditions in the NAc DA works to maintain our normal drives [8]. In fact, DA has come to be known as the “pleasure molecule” [5,9] and/or the “anti-stress molecule” [10]. When DA is released into the synapse, it stimulates a number of DA receptors (D1–D5), which results in increased feelings of well-being [11] and stress reduction [12]. Specifically acute ethanol administration increases striatal dopamine release and decreases cerebral glucose metabolism. The A1 allele of the ANKK1 Taq IA polymorphism is associated with lower dopaminergic tone and greater risk for alcoholism. In a pilot study, A1+ and A1– men (6/group) drank ethanol (0.75 ml/kg) or placebo beverages on each of 2 days. Positron emission tomography with F-18 fluorodeoxyglucose (FDG) was used to assess regional cerebral glucose metabolism as a measure of relative brain activity while participants performed a vigilance task. Significant findings were as follows: Ethanol decreased anxiety and fatigue in A1+ men but increased them in A1– men. Ethanol increased activity in the striatum and insula of A1+ men, but reduced activity in the anterior cingulate of A1– men. Reduced anxiety and fatigue in A1+ men were significantly associated with greater activity within a right orbitofrontal region previously implicated in cognitive control, and less activity in structures associated with anxiety (amygdala), fatigue (thalamus), and craving/reinforcement (striatum). In contrast, anxiety and fatigue changes were unrelated to brain activity in A1– men. Although these results require replication in a larger sample, alcohol-induced negative reinforcement may explain the greater risk for alcoholism associated with the A1 allele [12].

A consensus of the literature suggests that when there is a dysfunction in the brain reward circuitry or cascade, which could be caused by certain genetic variants (polygenic), especially in the DA system causing a hypodopaminergic trait as suggested by Gardner’ group [14], the brain of that person requires dopaminergic activation. Rats with electrodes implanted into the ventral tegmental nucleus (A10 cell body area) were treated with haloperidol for 3 weeks. Afterwards, the rats showed a 35% increase in self-stimulation rate, as compared to pre-drug control rates. This increase persisted for 3 weeks after drug withdrawal before returning to baseline rates. In addition, four rhesus monkeys with electrodes in the nucleus accumbens (one of the terminal projection areas of the A10 mesolimbic dopamine system) were given a three week treatment with haloperidol, after which all animals showed a significant, long-lasting decrease in self-stimulation threshold, as measured by a rate-independent reward paradigm. These studies suggest that blocking D2 sites results in DA receptor supersensitivity. This has important relevance for drug abuse relapse as we recently suggested in our paper on Deprivation-Amplification Relapse Therapy (DART) [15].

Dopaminergic deficit leads to multiple drug-seeking behavior [14,15]. This is because alcohol and psychostimulants like cocaine, heroin, marijuana, nicotine, and glucose all cause activation and neuronal release of brain DA, which in turn could help attenuate craving behavior especially in carriers of DRD2 A1 allele. Kirsch et al. [16] investigated the influence of the DRD2 Taq IA polymorphism and the selective D2 receptor agonist bromocriptine on the activation of the reward system by means of functional magnetic resonance imaging (fMRI). In a double-blind crossover study with 24 participants they found an increase of reward system activation from placebo to bromocriptine only in subjects carrying the A1 allele. Furthermore, only A1 carrier showed an increase of performance under bromocriptine. The results are interpreted as reflecting a specific sensitivity for dopamine agonists in persons carrying an A1 allele and may complement actual data and theories of the development of addiction disorders postulating a higher genetic risk for substance abuse in carrier of the A1 allele.

Further support of this notion is derived from the first report by Blum et al. [17] showing an association of the dopamine D2 TaqA1 allele with severe alcoholism and other work which found decreased D2 receptors in carriers of the A1 allele [18,19]. A recent multiple population study [20] from the National Institute on Alcohol Abuse and Alcoholism, supported the role of the D2 dopamine receptor gene (a haplotype block at 25.8 kb region) in Substance Use Disorder (SUD). Utilizing positron emission tomography (PET) others have found substantially lower levels of D2 receptors in alcohol and drug dependent subjects compared to non-dependent individuals [20]. Moreover, Volkow’s group found that subjects with high levels of D2 receptors did not like the effects of psychostimulants, while individuals with low D2 receptors enjoyed the effects of psychostimulants [21]. Subjects who liked the effects of methylphenidate had significantly lower D2 receptor levels (mean = 2.72 Bmax/Kd, SD = 0.3) than subjects who disliked its effects (mean = 3.16, SD = 0.3). Moreover, the higher the D2 levels found, the more intense were methylphenidate’s unpleasant
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