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Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti-reward systems

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1. ABSTRACT

Anhedonia is a condition that leads to the loss of feelings pleasure in response to natural reinforcers like food, sex, exercise, and social activities. This disorder occurs in addiction, and an array of related neuropsychiatric syndromes, including schizophrenia, depression, and Post Traumatic Stress Disorder (PTSD). Anhedonia may by due to derangements in mesolimbic dopaminergic pathways and their terminal fields (e.g., striatum, amygdala, and prefrontal cortex) that persist long after the traces of the causative drugs are eliminated (pharmacokinetically). Here we postulate that anhedonia is not a distinct entity but is rather an epiphenomenon of hypodopaminergic states and traits arising from the interaction of genetic traits and epigenetic neurobiological alterations in response to environmental influences. Moreover, dopaminergic activity is rather complex, and so it may give rise to differential pathophysiological processes such as incentive sensitization, aberrant learning and stress-like "anti-reward" phenomena. These processes may have additive, synergistic or antagonistic interactions with the concurrent reward deficiency states leading in some instances to more severe and long-lasting symptoms. Operant understanding of the neurogenetic antecedents to reward deficiency syndrome (RDS) and the elucidation of reward gene polymorphisms may provide a map for accessing an individual's genetic risk for developing Anhedonia. Prevention techniques that can restore homeostatic balance via physiological activation of dopaminergic receptors (D2/D3) may be instrumental for targeting not only anhedonia per se but also drug craving and relapse.

2. INTRODUCTION

Anhedonia is a condition that leads to loss of the ability to experience pleasure in response to

natural reinforcers like food, sex, and exercise, and social activities. Newer models consider motivational anhedonia; lack of motivation and activity without pleasure and consummatory anhedonia (1). Meanwhile, the debate regarding the neurobiological basis of anhedonia remains unsettled. There is, however, a broad consensus regarding the involvement of the mesolimbic dopaminergic reward pathways. These pathways do not exist in isolation but rather are found embedded within a complex network of interrelated systems; opioidergic, noradrenergic and serotonergic, to name a few, each of which exhibits a unique function within the context of pleasure-related behavior.

Anhedonia, accompanied by hyporesponsive reward circuits (2), is an important characteristic of neuropsychiatric syndromes including mood disorders, schizophrenia, and all Reward Deficiency Syndrome (RDS) behaviors including substance use disorders, post-traumatic stress disorder (PTSD), borderline personality disorder, and schizoid personality disorder (3). Keedwell & Linden (4) found that the brains of participants who were clinically depressed had to work harder to process rewarding experiences. Anhedonia is also a side effect of antidopaminergic neuroleptics or antipsychotic drugs which block dopamine (DA) binding to postsynaptic neuronal loci (5, 6). One reason for the high prevalence of nicotine addiction in people with psychiatric illness, especially those on psychiatric medications (7) is that smoking is used as self-medication to counter boredom in an attempt to reverse antipsychotic-related anhedonia (8). The clinically anhedonia has profound implication since it as a risk factor for suicide particularly in patients with substance use disorders (SUD)s (9).

Increases in dopamine levels in mesolimbic dopaminergic pathways including their terminal fields; the striatum, amygdala, and prefrontal cortex, are the sites where the rewarding effects of natural rewards, as well as, drugs of abuse underlying the subjective pleasure or “high” pursued by drug addicts occur. However, the precise nature of dopaminergic action is a subject of complementary/competing hypotheses encompassing reward anticipation, learning, and motivation (10-13). Work by Schultz and associates in monkeys demonstrated several thousand-fold variabilities in the speed of phasic DA release and offered a means to understand the relationship between DA and anhedonia. They found that DA mediates the (epigenetic) reactivity of the organism to the environment at different time scales. In simple terms, environmental cues will change the quantal neuronal release of dopamine from either fast impulse reward related to much slower and lower quanta release when the environmental cue is uncertain (13). These environmental cues will impact postsynaptic dopamine tone even when dopamine function is deficient as observed in Parkinson’s disease and RDS behaviors (9).

