"Liking" and "wanting" linked to Reward Deficiency Syndrome (RDS): Hypothesizing differential responsivity in brain reward circuitry. Current Pharmaceutical Design

ARTICLE *in* CURRENT PHARMACEUTICAL DESIGN · JANUARY 2012

Impact Factor: 3.29 · DOI: 10.2174/138161212798919110 · Source: PubMed

4 AUTHORS, INCLUDING:

Kenneth Blum
University of Florida
301 PUBLICATIONS **5,321** CITATIONS
SEE PROFILE

Marlene Oscar-Berman
Boston University
170 PUBLICATIONS **3,304** CITATIONS
SEE PROFILE

Mark S Gold
Washington University in St. Louis
529 PUBLICATIONS **8,141** CITATIONS
SEE PROFILE

"Liking" and "Wanting" Linked to Reward Deficiency Syndrome (RDS): Hypothesizing Differential Responsivity in Brain Reward Circuitry

Kenneth Blum[a,*], Eliot Gardner[b], Marlene Oscar-Berman[c] and Mark Gold[a]

[a]*Department of Psychiatry and McKnight Brain Institute, University of Florida, Gainesville, FL, USA;* [b]*Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA;* [c]*Department of Veterans Affairs Healthcare System, and Boston University School of Medicine, Boston, MA, USA*

Abstract: In an attempt to resolve controversy regarding the causal contributions of mesolimbic dopamine (DA) systems to reward, we evaluate the three main competing explanatory categories: "liking,""learning," and "wanting" [1]. That is, DA may mediate (a) the hedonic impact of reward (liking), (b) learned predictions about rewarding effects (learning), or (c) the pursuit of rewards by attributing incentive salience to reward-related stimuli (wanting). We evaluate these hypotheses, especially as they relate to the Reward Deficiency Syndrome (RDS), and we find that the incentive salience or "wanting" hypothesis of DA function is supported by a majority of the evidence. Neuroimaging studies have shown that drugs of abuse, palatable foods, and anticipated behaviors such as sex and gaming affect brain regions involving reward circuitry, and may not be unidirectional. Drugs of abuse enhance DA signaling and sensitize mesolimbic mechanisms that evolved to attribute incentive salience to rewards. Addictive drugs have in common that they are voluntarily self-administered, they enhance (directly or indirectly) dopaminergic synaptic function in the nucleus accumbens (NAC), and they stimulate the functioning of brain reward circuitry (producing the "high" that drug users seek). Although originally believed simply to encode the set point of hedonic tone, these circuits now are believed to be functionally more complex, also encoding attention, reward expectancy, disconfirmation of reward expectancy, and incentive motivation. Elevated stress levels, together with polymorphisms of dopaminergic genes and other neurotransmitter genetic variants, may have a cumulative effect on vulnerability to addiction. The RDS model of etiology holds very well for a variety of chemical and behavioral addictions.

Keywords: Reward deficiency syndrome (RDS), neuroimaging, dopamine, "wanting" and "liking".

NEUROBIOLOGY OF REWARD DEFICIENCY SYNDROME

The term, Reward Deficiency Syndrome (RDS) was first coined by Blum *et al*. [2,3] and refers to an insufficiency of *usual feelings of satisfaction*. RDS results from a dysfunction in the "brain reward cascade," a complex interaction among neurotransmitters(primarily dopaminergic and opiodergic). Individuals who have a family history of alcoholism or other addictions may be born with a deficiency in the ability to produce or use these neurotransmitters. Exposure to prolonged periods of stress and alcohol or other substances can also lead to a corruption of the brain reward cascade function. In any case, when the neurotransmitters are low or are blocked from reaching the intended brain receptors, individuals often feel discomfort or pain. Behaviors resulting from a failure of the system that normally confers satisfaction include drug and alcohol abuse, overeating, heavy cigarette smoking, gambling, and hyperactivity. Blum and colleagues [2,3] have linked these disorders to a genetic defect, especially to dysfunction of dopamine receptors.

Dopamine (DA) is a powerful brain neurotransmitter that controls feelings of well being. It interacts with other powerful brain chemicals and neurotransmitters (e.g., serotonin and the opioids), each of which binds to specific receptors serving particular intercellular functions in the control of moods and cravings. The binding of the neurotransmitter to neuronal receptors triggers a reaction that is part of the cascade. Disruption of these intercellular cascades results in aberrant behavior in RDS, including addictions, impulsivity, and excessive risk taking.Thus, people who have a defect in the DRD2 DA receptor gene, lack a sufficient number of DA receptors in their brains to produce the brain reward cascade. In turn, this leads to RDS, including abnormal cravings and resultant anomalous conduct. RDS is a complicated concept linking reward seeking with genetic antecedents to dopaminergic traits, and important issues have been pursued by many since its inception in 1996.

