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Review Article

Inducing Dopamine Homeostasis to Combat Brain-Gut Functional Impairment as a Function of Behavioral and Neurogenetic Correlates of Reward Deficiency Syndrome (RDS)

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Abstract

Reward Deficiency Syndrome (RDS) encompasses a spectrum of addictive and compulsive behaviors, including substance use disorders, obesity, and behavioral addictions, rooted in dysregulated dopaminergic and endorphinergic pathways. Genetic, epigenetic, and environmental factors interact to compromise the Brain Reward Cascade (BRC), resulting in hypodopaminergia and impaired endogenous opioid signaling. Polymorphisms in key genes, such as DRD2, PENK, and OPRM1, along with epigenetic modifications, can reduce dopamine or endorphin function, increasing vulnerability to compulsive behaviors and addiction. Animal and human studies demonstrate overlapping neurobiological mechanisms across substance and non-substance addictions, implicating the mesolimbic system, prefrontal cortex, and hypothalamic-gut axis. Obesity, as a subtype of RDS, illustrates the interplay of homeostatic and hedonic reinforcement, with metabolic hormones like leptin and ghrelin modulating ventral tegmental area (VTA) dopamine activity. Food and drug addictions share common neurogenetic pathways, and gene-environment interactions influence the propensity for addictive behaviors, including post-bariatric surgery "addiction transfer". Emerging strategies focus on pro-dopamine regulation, aiming to restore dopaminergic homeostasis through nutraceuticals, lifestyle interventions, and personalized medicine. Genetic Addiction Risk Severity (GARS) testing enables early identification of at-risk individuals, informing targeted prevention and treatment approaches. Policy recommendations emphasize safe, evidence-based integration of pro-dopamine therapies with behavioral and pharmacologic interventions, ensuring quality, transparency, and equitable access. Collectively, these findings underscore the importance of understanding the neurogenetic underpinnings of RDS to develop individualized, mechanistically informed interventions for addiction, obesity, and related disorders.

Keywords: *Dopamine; Brain-Gut Functional Impairment; Reward Deficiency Syndrome (RDS)*

Abbreviations

2-AG: 2-Arachidonoylglycerol; 5-HT2A: 5-Hydroxytryptamine (Serotonin) 2A Receptor; Ach: Acetylcholine; ADHD: Attention-Deficit/Hyperactivity Disorder; AgRP: Agouti-Related Peptide; ARC: Arcuate Nucleus (of the Hypothalamus); ASAM: American Society of Addiction Medicine; BMI: Body Mass Index; BRC: Brain Reward Cascade; CB1: Cannabinoid Receptor Type 1; DA: Dopamine; DRD2: Dopamine D2 Receptor (Gene); DRN: Dorsal Raphe Nucleus; DDS: Dopamine Deficiency Syndrome; fMRI: Functional Magnetic Resonance Imaging; GABA: Gamma-Aminobutyric Acid; GABAA/GABAB: GABA Type A/Type B Receptors; GARS: Genetic Addiction Risk Severity (Test); GLU: Glutamate; GLU M3: Muscarinic M3 (Glutamatergic Modulation Noted in Text); GMP: Good Manufacturing Practices; ISO: International Organization for Standardization; KB220: Pro-Dopamine Regulator Formulation (Prototype Family); LHA: Lateral Hypothalamic Area; MAT: Medication-Assisted Treatment; MDD: Major Depressive Disorder; MME: Membrane Metallo-Endopeptidase (Gene); miRNA: Micro-Ribonucleic Acid; NMDA: N-Methyl-D-Aspartate (Glutamate) Receptor; NAc: Nucleus Accumbens; NSF: National Science Foundation; OPRM1: Opioid Receptor Mu 1 (Gene); OPDS: Opioid Peptide Deficiency Syndrome; OUD: Opioid Use Disorder; PCA: p-Chlorophenylalanine (Tryptophan Hydroxylase Inhibitor); PENK: Proenkephalin (Gene); PET: Positron Emission Tomography; PFC: Prefrontal Cortex; POMC: Pro-opiomelanocortin; PTSD: Post-Traumatic Stress Disorder; PVN: Paraventricular Nucleus (of the Hypothalamus); RDS: Reward Deficiency Syndrome; rsFC: Resting-State Functional Connectivity; TIDA: Tuberoinfundibular Dopaminergic (Neurons/Pathway); TIQ(s): Tetrahydroisoquinoline(s); USP: United States Pharmacopeia; VMH: Ventromedial Hypothalamus; VMN: Ventromedial Nucleus (of the Hypothalamus); VTA: Ventral Tegmental Area; CMMI: Center for Medicare and Medicaid Innovation; SNP: Single-Nucleotide

Introduction

Individuals with mood disorders or with addiction, impulsivity, obsessive-compulsive behavior, and some personality disorders often exhibit a shared dysfunction in reward processing, where endogenous endorphin processing and the response to exogenous dopaminergic stimulants are compromised. Reward Deficiency Syndrome (RDS) is a polygenic trait implicating insufficient crosstalk between the known reward pathway, neuroendocrine systems, and motivational systems [1]. Collectively, these conditions engage underlying reward deficiency mechanisms across multiple brain centers. Because of the broad, overlapping behavioral manifestations sharing a common root of hypodopaminergia, the basic endophenotype recognized as RDS has been likened to a "behavioral octopus" [2,3] (See figure 1).