3. ANHEDONIA AND FOOD ADDICTION

While it is important to continually perform both animal and human research conceptualizing the commonality of food and drug addiction, it is clear that highly reinforcing drugs of abuse reduce interest in eating while withdrawal of some of these drugs increase eating (14). In clinical settings “never get too hungry” is an anti-drug relapse mantra (15). Anhedonia during withdrawal states or due to other causes appears to result from the neurochemical effects of both substances such as glucose and opioids. Neuroimaging data, related to reward circuit responsitivity and weight gain, adequately address this concept in humans (16, 17). Work by Ahmed (18), in the Oxford publication “Food and Addiction” proposes that in nonhungry, nonthirsty rats, the taste sensation associated with ingestion of sweetened water is clearly more rewarding than artificial sensations from intravenous cocaine, independent of prior cocaine history. Moreover, this conclusion was generalized to intravenous heroin; however, heroin was more potent than cocaine in competing with a sweet taste, especially with chronic heroin use (19).

Along these lines, Johnson *et al.* (20) proposed that Attention Deficit Hyperactivity Disorder (ADHD) may associate with disrupted dopamine signaling whereby dopamine D2 receptor numbers are decreased in reward-related brain regions. They correctly point out that the same pattern exists in various RDS behaviors; drug or food (sugar) addiction and obesity. In simple terms, these authors hypothesize that chronic sugar intake could lead to reduced mesolimbic dopamine signaling or a hypodopaminergic state that contributes to ADHD symptomatology. This mesolimbic reduced signaling may have real relevance in low dopamine tone in ADHD as measured by Badgaiyan *et al.* (21) raising the question of “the Chicken or Egg.” The DRD2 A1 allele, with a well-known 30-40% lower D2 receptor density than the normal A2, has a genetic association with ADHD. This DRD2 A1 deficit would suggest an additive insult; a co-morbid enhanced craving for sugar or other neuronal releasers of dopamine at the nucleus accumbens (NAc). reward site. Also, Badgaiyan *et al.* (21) found that in ADHD the phasic dopamine response to stimuli is heightened thereby providing continued impetus to seek out sugar and possibly anhedonia (“sugar blues”).

4. ANHEDONIA IN RDS BEHAVIORS

Reward Deficiency Syndrome, first coined by Blum *et al.* in 1996, (22) has received considerable attention and represents a conceptual framework for understanding the role of, for example, dopaminergic

genetics and epigenetics in not only drug and alcohol abuse, but all addictive, impulsive and compulsive behaviors. There are many clinical subtypes, and even schizophrenia has been included in this list (22).

Addictive drugs enhance the functioning of the reward circuitry after they are self-administered by laboratory animals. The core reward circuitry is an 'in-series' circuit that links the ventral tegmental area (VTA), the nucleus accumbens (NAc) and the ventral pallidum via the medial forebrain bundle. As mentioned earlier, although originally believed to encode a set point for hedonic tone, these circuits are now, thought to be far more complex, being involved in the mediation of encoding for attention, reward expectancy, disconfirmation of reward expectancy, and incentive motivation. Moreover, 'hedonic dysregulation' or anhedonia, of these circuits might facilitate addiction.

The crucial addictive-drug-sensitivity component is the 'second-stage' dopaminergic component in this reward circuitry (23). Addictive drugs have in common that they enhance dopaminergic reward synaptic function (directly or indirectly or even trans-synaptically) in the NAc. Nucleus accumbens DA levels regulate drug self-administration to maintain a desired hedonic level and keep NAc DA, within a specific, elevated range (22). Chronic use of some classes of addictive drugs like opiates results in the development tolerance to the euphoric effects. Post-use dysphoria then dominates the reward circuit hedonic tone, and people who are addicted use drugs to get back to normal ('get straight'). The brain circuits that mediate the pleasurable effects of addictive drugs are different anatomically, neurophysiologically and neurochemically from those mediating physical dependence, as well as, from those mediating craving NAc and relapse (pre-frontal cortex –cingulate gyrus and central amygdala). Gardner, (24), pointed out that drug addiction involves a progression from occasional (recreational) to impulsive and finally compulsive (habitual) use. The behaviors progress from reward-driven to habit-driven drug-seeking. Moreover, they correlate with neuroanatomical progress from the ventral striatum NAc to dorsal striatal control over drug-seeking behavior.