RDS and Drug Abuse. According to Gardner [4], addictive drugs have in common that they are voluntarily self-administered by laboratory animals (usually avidly), and that they enhance the functioning of the reward circuitry of the brain (producing the 'high' that the drug user seeks). The core reward circuitry consists of an in-series circuit linking the ventral tegmental area (VTA), nucleus accumbens (NAc) and ventral pallidum *via* the medial forebrain bundle. Although originally believed simply to encode the set point of hedonic tone, these circuits now are believed to be functionally far more complex, also encoding attention, expectancy of reward, disconfirmation of reward expectancy, and incentive motivation. It has been speculated that hedonic dysregulation within these circuits may lead to addiction [5]. A second-stage dopaminergic component in this reward circuitry is the crucial addictive-drug-sensitive component. All addictive drugs also have in common that they enhance (directly or indirectly or even transsynaptically) dopaminergic reward synaptic function in the NAc [6]. For addictive drugs (e.g., opiates), tolerance to the euphoric effects develops with chronic use. Post-use dysphoria then comes to dominate reward circuit hedonic tone, and addicts no longer use drugs to get high, but simply to get back to normal (to "get straight"). Importantly, the brain circuits mediating pleasurable effects of addictive drugs are anatomically, neurophysiologically, and neurochemically different from those mediating physical dependence, and from those mediating craving and relapse. There are important genetic variations in vulnerability to drug addiction (e.g., variations in the gene encoding the dopamine D2 receptor — the DRD2 gene). Concomitantly, environmental factors such as stress (high stress combined with polymorphisms in dopaminergic genes, as well as other neurotransmitter genetic variants), and social defeat also alter brain-reward mechanisms in such a manner as to impart vulnerability to addiction [7]. Thus, elevated stress levels, together with polymorphisms of dopaminergic genes and other neurotransmitter genetic variants, may have a cumulative effect on vulnerability to addiction

*Address correspondence to this author at the Department of Psychiatry and McKnight Brain Institute, University of Florida, Gainesville, FL 32610, USA; Tel:/Fax: ??????????????????????????????;
E-mail: drd2gene@aol.com

1381-6128/11 $58.00+.00

[8]. A bio-psycho-social model of etiology holds very well for addiction. According to Conner *et al.* [9], addiction appears to correlate with a hypodopaminergic dysfunctional state within the reward circuitry of the brain, producing an addiction-prone personality.

Neuroimaging studies in humans add credence to this hypothesis. Credible evidence also implicates serotonergic, opioid, endocannabinoid, GABAergic, and glutamatergic mechanisms in addiction as denoted in the brain reward cascade hypothesis [10]. Critically, drug addiction progresses from occasional recreational use to impulsive use, to habitual compulsive use. This correlates with a progression from reward-driven to habit-driven drug-seeking behavior. This behavioral progression correlates with a neuroanatomical progression from ventral striatal/NAc to dorsal striatal control over drug-seeking behavior. The three classical sets of craving and relapse triggers are reexposure to addictive drugs, stress, and reexposure to environmental cues (people, places, and things) previously associated with drug-taking behavior. Drug-triggered relapse involves the NAc and the neurotransmitter DA, especially supersensitivity of DA receptors [11]. Stress-triggered relapse involves (a) the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the neurotransmitter corticotrophin-releasing factor, and (b) the lateral tegmental noradrenergic nuclei of the brain stem and the neurotransmitter norepinephrine. Cue-triggered relapse involves the basolateral nucleus of the amygdala, the hippocampus, and the neurotransmitter glutamate.

RDS and Overeating. Stice *et al.* [12-15] and others [16-19] found a substantial difference between dorsal striatal activation to receipt of palatable food and anticipated receipt of palatable food. Indeed, blunted response of the mesocorticolimbic system to receipt of chocolate milkshake predicted future weight gain [12,13], while elevated response of these same regions to a cue signaling impending receipt of milkshake (anticipation) also predicted future weight gain [13]. This observed difference is an example of the separation between hedonic "liking" and non-pleasurable motivational "wanting" that Berridge *et al.* [1,21-23] postulated

Interestingly, brain regions within the reward circuitry respond differentially in obese compared to lean probands, suggesting potential mechanisms for weight gain in humans [12]. Ng *et al.* [15] found that obese relative to lean women showed greater activation in somatosensory (Rolandic operculum), gustatory (frontal operculum), and reward valuation regions (amgydala, ventromedial prefrontal cortex) in response to intake and anticipated intake of milkshake versus tasteless solution, with little evidence of altered striatal activation. Obese relative to lean women also showed greater activation in the Rolandic operculum, frontal operculum, and ventromedial prefrontal cortex in response to isocaloric milkshakes labeled regular versus low fat. The authors suggested that hyperresponsivity of somatosensory, gustatory, and reward valuation brain loci may be related to overeating and that top-down processing influence reward encoding, which could further contribute to weight gain. The same investigators published convincing evidence that similar patterns of neural activation are implicated in addictive-like eating behavior and substance dependence: elevated activation in reward circuitry (dorsolateral prefrontal cortex and caudate) in response to food cues and reduced activation of inhibitory regions (lateral orbitofrontal cortex) in response to food intake [14].