Figure 1: *RDS as a behavioral Octopus [2].*

In previous publications [2], our group assessed well-characterized animal models for construct validity and their suitability as potential models for RDS. Animal models spanning substance use disorder, major depressive disorder (MDD), early-life stress, immune dysregulation, attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), compulsive gambling, and compulsive eating are reviewed. Across these paradigms, convergent evidence points to recruitment of underlying reward deficiency mechanisms in multiple brain centers. Reflecting their wide, overlapping behavioral phenotypes rooted in hypodopaminergia, RDS has been likened to a "behavioral octopus".

There are multiple neurotransmitters involved in the processing of reward and punishment, with at least six major transmitter pathways and numerous second messengers. These neurotransmitter networks function within the mesolimbic circuit and prefrontal cortex (PFC), where they regulate "wanting" and culminate in neuronal dopamine release [4] (See figure 2). This figure summarizes the established Brain Reward Cascade (BRC) and the addiction-relevant correlates and neurotransmitters.

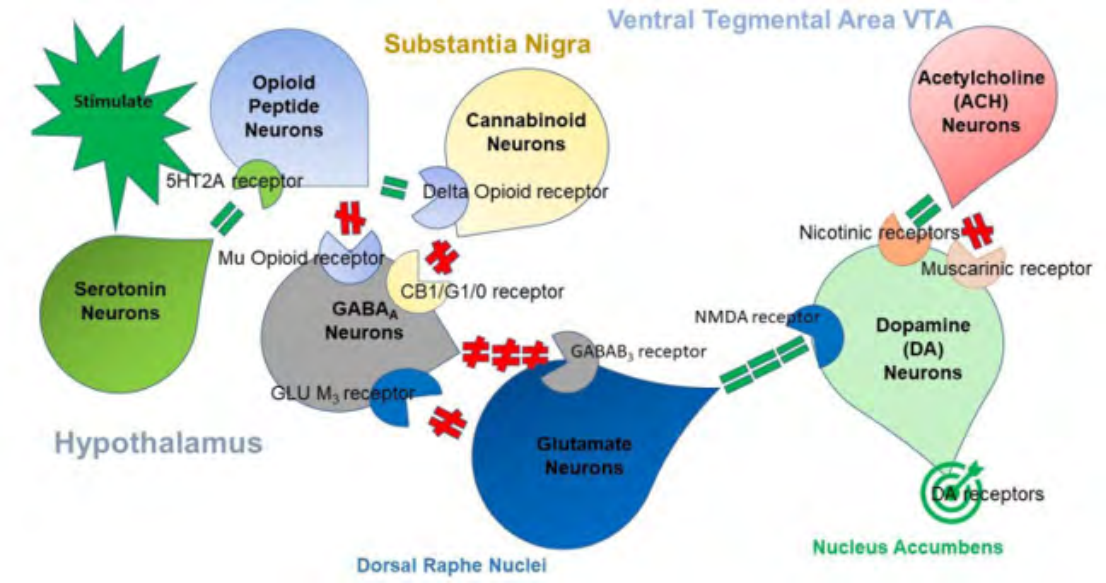

Figure 2: *The brain reward cascade.*

The figure illustrates interactions among ≥7 major neurotransmitter pathways comprising the BRC. In the hypothalamus, environmental inputs trigger serotonin release which, via 5-HT2A receptors (green "="), activates opioid peptide neurons to release peptides. These opioids exert two effects, likely via distinct receptors: (i) inhibition (red "#") through μ-opioid receptors (e.g., enkephalin) projecting to GABAA neurons in the Substantia Nigra; (ii) stimulation (green "=") of cannabinoid neurons (anandamide, 2-arachidonoylglycerol) via β-endorphin-linked δ-receptors, which then inhibit GABAA neurons in the Substantia Nigra. Cannabinoids, primarily 2-AG, can also indirectly disinhibit (red "#") GABAA neurons via Gi/o-coupled CB1 receptors in the Substantia Nigra. In the dorsal raphe nuclei (DRN), glutamatergic neurons can indirectly disinhibit GABAA neurons in the Substantia Nigra via GLU M3 receptors (red "#"). When engaged, GABAA neurons strongly (red "#") inhibit VTA glutamatergic drive, in part via GABAB neurons. At the nucleus accumbens (NAc), ACh can act on muscarinic (red "#") and nicotinic (green "=") receptors. Finally, VTA glutamatergic inputs engage NMDA receptors (green "=") on dopamine neurons, promoting dopamine release in the NAc (bullseye), which corresponds to euphoria or "wanting". Low dopamine release (e.g. endorphin deficiency) is associated with dysphoria, whereas well-being depends on a homeostatic tonic dopamine set point (See figure 2).