Variations in vulnerability to drug addiction are due to genetics, yet exposure as an adult or during childhood and *in utero*, to environmental factors such as stress, trauma, and social defeat also epigenetically alter brain reward mechanisms and symbiotically impart vulnerability to addiction. The etiology of substance abuse and even schizophrenia hold very well to the 'bio-psycho-social' model (25, 26). Human neuroimaging studies add credence to the hypothesis that addiction to cocaine (27) or other substances correlates with a hypodopaminergic dysfunctional state within the reward circuitry of the brain as suggested by the RDS model (28). Serotonergic, opioid, endocannabinoid, GABAergic and glutamatergic mechanisms are implicated in addiction by credible evidence. For example, a recent study using magnetic resonance imaging points to a role for polymorphisms of catabolic enzymes like Catechol-O-Methyl –Transferase (COMT) in white matter integrity (29). Three standard triggers for craving and relapse are (a) re-exposure to the addictive drug, (b) stressors, and (c) reexposure to people, places, and objects (environmental cues) previously associated with drug-taking behavior. Drug-triggered relapse involves the NAc and the neurotransmitter DA. Relapse triggered by stress involves the central nucleus of the amygdala, the bed nucleus of the stria terminals, corticotrophin-releasing factor, and the lateral tegmental noradrenergic nuclei of the brain stem and the neurotransmitter norepinephrine. Finally, relapse triggered by environmental cues involves the basolateral nucleus of the amygdala, the hippocampus, and the neurotransmitter glutamate. Knowledge of the neuroanatomy, neurophysiology, neurochemistry, neuropharmacology and neurogenetics of the activity of addictive drugs is producing some strategies for Pharmacogenomics and nutrigenomic treatment of RDS behaviors (30). In fact, one interesting natural substance L-acetyl-carnitine, a substance having acetylcholine-like pharmacological activity (31) has been shown to attenuate anhedonia associated with alcohol dependence (32).

5. ANHEDONIA HYPOTHESIS AND DOPAMINE CHARACTERIZED AS A "PLEASURE" MOLECULE

Before the RDS concept, the anhedonia hypothesis of neuroleptic action (33) was, from its inception, the DA hypotheses of reward (34) or reinforcement (35). Dackis & Gold placed significant value on the role of DA depletion in cocaine-seeking behavior and relapse (36). Moreover, the dopamine hypotheses were themselves deviations from an earlier noradrenergic theory of reward introduced by Larry Stein (37). The anhedonia hypothesis (38) was that brain dopamine plays a critical role in the subjective pleasure associated with positive rewards. According to Wise (39, 40), the hypothesis "was intended to draw the attention of psychiatrists to the growing evidence that dopamine plays a critical role in the objective reinforcement and incentive motivation associated with food and water, brain stimulation reward, and psychomotor stimulant and opiate reward" (39).

Neuroleptics are drugs used to treat schizophrenia a condition involving anhedonia. They act like D2 receptor inhibitors known to block the postsynaptic interaction of dopamine released into the synapse. Some studies revealed that neuroleptics attenuated the positive reinforcement that we normally

associate with pleasure in laboratory animals (41, 42). Psychiatrists, have correctly pointed out that the acute actions of neuroleptics, blockng postsynaptic dopamine interaction, were reflected in animal studies whereas in human schizophrenia neuroadaptations to chronic neuroleptic administration, appear to alleviate symptoms indued by elevated DA in schizophrenia, without effecting the symptoms of neuroleptic induced decreased DA including anhedonia and RDS (25, 43).