Berridge [20] pointed out that brain reward systems mediate both motivational wanting and hedonic liking for food and drug rewards. In a recent article regarding brain mechanisms of hedonic liking, he and associates found cubic-millimeter hedonic hotspots in NAc and ventral pallidum for opioid amplification of sensory pleasure. The investigators also considered brain "wanting" or incentive salience systems [21,22] important to appetite, such as mesolimbic DA systems and opioid motivation circuits that extend beyond the hedonic hotspots. They considered potential ways in which wanting and liking might relate to overeating, suggesting that hedonic liking may have a different substrate than motivational non-hedonic wanting.

Peciña *et al.* [23], using a genetic mutant approach examined the consequences of elevated synaptic DA on: (a) spontaneous food and water intake, (b) incentive motivation and learning to obtain a palatable sweet reward in a runway task, and (c) affective liking reactions elicited by the taste of sucrose. A DA-transporter knockdown mutation that preserves only 10% of normal DA transporter, and therefore causes mutant mice to have 70% elevated levels of synaptic DA, was used to identify DA effects on food intake and reward. They found that hyperdopaminergic DA-transporter knockdown mutant mice had higher food and water intake. In a runway task, the animals demonstrated enhanced acquisition and greater incentive performance for a sweet reward. Hyperdopaminergic mutant mice left the start box more quickly than wild-type mice, required fewer trials to learn, paused less often in the runway, resisted distractions better, and proceeded more directly to the goal. Those observations suggested that hyperdopaminergic mutant mice attributed greater incentive salience (wanting) to a sweet reward in the runway test. But sucrose taste failed to elicit higher orofacial hedonic liking reactions from mutant mice in an affective taste reactivity test. These results indicated that chronically elevated extracellular DA facilitated wanting and learning of an incetive motivation task for a sweet reward, but elevated DA did not increase liking reactions to the hedonic impact of sweet tastes. In contrast, an increase in liking reactions was due to a hypodopaminergic or deficient trait possibly tied to polymorphic genes including the DRD2 A1 allele [24-26].

Treating RDS. Considering the hypothesis that treating RDS (e.g., drug addiction such as cocaine dependence) should include, at least in part, DA D2 agonist agonistic therapy, Peng *et al.* [27] evaluated the slow-onset long-acting monoamine reuptake inhibitor 31,345, a trans-aminotetralin analog, in a variety of addiction-related animal models. Their findings suggested that 31,345 is a cocaine-like slow-onset long-acting monoamine transporter inhibitor that may act as an agonist therapy for cocaine addiction. However, its pattern of action appeared to be significantly different from that of methadone used as an agonist opioid therapeutic modality. Peng *et al.* [27] suggested that ideal agonist substitutes for cocaine should fully emulate methadone's actions, that is, functionally antagonizing cocaine's action while blocking monoamine transporters to augment synaptic DA.

It terms of agonist therapy, it is important to realize that the baseline amount of DA receptors has predictability as to differential clinical outcomes in RDS. Cohen *et al.* [28] studied 10 subjects with an allele on the Taq1A DRD2 gene, which is associated with reduced DA receptor concentration and decreased neural responses to rewards (A1+ subjects). Subjects were scanned twice, once on placebo and once on cabergoline, a D2 receptor agonist. Consistent with an inverted-U relationship between the DRD2 polymorphism and drug effects, cabergoline increased neural reward responses in the medial orbitofrontal cortex, cingulate cortex, and striatum for A1+ subjects, but decreased reward responses in these regions for A1- subjects. In contrast, cabergoline decreased task performance and fronto-striatal connectivity in A1+ subjects but had the opposite effect in A1- subjects. The importance of possessing the DRD2 A1 allele in drug addiction and its treatment is in agreement with other studies by Lawford *et al.* [29] and by Blum *et al.* [30].

NEUROIMAGING AND NEURAL SUBSTRATES IN RDS BEHAVIORS

Ko *et al.* [31] identified the neural substrates of online gaming addiction through evaluation of the brain areas associated with the cue-induced gaming urge. Ten participants with online gaming addiction and 10 control subjects without online gaming addiction were tested. They were presented with gaming pictures and paired mosaic pictures while undergoing functional magnetic resonance

imaging (fMRI) scanning. The contrast in blood-oxygen-level dependent (BOLD) signals when viewing gaming pictures and when viewing mosaic pictures was used to evaluate the brain activations. In their experiment, right orbitofrontal cortex, right NAc, bilateral anterior cingulate, bilateral medial frontal cortex, right dorsolateral prefrontal cortex, and right caudate nucleus were activated in the addicted group in contrast to the control group. Activation of the above brain areas was positively correlated with self-reported gaming urge and recall of gaming experiences provoked by gaming pictures. The results demonstrated that the neural substrate of cue-induced gaming urge/craving in online gaming addiction is similar to that of cue-induced craving in substance dependence [32,33]. The authors noted a commonality between the brain regions contributing to craving in substance dependence and those involved in online gaming. Thus, the gaming urge/craving in online gaming addiction and craving in substance dependence might share the same neurobiological mechanism as defined by RDS.

In a study using fMRI to examine brain activation of the DA reward system during a gambling task, Cohen *et al*. [34] elegantly showed that individual differences in extraversion and the presence of the A1 allele on the DA D2 receptor gene predicted activation magnitudes. In two separate experiments, participants probabilistically received rewards either immediately following a behavioral response, or after a 7.5 s anticipation period. Although group activation maps revealed anticipation- and reward-related activations in the reward system, individual differences in extraversion and the presence of the D2 Taq1A allele predicted considerable inter-subject variability in the magnitudes of reward-related, but not anticipation-related, activations. The authors noted that their findings support a link between genetics, personality traits, and brain functioning.

Drug-related stimuli may induce craving in addicted patients, prompting drug-seeking behavior. In addition, studies have shown addicted patients to be less sensitive to pleasant, non-drug-related stimuli, indicating a deficiency in normal hedonic response or anhedonia [24]. Zijlstra *et al*. [35] found that the VTA was prominently involved in cue-induced opioid craving evoked by heroin-associated stimuli, in addition to the involvement of more anatomically-distributed mesolimbic and mesocortical pathways as identified in previous research. Their study provides additional evidence supporting the presence of reduced brain activation in heroin-dependent patients in response to pleasant non-drug-related stimuli, with greater activation to drug-cues.

INCENTIVE SALIENCE THEORY AND REWARD MECHANISMS

Obesity is characterized by the over-consumption of palatable/rewarding foods, reflecting an imbalance in the relative importance of hedonic versus homeostatic signals. The incentive salience hypothesis of food reward recognizes not only a hedonic/pleasure component (liking) but also an incentive motivation component (wanting). Most importantly, the neurobiological functioning of the brain's reward mechanisms is such that the mesoaccumbal DA system confers incentive motivation not only for natural rewards such as food but also for artificial rewards such as addictive drugs. This mesoaccumbal DA system receives and integrates information about the incentive/rewarding value of foods with information about metabolic status. According to Egecioglu *et al*. [36], problematic over-eating likely reflects a changing balance in the control exerted by hypothalamic versus reward circuits and/or an allostatic shift in the hedonic set point for food reward. These same investigators have shown that ghrelin activates the mesoaccumbal DA system and that central ghrelin signaling is required for reward from both addictive drugs (e.g., alcohol) and palatable foods.

Whereas ghrelin initially emerged as a stomach-derived hormone involved in energy balance, hunger, and meal initiation *via* action in food hunger-related hypothalamic circuits, it now seems clear that ghrelin also has a role in motivated reward-driven behaviors through activation of the so-called cholinergic-dopaminergic reward link [37,38]. According to Dickson *et al*. [38], this reward link comprises a DA projection from the VTA to the NAc together with a cholinergic input, arising primarily from the laterodorsal tegmental (LDTg) area. Moreover, ghrelin administration into the VTA or LDTg activates this cholinergic-dopaminergic reward link, suggesting that ghrelin may increase the incentive value of motivated behaviors such as reward-seeking (wanting or incentive motivation). Importantly, direct injection of ghrelin into the brain ventricles or into the VTA increases the consumption of rewarding foods as well as alcohol in mice and rats. Studies in rodents show beneficial effects of ghrelin receptor (GHS-R1A) antagonists to suppress the intake of palatable food, to reduce preference for caloric foods, to suppress food reward and motivated behavior for food [39]. Ghrelin receptor (GHS-R1A) antagonists also have been shown to reduce alcohol consumption, suppress reward induced by alcohol, cocaine, and amphetamine. Further, variations in the GHS-R1A and pro-ghrelin genes have been associated with high alcohol consumption, smoking, and increased weight gain in alcohol dependent individuals, as well as with bulimia nervosa and obesity [40]. We suggest that these findings with ghrelin antagonists and related genes affect multiple addictive behaviors as predicted by RDS theory.

Work on salient bio-behavior has recently emerged from many laboratories. Davis *et al*. [41] suggested that obesity research suffers from an over-inclusion paradigm whereby all participants with a body mass index beyond a certain cutoff value (e.g., 30) are typically combined in a single group and compared to those of normal weight. They examined genetic and psychological indicators of hedonic eating in obese adults and binge eating disorder (BED). Their analyses focused on DA and opioid genetic markers because of their conjoint association with the functioning of brain reward mechanisms. Three functional polymorphisms related to the D2 receptor (DRD2) gene, as well as the functional A118G polymorphism of the mu-opioid receptor (OPRM1) gene were targeted. They found that significantly more obese controls had the loss-of-function A1 allele of Taq1A compared to their BED counterparts, whereas the gain-of-function G allele of A118G occurred with greater frequency in the BED group. A significant gene-gene combination X2 analysis also indicated that of those participants with the gain-gain genotype (G+ and A1), 80% were in the BED group whereas only 35% with the loss-loss genotype (G- and A1+) were in this group. BED subjects had significantly higher scores on a self-report measure of hedonic eating. Their findings may suggest that BED is a biologically based subtype of obesity or RDS, and that being prone to binge eating may be influenced by a hyper-reactivity to the hedonic properties of food — a predisposition that according to Davis *et al*. [41] is easily exploited in our current environment with its highly visible and easily accessible surfeit of sweet and fatty foods. Their conclusion that DA is for "wanting" and opioids are for "liking" may be too simplistic. It is important to realize that neurotransmitter action is a progressive cumulative interactive cascade of events and that no one single-nucleotide polymorphism (SNP) nor one single neurotransmitter provides such distinctive effects.