Wise (40) also points out that despite its limited heuristic value for the understanding of schizophrenia, the anhedonia hypothesis has sponsored biological theories of reinforcement, motivation, and the neuroepigenetics of addiction (44). Brain dopamine plays a major role in reinforcement of response habits, conditioned preferences, and synaptic plasticity in cellular models of learning and memory (45). The idea of the central role of DA in reinforcement is also the basis of the psychomotor stimulant theory and most neuroadaptation theories of addiction, and also to conditioned reinforcement and reward deficiency prediction. Properly understood, it is also fundamental to the theories of incentive motivation (46). It is known that distinct populations of D1- and D2-dopamine receptor expressing medium spiny neurons (D1-/D2-MSNs) comprise the NAc and stimulation of D1-MSNs promote activity, while activation of D2-MSNs inhibit motivated behavior. Heinsbroek and colleagues (47) most recently reported that either increasing activity in D1-MSNs or decreasing activity in D2-MSNs augmented cue-induced reinstatement. In fact, they also found using optogenetic implementation, that GABAergic long-term depression (LTD) was abolished in D2-. but not in D1-MSN synapses of mice trained to self-administer cocaine. Moreover, in cocaine-trained mice a mu opioid receptor antagonist restored GABA currents in D2-, but not D1-MSN synapses, thus, increased enkephalin tone on presynaptic mu receptors was responsible for occluding the LTD. Accordingly, a behavioral function for D1-MSN innervation of the ventral pallidum identified by these results suggests that loss of LTDGABA in D2-MSN, but not D1-MSN input to ventral pallidum may promote cue-induced reinstatement of cocaine-seeking behavior (49).

The notion that DA might be necessary for pleasure itself came in part from the subjective reports of patients (48) and healthy volunteers (49, 50) given neuroleptic treatments. The dysphoria caused by neuroleptics is quite consistent with the concept that they attenuate the normal pleasures of life. Consistent with this view (51, 52) drugs like cocaine and amphetamine and even palatable food substances are presumed to be addictive because of the pleasure they impart (53) by increasing extracellular dopamine levels (54-56). Furthermore, although controversial, (57) the neuroleptic pimozide, a competitive antagonist at dopamine receptors, has been reported to decrease euphoria induced by IV amphetamine in healthy volunteers (58, 59). The cannabinoids (THC) can increase sucrose palatability so that after pretreatment with THC sucrose, acquires the ability to induce DA release in the NAc shell and after repeated exposure to this hedonic taste, this property will undergo adaptation (habituation) (60).

Finally, Bressan and Crippa (61) reviewed preclinical data concerning the role of DA in reward and pleasure behaviors. They utilized a computer-based search of the literature, augmented by extensive bibliography guided article reviews to find basic information on dopamine and symptoms such as dysphoria, anhedonia, and depression. Their results indicated that central dopaminergic neurotransmission is complex, having multiple actions at each level of the mesocorticolimbic reward pathway. Moreover, DA has a role in reward processing and indeed influences the ability to experience pleasure. The authors highlight that dysfunction of reward circuit DA transmission is related to symptoms including apathy anhedonia, and dysphoria found in several neuropsychiatric disorders. Disorders that involve DA dysfunction include; Parkinson's disease, depression, drug addiction, and neuroleptic-induced dysphoria. However, there are others (11, 62) who refute the idea that dopamine is indeed a "pleasure molecule" and question its role in orgasmic response during copulation.

6. REWARD GENES AND ANHEDONIA: POTENTIAL THERAPEUTIC TARGETS

Many reward based genes have distinctive effects regarding mood including anhedonia. A PubMed search of these reward genes and associated polymorphisms in psychiatric disorders or "Psychiatric Genetics" has resulted in over 18,000 papers. A selective sampling includes many important references having relevance to both hedonic and anhedonic responses (13, 63-110).