RELAPSE AND DA SUPER-SENSITIVITY AT RECEPTORS

In an earlier paper on deprivation-amplification relapse therapy (DART) [11], we postulated that relapse to drugs of abuse and other addictions may be due to DA D2 receptor super-sensitivity. Specifically, although carriers of the A1/A2 genotype may have reduced numbers of D2 receptors but normal amounts of presynaptic DA, when they gamble(an activity that involves anticipation of reward), they may be subjected to excessive release of DA. Interestingly, different cues and/or substances have been associated with different amounts of NAc DA release. For example, food caused a 6% release of DA, music a 9% release, and cocaine a 22% release

[42]. Food also produced a blunted striatal response to palatable food consumption in women who gained weight over short period of time relative to weight-stable women [12]. Gambling associated with aberrant DA genetics [43], produced a hypersensitive response [44]. We conjecture that the stress associated with gambling produces a dramatic increase in release of DA into the synapse [45], but that food fails to produce that degree of DA flooding.

Blum *et al*. [11] noted that a super sensitivity might exist even in DRD2 A1 positive subjects with reduced (30-40%) D2 receptors. This super sensitivity may be due to deprivation-amplification. It is known that reduced numbers of D2 receptors (possibly *via* D2 polymorphisms or other means), produces a super sensitivity of the remaining D2 receptors [46]. In support of this idea, Harrison and LaHoste [46] reported that striatal DA receptors became supersensitive when dopaminergic input was removed through either surgical denervation or pharmacological depletion, or by means of gene polymorphisms.

When dopaminergic input to the striatum is removed surgically or pharmacologically, the receptors become highly sensitive.Although alterations such as increased D2 receptor binding and increased receptor-G protein coupling have been described in supersensitive striatal tissue, their roles in the mechanism of super sensitivity remain uncertain. The Ras Homolog Enriched in Striatum (Rhes) is similar to members of the Ras-like GTP-binding protein family, and it isexpressed in brain areas that receive dopaminergic input. Harrison and LaHoste [46] have tested whether alterations in Rhes expression accompanied treatments that promote DA receptor super-sensitivity in rats. Removal of DA input to the striatum by denervation with 6-hydroxydopamine resulted in a decrease in Rhes mRNA expression throughout the striatum, as measured with quantitative in situ hybridization. The decrease was detected as early as two weeks and as late as seven months after surgery. Furthermore, a decrease in Rhes mRNA was evident after repeated or acute treatment with reserpine (a DA depleator). Chronic daily injection of rats with the D2 antagonist eticlopride, which is known to up-regulate D2 receptors without inducing profound receptor super sensitivity, did not alter the expression of Rhes mRNA in the striatum. Thus, changes in Rhes mRNA expression were strictly correlated with receptor super sensitivity, perhaps as a result of continuous removal of dopaminergic input, as may be the case in genetically induced RDS [46]. These findings suggest that Rhes mRNA expression is maintained by DA and may play a role in determining normal DA receptor sensitivity. This is just one example of how DA receptor super sensitivity may manifest itself. Thus, blunted or heightened effects from psychoactive substances (e.g., alcohol, cocaine, heroin, nicotine, glucose, etc.) and behaviors (sex, gambling, etc.) seem quite complex and may well relate to molecule-receptor interactions relative to anticipatory behaviors. We hypothesize that these seemingly diverse effects may be substrate-dependent and reward-deficiency independent. Further investigation, therefore, is needed to unravel the mechanisms governing reward dependence behaviors.

IS DOPAMINE'S ROLE "WANTING,""LEARNING" OR "LIKING"?

While it may seem difficult to differentiate the role of DA in brain reward mechanisms, a number of investigators have attempted to do so. Robinson *et al.* [47] examined whether DA regulates liking, wanting, and/or learning about rewards during goal-directed behavior. The researchers tested genetically engineered dopamine-deficient (DD) mice for acquisition of an appetitive T-maze task with and without endogenous DA signaling. They established that DD mice treated with L-dihydroxyphenylalanine (L-dopa) performed similarly to controls on a T-maze task designed to measure liking, wanting, and learning about rewards. However, further experiments, which tested saline-, caffeine-, and L-dopa-treated DD mice on the T-maze, separated performance factors from cognitive processes, and the findings revealed that DA was not necessary for mice to like or learn about rewards, but it was necessary for mice to seek (want) rewards during goal-directed behavior. In essence, Robinson *et al.* [47] demonstrated that reward learning could proceed normally in the brains of DD mice, even though they contained no DA at the time of learning, if the mice were given caffeine just before learning. Caffeine activated the DD mice by an unknown non-dopaminergic mechanism, allowing them to learn where to obtain food reward in a T-maze runway. Their reward-learning-without-DA was revealed on a subsequent test day, when DA function was restored by L-dopa administration. Robinson *et al.* [47] concluded that DA was not needed for normal learning about rewards, nor for hedonic liking of rewards during learning, but rather specifically for a motivational wanting component of reward — incentive salience. These results agree with the findings of Davis [41] (as previously cited) suggesting that DA is for "wanting" and opioids are for "liking".

Wilson *et al.* [48] systematically explored the role of neurotransmitters in "wanting" and "liking". They tested rats following acute, systemic administration of drugs that globally enhance serotonin and noradrenaline (imipramine), DA (GBR 12909), and opioid (morphine) function in a behavioral task designed to measure wanting and liking. Imipramine augmented the effects of delay and taste on reward "wanting", GBR 12909 attenuated the effects of delay on reward "wanting" and the effects of taste on reward "liking," and morphine reduced the effect of delay on a measure of reward "wanting." Since morphine failed to affect reward "liking," but previously had been found to enhance reward "liking" in taste reactivity tests, and since DA seemed to affect both "wanting" and "liking," these data underscore the complexity of this concept, as well as the need for more definitive research.

However, there is evidence that DA's function is not one of inducing pleasure per se but instead is required for seeking pleasure. The findings of Schmidt *et al.* [49] did not support the anhedonia hypothesis of central dopaminergic dysfunction as proposed other by investigators [50-52]. Rather, affective flattening reflected by DA receptor sensitivity may result from the lack of an affective response towards reward-indicating stimuli. These findings indicated that patients with dopaminergic dysfunction were not unable to experience pleasure, but may have failed to be motivated by environmental stimuli to seek reward. The complex nature of reward mechanisms is further evidenced by the work of Mirenowicz and Schultz [53], suggesting that DA neurons in monkeys were activated by unpredicted appetitive stimuli such as food and liquid rewards and by conditioned reward-predicting stimuli. They further found that in contrast to appetitive events, primary and conditioned aversive stimuli either failed to activate DA neurons or induced weaker responses than appetitive stimuli. Thus, DA neurons preferentially reported environmental stimuli with appetitive rather than aversive motivational value.

Of note, the idea that aversive and appetitive stimuli have some similar effects is an important element for the view that DA signals salience. However, it is not only DA that behaves in this way. Peptides such as corticotropin-releasing hormone also respond similarly to both types of stimuli, although the extent of the changes is not the same.Finally, Koob and Volkow [54] in discussing the neurocircuitry of addiction, emphasized the role of both impulsivity and compulsivity leading to a tripartite addiction cycle involving three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving). Impulsivity and compulsivity, as well as the various stages in the cycle, are tied to specific brain systems. Clearly, the picture is not a simple one.

BROADER IMPLICATIONS

According to an English study by Sharot and associates [55], the brain chemical DA influences how people make simple and complex decisions, from what to make for dinner to whether to

have children. "Humans make much more complex decisions than other animals — such as which job to take, where to vacation, whether to start a family — and we wanted to understand the role of dopamine in making these types of decisions." The investigators showed that L-dopa enhanced dopaminergic function during the imaginative construction of positive future life events, subsequently enhanced estimates of the hedonic pleasure ("liking") to be derived from these same events. These findings provided indirect evidence for the role of DA in the modulation of subjective hedonic expectations in humans.

CONCLUSIONS

The initial RDS hypothesis suggested that a dysregulation or dysfunction of mesolimbic DA induces a motivation for seeking reward based stimuli [2,3].Later,substantial subsequent evidence accrued to showthat a driving force for drug use was 'liking' and not just 'wanting'[51-52,56], but some evidence also showed the role of 'learning' [23]. Based upon the accumulation of evidence, we recommend that RDS should now be redefined to specify the distinct role of DA for "wanting,""learning," or liking". However, the RDS hypothesis continues to posit that hypodopaminergic function predisposes an individual to seek psychoactive substances and behaviors to release DA in reward circuits of the brain to overcome DA deficits. Although originally believed to simply encode the set point of hedonic tone, these DA circuits currently are believed to be functionally far more complex, also encoding attention, expectancy of reward, disconfirmation of reward expectancy, and incentive motivation. Hedonic dysregulation within these circuits may lead to addiction [5]. The second-stage dopaminergic component in this reward circuitry is the crucial addictive-drug-sensitive component. All addictive drugs have in common that they enhance (directly or indirectly or even transsynaptically) dopaminergic reward synaptic function in the NAc [6]. Drug self-administration is regulated by NAc DA levels, and is done to keep NAc DA within a specific elevated range (to maintain a desired hedonic level). Moreover, it is important to keep in mind that an older DA hypothesis [57], a single system model, posited that the neurotransmitter DA played a fundamental role in mediating the rewarding properties of all classes of stimuli. In contrast, both nondeprived/deprived and saliency attribution models claim that separate systems make independent contributions to reward. The former identifies the psychological boundary defined by the two systems as being between states of nondeprivation (e.g., food sated) and deprivation (e.g., hunger). The latter identifies a boundary between liking and wanting systems. In doing so, the newer understanding by Berridge and others [1,54] does not negate the underlying root cause of addiction as proposed by the RDS concept. In our view the role of DA deficiency remains key in reward seeking behavior. Further research using imaging tools will provide important adjunctive information necessary to characterize fully the role of DA in reward circuitry and in RDS behaviors.