Regarding anhedonia per se, a brief search provides a few recent strong examples of how specific gene polymorphisms affect the mood and more specifically anhedonia. Understanding these gene-environment interactions may provide important insight for future therapies. There is mounting evidence that the NAc has a central role in the pathophysiology of anhedonia. The hypothesis has been that anhedonia, is a core symptom of depression, and might be related to dysfunction of the NAc brain region a fundamental component of the reward circuitry. Bessa *et al.* (111) have shown that medium spiny neurons in the NAc have hypertrophied in animals displaying anhedonic behavior. These animals have also shown increased expression of the genes that encode synaptic protein brain-derived synapsin 1, brain region neurotrophic

factor, and neural cell adhesion molecule (genes associated with dopaminergic regulation). The authors propose that stress induces anhedonic behavior is related to specific changes in the neuronal morphology and the gene-expression of the NAc.

Clinically, the gene expressions that caused by stress are, in effect, reversed after treatment with antidepressants. Furthermore, transcriptional profiling of the NAc for Rho GTPase-related genes, known regulators of synaptic structure, resulted in a sustained reduction in RAS-related C3 botulinum toxin substrate 1 (RAC1) expression after chronic social stress. Golden *et al.* (112) found that overexpression of constitutively active RAC1 in the NAc of mice after chronic social defeat stress; reverses anhedonia. Interestingly, TREK1 is another crucial gene expressed in reward-related basal ganglia regions. The TREK1 genetic variation may associate with anhedonic symptoms of depression as well as the Trace Amine-Associated Receptor 1 (TAAR-1) (113). Dillon *et al.* (114) found that the total number of "protective" TREK1 alleles was associated with stronger responses to monetary incentive gains in several other reward-related regions, including the dorsal anterior cingulate cortex, orbitofrontal cortex, and mesial prefrontal cortex. The authors conclude that future studies in depressed samples should evaluate whether variation in neural responses to rewards could contribute to the association between TREK1 and antidepressant response in humans.

Law *et al.* (115) found that in mood disorder, early stressors, such as parental separation, are vulnerability factors which provoke hippocampal gene expressions. They conclude that deprivation in the early life of a nonhuman primates, without subsequent stressors, has long-term effects the expression of genes implicated in synaptic function and plasticity within the hippocampus. The reductions in serotonin 1A and GAP-43 receptor expression are similar to findings in mood disorder and support the possibility that these reductions reflect an early developmental contribution to anhedonia vulnerability. It is well established that drugs of abuse alter expression of AMPA-type glutamate receptor subunits (GluRs) in the NAc. Todtenkopf and colleagues (116) found that elevated GluR1 in NAc shell increases intracranial self-stimulation (ICSS) thresholds, similar to the effects caused by treatments that cause anhedonia and dysphoria (pro-depressive effects) in rats and humans, for example, drug withdrawal, like kappa-opioid agonists. On the other hand, elevated GluR2 decreases ICSS thresholds, an effect like that caused by drug abuse reward.

Human neuroimaging studies have demonstrated that inflammatory cytokines target basal ganglia function and presynaptic DA, leading to symptoms of anhedonia. Felger *et al.* (117) found that *in vivo* microdialysis demonstrated decreased release of DA after four weeks of Interferon (IFN)-alpha administration compared to saline. PET neuroimaging also showed decreased DA release after four weeks of IFN-alpha as evidenced by reduced displacement of the DA ligand 11C-raclopride following amphetamine administration. Additionally, four weeks of IFN-alpha associated with decreased D2R binding but no change in the DA transporter. Importantly, during IFN-alpha administration, sucrose consumption was attenuated and correlated with decreased DA release at four weeks as measured by *in vivo* microdialysis. From these results, the authors conclude that chronic peripheral IFN-alpha exposure reduces striatal DA release and occurs with anhedonia-like behavior in non-human primates.

Cocaine is often proposed as the extreme but an ideal model for all stimulant addiction can be self-administered, to the point of death, in animal studies. Withdrawal from psychostimulants, like cocaine or amphetamines, in animal models, are useful for screening antidepressants (118). In humans post cocaine or amphetamine addiction leads to a 'burn out' which looks very much like depression with psychomotor retardation. However, once that passes, individuals in recovery report hyperphagia and hypersexuality associated with anhedonia. This anhedonia is a major factor in craving and relapse. The DSM-V recognizes that social, occupational and recreational activities decrease and are replaced by repeated drug use while previously rewarding experiences like food, job, and family become devalued as dependent persons, despite serious negative consequences to seek and use the drug.