ACKNOWLEDGEMENTS

Marlene Oscar Berman, Ph.D. is the recipient of grants from NIAAA (R01 AA07112, K05 AA 00219) and from the Medical Research Service of the US Department of Veterans Affairs.

CONFLICT OF INTEREST

Kenneth Blum, PhD owns stock in LifeGen, Inc., the exclusive distributor worldwide of patents related to Reward Deficiency Syndrome (RDS).

REFERENCES

[1] Berridge KC The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 2007; 191(3): 391-431

[2] Blum K, Sheridan PJ, Wood RC, *et al*. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome.J Royal Soc Med 1996; 89(7): 396-400.

[3] Blum K, Braverman ER, Holder JM, *et al*. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors.J Psychoactive Drugs 2000; 32: Suppl i-iv, 1-112

[4] Gardner EL. Addiction and brain reward and antireward pathways. Adv Psychosom Med 2011; 30: 22-60.

[5] Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 2005; 8(11): 1442-4.

[6] Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats.Proc Natl Acad Sci USA 1988; 85(14): 5274-8.

[7] Madrid GA, MacMurray J, Lee JW, Anderson BA, Comings DE. Stress as a mediating factor in the association between the DRD2 TaqI polymorphism and alcoholism.Alcohol 2001; 23(2): 117-22.

[8] Imperato A, Puglisi-Allegra S, Casolini P, Zocchi A, Angelucci L. Stress-induced enhancement of dopamine and acetylcholine release in limbic structures: role of corticosterone.Eur J Pharmacol 1989; 20;165(2-3): 337-8.

[9] Conner BT, Hellemann GS, Ritchie TL, Noble EP.Genetic, personality, and environmental predictors of drug use in adolescents.J Subst Abuse Treat 2010; 38(2): 178-90.

[10] Blum K, Chen AL, Braverman ER, *et al*. Attention-deficit-hyperactivity disorder and reward deficiency syndrome.Neuropsychiatr Dis Treat 2008; 4(5): 893-918.

[11] Blum K, Chen TJ, Downs BW, Bowirrat A, Waite RL, *et al*. Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: proposing "deprivation-amplification relapse therapy" (DART). Postgrad Med 2009; 121(6): 176-96.

[12] Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. J Neurosci 2010; 30(39): 13105-9.

[13] Stice E, Yokum S, Bohon C, Marti N, Smolen A. Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4.Neuroimage 2010; 50(4): 1618-25.

[14] Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. Arch Gen Psychiat 2011;68(8): 808-16.

[15] Ng J, Stice E, Yokum S, Bohon C. An fMRI study of obesity, food reward, and perceived caloric density. Does a low-fat label make food less appealing? Appetite 2011; 57(1): 65-72.

[16] Zhang Y, von Deneen KM, Tian J, Gold MS, Liu Y. Food addiction and neuroimaging.Curr Pharm Des 2011;17(12): 1149-57.

[17] Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience.Nat Rev Neurosci 2005; 6(9): 691-702

[18] Elliott R, Newman JL, Longe OA, William Deakin JF. Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems. Neuroimage 2004; 21(3): 984-90.

[19] Volkow ND, Wang GJ, Fowler JS, *et al*. "Nonhedonic" food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. Synapse 2002; 44(3): 175-80.

[20] Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study.Neuroimage 2010; 52(4): 1696-703.

[21] Berridge KC. Wanting and liking: Observations from the neuroscience and psychology laboratory.Inquiry (Oslo) 2009; 52(4): 378.

[22] Tindell AJ, Smith KS, Berridge KC, Aldridge JW. Dynamic computation of incentive salience: "wanting" what was never "liked."J Neurosci 2009; 29(39): 12220-8.

[23] Peciña S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards.J Neurosci 2003; 23(28): 9395-402.

[24] Fushan AA, Simons CT, Slack JP, Drayna D. Association between common variation in genes encoding sweet taste signaling components and human sucrose perception. Chem Senses 2010; 35(7): 579-92.

[25] Garcia-Bailo B, Toguri C, Eny KM, El-Sohemy A. Genetic variation in taste and its influence on food selection. OMICS 2009;13(1): 69-80.

[26] Ren X, Ferreira JG, Zhou L, Shammah-Lagnado SJ, Yeckel CW, de Araujo IE. Nutrient selection in the absence of taste receptor signaling. J Neurosci 2010; 30(23): 8012-23.

[27] Peng XQ, Xi ZX, Li X*, et al.* Is slow-onset long-acting monoamine transport blockade to cocaine as methadone is to heroin? Implication for anti-addiction medications. Neuropsychopharmacol 2010; 35(13): 2564-78.

[28] Cohen MX, Young J, Baek JM, Kessler C, Ranganath C. Individual differences in extraversion and dopamine genetics predict neural reward responses. Brain Res Cogn Brain Res 2005; 25(3): 851-61.