Findings by Carelli and West (119) reveal that cocaine-conditioned cues elicit a 'cocaine-need state' that is aversive, encoded by a distinct subset of NAc neurons, and rapid dopamine release that induces cocaine-seeking behavior. Other experiments (88) revealed that bidirectional control (inhibition or excitation) of specified midbrain dopamine neurons immediately and bi-directionally modulate (120) (induces or relieves) multiple independent depressive symptoms such as anhedonia caused by chronic stress. These authors also found that optogenetic recruitment of these dopamine neurons potently alters neural encoding of anhedonia in downstream in the NAc of freely moving rodents. This work suggests that processes affecting anhedonia may involve alterations in the neural encoding of action in limbic circuitry (121). Accordingly, even high-fat diets attenuate dopamine signaling with an increase in anhedonia associated behaviors in rodents similar to drugs of abuse (122). The similarity further suggests that agonistic dopaminergic functioning may induce anti-anhedonia.

The role of chronic stress in rodents suggest an effect on dopamine D1 receptor excitation of melanocortin 4 receptor which is responsible in part of inducing anhedonia. Lim *et al.* (123) found that despite increases in behavioral measurements of anhedonia elicited by stress, measurements of behavioral despair are not increased; they are prevented by blocking these melanocortin 4 receptor (MC4R)-mediated synaptic changes *in vivo*. Further in an animal model with experimentally induced chronic social defeat stress (CSDS) reduced dopaminergic activity was observed (123). This work suggests that specific alteration of dopaminergic reward processes might be altered by CSDS induced anhedonia. Additionally, in the social defeat model of depression in rats, hypothalamic dynorphin and orexin were diminished, noteworthy because most hypothalamic orexin cells co-express dynorphin. Accordingly, these observations suggest that in anhedonia, orexin and dynorphin function may be out of balance between the mesocortical dopaminergic regions and the hypothalamus (124, 125).

7. ANTI-REWARD SYSTEM

The decrease in dopamine production is progressively worsened by the release of the k opioid receptors' agonist, dynorphin. This type of between-system anti-reward neuroadaptation is also characterized by the massive outpouring of stressogenic neurotransmitters like norepinephrine and corticotropin-releasing factor, which worsen anhedonia. Additionally, anhedonia needs to be examined in the context of the incentive motivation theory which considers the brain reward function as composed of core motivational and emotional processes termed "wanting" and "liking" respectively. Decreases in striatal dopamine concentrations underlying reward deficiency prompt sensitization in the key effector systems. Effector systems include pre- and post-synaptic dopamine receptors, presynaptic dopamine transporters, and the enzymes involved in dopamine's metabolism are all are responsible for transforming normal motivational "wanting" responses into the heightened salience engendered by drugs or drug-related cues. This sensitization is construed to be an animal homolog of human craving (126). "Aberrant learning theory" is a closely related concept which suggests that new rewards are predicted by interactions between tonic and phasic spikes in dopaminergic neurons phasic firing by the expectancy of the old rewards or encoding (learning) new rewards (57, 65). Hence, neural adaptations to hypodopaminergia of reward deficiency may not only lead to low signal-to-noise detection capability for natural rewards, but also to the motivational significance of cues that predict delivery of drugs, are overlearned meaning that drugs are constantly perceived to be better than expected (92, 127, 128).

Types of the interactions with reward deficiency are determined by; nature, the concurrent neuroadaptations, and modulating variables like stress levels or baseline neurobiology and neuro-psychopathology. The additive and potentially synergistic interaction between reward deficiency and anti-reward (127) were discussed above. Competition may be the another prominent interaction because incentive sensitization produces the opposite to reward deficiency, increases in motivational salience (26). Increases in motivation which lead to further hypofunctionality of the brain circuits mediating reward and motivation, clinically noticeable as a diminution of drives and capacity to experience pleasure (26), viz., RDS (2).

Interventions with the goal of restoring the balance between reward and anti-reward networks in patients with chronic pain may help to decrease their risk for suicide (129). Elman and associates suggest the Combined Reward Deficiency and Anti-Reward Model (CReAM) in which biopsychosocial variables can modulate brain reward, motivation, and stress functions can interact in a 'spiraling downward' fashion which exacerbates the intensity, chronicity, and comorbidities of chronic pain syndromes (127).

Certainly, the role of serotonin, orexin, and dopamine have been studied and elucidated regarding stress induction and influence on corticosterone activity (130). Most recently Zoratto *et al.* (131) have shown that in adult tryptophane-depleted and corticosterone augmented rats, offspring showed significantly increased anhedonia-related behaviors; reduced striatal and increased hypothalamic BDNF and reduced dopamine and serotonin in the prefrontal cortex and turnover in the hippocampus. Zoratto *et al.* (131) proposed that neonatal variations in functionality of the serotonergic system and HPA axis may contribute to induce anhedonia in adulthood.

It is well established that the nucleus accumbens shell (NAc S) is implicated in controlling stress responses through corticotrophin-releasing factor (CRF). As well as studies indicating that CRF in the NAc S increases appetitive motivation, there is indirect evidence indicating that NAc S CRF may also cause aversive responses and that these behaviors such as anhedonia may be mediated through local DA and acetylcholine (ACh) systems (132). Chen *et al.* found that NAc S CRF can induce some aversive behaviors; they include approach behavior. swim depression (a mouse model of depression), anhedonia, and anxiety. They propose that these behaviors through enhanced activation of ACh and DA in the NAc S, respectively, support a role for this brain area in mediating the effects of stress and anhedonia and involvement of multiple neurotransmitter deficits (132-135).

8. ANHEDONIA STATE OF THE ART

Over the last two years, some important papers have extended our knowledge about anhedonia. Signaling deficits in central, subcortical DA regions may underlie symptom severity, in particular, anhedonia in healthy subjects and schizophrenia. After genotyping for some dopamine-related gene polymorphisms (DRD4, DRD2/ANKK1, DAT1, and COMT) assessing DA receptor type 2 (D2R) binding, Eisenstein *et al.* (136) found that elevated subcortical dopaminergic signaling capacity is associated with less negative symptom severity. This finding supports the RDS concept. They also found that higher striatal D2R binding was associated with less physical and social anhedonia. This work suggests that subcortical DA function may contribute to negative symptom severity and self-reported anhedonia, independent of diagnostic status. From a clinical perspective, Stemat and Katzman (137) further support an umbrella concept such as RDS, by suggesting that patients diagnosed with major depressive disorder (MDD), SUD, and ADHD, all have low hedonic tone. The neuropathology of depressive-like behaviors is based on an anhedonic trait /state supported by the fact that the VTA DA neurons encode reward and motivation. Peroxisome proliferator-activated receptors type-α (PPARα) acutely regulate VTA dopamine neuron firing via β2 subunit-containing nicotinic acetylcholine receptors (β2*nAChRs) through phosphorylation, and this effect is predictive of antidepressant-like effects. Scheggi *et al.* (138) proposed that regulating PPARα with subsequent normalization of dopaminergic activity should reduce anhedonia.