[29] Lawford BR, Young RM, Rowell JA*, et al*. Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. Nat Med 1995; 1(4): 337-41.

[30] Blum K, Chen TJH, Chen ALC*, et al.* Dopamine D2 receptor TAq A1 allele predicts treatment compliance of LG839 in a subset analysis of pilot study in the Netherlands. Gene Therapy Mol Biol 2008; 12: 129-140.

[31] Ko CH, Liu GC, Hsiao S*, et al*. Brain activities associated with gaming urge of online gaming addiction. J Psychiatr Res 2009; 43(7): 739-47.

[32] Tapert SF, Brown GG, Baratta MV, Brown SA. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. Addict Behav 2004; 29(1): 33-50.

[33] Han DH, Hwang JW, Renshaw PF. Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction. Exp Clin Psychopharmacol 2010; 18(4): 297-304.

[34] Cohen MX, Krohn-Grimberghe A, Elger CE, Weber B. Dopamine gene predicts the brain's response to dopaminergic drug. Eur J Neurosci 2007; 26(12): 3652-60.

[35] Zijlstra F, Veltman DJ, Booij J, van den Brink W, Franken IH. Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. Drug Alcohol Depend2009; 99(1-3): 183-92.

[36] Egecioglu E, Skibicka KP, Hansson C*, et al*. Hedonic and incentive signals for body weight control. Rev Endocr Metab Disord. 2011; 12(3): 141-51.

[37] Abizaid A, Liu Z-W, Andrews ZB, *et al*. Ghrelin modulates the activity and synaptic input organizationof midbrain dopamine neurons while promoting appetite. J Clin Invest 2006; 116(12): 3229-39.

[38] Dickson SL, Egecioglu E, Landgren S, Skibicka KP, Engel JA, Jerlhag E. The role of the central ghrelin system in reward from food and chemical drugs. Mol Cell Endocrinol2011; 340(1): 80-7.

[39] Jerlhag E, Engel JA. Ghrelin receptor antagonism attenuates nicotine-induced locomotor stimulation, accumbal dopamine release and conditioned place preference in mice. Drug Alcohol Depend 2011; 117(2-3): 126-31.

[40] Jerlhag E, Egecioglu E, Landgren S*, et al*. Requirement of central ghrelin signaling for alcohol reward. Proc Natl Acad Sci USA 2009; 106(27): 11318-23.

[41] Davis CA, Levitan RD, Reid C*, et al*. Dopamine for "wanting" and opioids for "liking": a comparison of obese adults with and without binge eating. Obesity (Silver Spring) 2009; 17(6): 1220-5.

[42] Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music.Nat Neurosci 2011; 14(2): 257-62.

[43] Lobo DS, Souza RP, Tong RP*, et al*. Association of functional variants in the dopamine D2-like receptors with risk for gambling behaviour in healthy Caucasian subjects. Biol Psychol 2010; 85(1): 33-7.

[44] O'Sullivan SS, Wu K, Politis M*, et al*. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain 2011; 134(Pt 4): 969-78.

[45] Sullivan RM. Hemispheric asymmetry in stress processing in rat prefrontal cortex and the role of mesocortical dopamine. Stress 2004; 7(2): 131-43.

[46] Harrison LM, LaHoste GJ. Rhes, the Ras homolog enriched in striatum, is reduced under conditions of dopamine supersensitivity. Neuroscience 2006;137(2): 483-92.

[47] Robinson S, Sandstrom SM, Denenberg VH, Palmiter RD. Distinguishing whether dopamine regulates liking, wanting, and/or learning about rewards. Behav Neurosci2005; 119(1): 5-15.

[48] Wilson DI, Laidlaw A, Butler E, Hofmann D, Bowman EM. Development of a behavioral task measuring reward "wanting" and "liking" in rats. Physiol Behav 2006; 30;87(1): 154-61.

[49] Schmidt K, Nolte-Zenker B, Patzer J, Bauer M, Schmidt LG, Heinz A. Psychopathological correlates of reduced dopamine receptor sensitivity in depression, schizophrenia, and opiate and alcohol dependence. Pharmacopsychiatry 2001; 34(2): 66-72.

[50] Nader K, Bechara A, van der Kooy D. Neurobiological constraints on behavioral models of motivation. Annu Rev Psychol 1997; 48: 85-114.

[51] Berridge KC. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav. 2009; 97(5): : 537-50.

[52] Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning.Curr Opin Pharmacol 2009; 9(1): 65-73.

[53] Mirenowicz J, Schultz W. Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli.Nature 1996; 379(6564): 449-51.

[54] Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacol Rev 2010; 35: 217-38.

[55] Sharot T, Shiner T, Brown AC, Fan J, Dolan RJ. Dopamine enhances expectation of pleasure in humans. Curr Biol 2009; 29;19(24): 2077-80.

[56] Kornetsky C. Brain-stimulation reward, morphine-induced oral stereotypy, and sensitization: implications for abuse. Neurosci Biobehav Rev 2004; 27(8): 777-86.

[57] Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis.Neurosci Biobehav Rev 1985; 9(3): : 469-77.