It has been hypothesized by many that striatal dopamine receptor neurons D1expression have associated with positive reinforcement and reward, whereas D2 neurons associate with negative reinforcement and aversion. However, most recently, Soares-Cunha *et al.,* (139) found that in control animals and in a model that presents Anhedonia and motivational deficits; activating NAc D2 neurons increases cue-induced motivational drive. Conversely, optogenetic inhibition of D2 neurons decreases motivation. Their results suggest that the classic view of D1-D2 functional antagonism does not hold true for all dimensions of reward-related behaviors and those D2 neurons may play a more prominent pro-motivation role than originally anticipated. Also, work of Ferenczi *et al.* (140) strongly suggests that by using optogenetic functional magnetic resonance imaging (fMRI) to visualize neural activity in rats, seen locally, striatal activity is driven by dopamine neuron stimulation. Whereas locally medial prefrontal cortex (mPFC) excitability increases, reduce striatal response and drives for behavioral dopaminergic stimulation. This chronic mPFC overactivity stably suppresses natural reward-motivated behaviors and specific new brain-wide functional interactions induced which are predictive of the degree of anhedonia in individuals. Interestingly, Shen *et al.* (141) revealed that D1-D2 receptor heteromer induces development occurring in the NAc induces rapid anti-depressant (hedonia) and anxiolytic actions. They suggested that the development of D1-D2 receptor heteromer may have value as a novel therapeutic target. Enman *et al.* (142) found evidence showing that reduced D2 activity but not D1 activity caused anhedonia and therefore also reduced cocaine-induced reward behavior. Finally, Morie *et al.* (143) using high –density electrical mapping in cocaine abusers showed that anhedonia is independent of executive dysfunction. Executive dysfunction was found in their map to most strongly associated with duration (severity) of drug abuse.

Berridge and Kringelbach (144) accurately suggest that “pleasure is mediated by well-developed mesocorticolimbic circuitry and serves adaptive functions. In affective disorders, anhedonia (lack of pleasure) or dysphoria (negative affect) can result from breakdowns of that hedonic system.”

9. CONCLUSION

Neurobiological reward processing dysregulation is how, pleasure in previously rewarding stimuli, is lost. Anhedonia is actualized as a core symptom of MDD. The brain’s mesolimbic dopamine reward circuit is integral to processing the rewarding salience of stimuli to guide actions (wanting), while, pleasure itself, (liking), may be generated within the limbic circuitry hedonic hot spots (144).The manifestation of anhedonia and associated symptoms of depression like appetite changes, feelings of sadness, and psychomotor effects, reflect altered brain reward circuitry as a common underlying disease process. Studies of cocaine self-administration, abstinence, and post-abstinence in laboratory animals and humans has emphasized the importance of dopamine, pleasure, and anhedonia (117). Mapping the neurogenetic antecedents of RDS behaviors may provide a method for risk assessment of an individual for developing anhedonia. However, especially following long-term drug abuse of, for example, psychostimulants, it is likely that anhedonia reflects drug induced epigenetic mesolimbic changes compounded by genetic antecedents. The response is low hedonic tone (137) suggesting that agonistic dopaminergic functioning may induce anti-anhedonia. Thus, treatment to attenuate anhedonia is to provide natural activation of dopaminergic receptors (D2/D3) at the brain sites for craving and relapse and to increase dopamine sensitivity. Additional studies are necessary. In the meantime, diet, exercise, and other approaches to ‘normalize’ the dopamine system make sense.

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Abbreviations: ACh: acetylcholine, ANKK1: ankyrin repeat and kinase domain containing 1 is a gene which controls the synthesis of dopamine in the brain, ANOVA: analysis of variance, ASAM: American Society of Addiction Medicine, COMT: catechol-O-methyltransferase (an enzyme), CRF: cortiocotropin-releasing factor, CSDS: chronic social defeat stress, DA: dopamine, DAT1: dopamine transporter polymorphism associated with ADHD, D2/D3: dopamine receptors, DRD2: dopamine receptor D2 , GABA: ?-amino-butyric acid, IFN-a: interferon-alpha is a pleiotropic cytokine; part of the immune response signaling pathway, ICSS: intracranial self-stimulation, mRNA: messenger RNA, molecules that convey genetic information from DNA to ribosomes, NAc: nucleus accumbens, PFC: prefrontal cortex, RAS: family of related proteins belonging to GTPase class and is involved in cellular signal transduction., RDS: reward deficiency syndrome, SHAPS: Snaith-Hamilton-Pleasure-Scale, SNP: single-nucleotide polymorphism - most common type of genetic variation, Taq1A: polymorphism that can influence DRD2 receptor expression, TREK: Outward rectifying potassium channel

Key Words: Anhedonia, Hedonia, Dopamine, Reward Deficiency Syndrome, Neurogentics, Neurobiology, Review

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