The cascading interaction of these neurotransmitters and second messengers' results in the correct release of dopamine within the NAc and across many brain regions. These regions are involved in motivation, cognition (memory), pleasure, stress reduction, drug reinstatement, decision-making, recall, wellbeing, and especially cravings [5]. The result is to provide *homo sapiens* with a usual happiness set-point (Figure 3) identified as resting-state functional connectivity (rsFC).

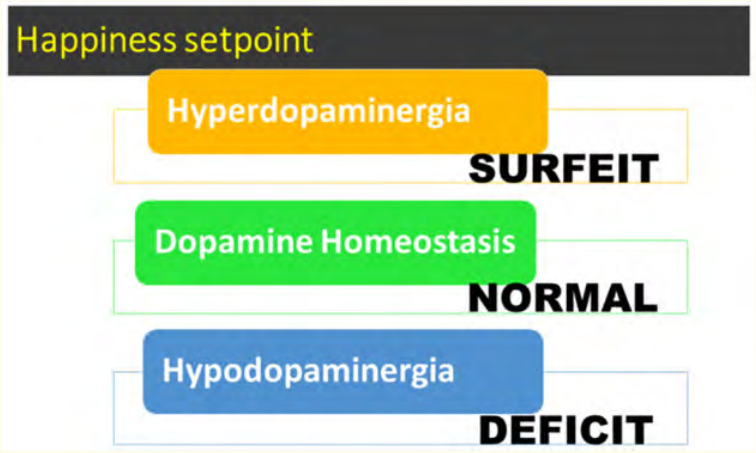

Figure 3: *A simple schematic of tonic happiness-set-point based on dopamine release, as explained in 2.*

Over the last six decades (since 1968), understanding of how psychoactive drugs influence behavior has advanced markedly, emphasizing complex actions within neuronal pathways-especially the mesolimbic system and the prefrontal-cingulate cortex. Earlier theories in opioid use have been re-evaluated [6]. Recovery frameworks (e.g. the 12-step program and fellowship) and ASAM's updated definition of "addiction" have strongly influenced younger cohorts. Broad acceptance that addiction is a brain disorder is reshaping addiction medicine [7].

Early work on serotonin and brain reward circuitry showed that depleting brain serotonin amplifies stress-like responses in rodents trained for electrical self-stimulation. They used p-chlorophenyl alanine (PCA), a tryptophan hydroxylase inhibitor that selectively depletes brain serotonin content [8]. These findings suggested that PCA is anxiogenic and that serotonin exerts anti-anxiety effects. Building on Myers and Cicero [5] and recognizing that pineal serotonin levels are low during the dark phase, Geller's group tested whether darkness enhances ethanol drinking in rodents. The first experiment showed that rats placed in a dark closet drank more alcohol than those housed in the light [9,10]. They hypothesized that elevated pineal melatonin increased drinking. Subsequently, injections of melatonin in rats exposed under "normal" (nine hours of darkness during a 24-h day) photoperiods revealed this to be accurate since they also displayed augmented ethanol intake; consequently, several experiments validated these results [9,11,12]. Convergent experiments showed that nighttime adenylate cyclase-driven stimulation of N-acetyltransferase (and conversion to melatonin) increases ~three-fold, further supporting this model [13-15]. Another line of work proposed that dopamine condensation products (isoquinolines) contribute to ethanol consumption.

In 1970, Davis and Walsh [16] proposed that a product of alcohol, tetrahydropapaverline, a benzyltetrahydroisoquinoline alkaloid derivative of the biogenic amine, dopamine, and acetaldehyde, condenses and can induce ethanol intake in rodents. Contemporaneous studies implicated biogenic amines (e.g., norepinephrine) and later indoleamine (serotonin) aldehyde condensation products-salsolinol and carbochol, respectively-in alcoholism [17,18]. Together, these data suggested shared neurochemical mechanisms for alcohol and opiate addiction. Controversy spurred additional work showing that ethanol intake elevates brain salsolinol [19,20]; salsolinol increases ethanol intake [18]; salsolinol exhibits opiate-like agonism [19-21]; and salsolinol-induced withdrawal tremors are blocked by narcotic antagonists [22-24].

Following these findings, the 1970s heralded an era of "Sex, Drugs, and Rock 'n' Roll" [25]. In the 1980s, Gold's group proposed the dopamine depletion hypothesis for recreational cocaine use and suggested bromocriptine to reduce cravings [26]. By the 1990s, neuroimaging began illuminating neurogenetic and neurobiological mechanisms of substance abuse [27,28]. While we contend that RDS is a nosology encompassing all addictive behaviors, specific drug and non-drug behaviors still require targeted consideration.

Understanding endorphin deficiency syndrome and opioid deficiency syndrome

Induction of Opioid Peptide Deficiency Syndrome may reflect genetic and epigenetic insults to reward circuitry specific to opioid peptides (endorphins, enkephalins, dynorphins). Genetic contributors include polymorphisms in Membrane metal-endopeptidase (MME), a carboxypeptidase that inactivates endogenous opioid peptides. Comings., *et al*. [29] identified a dinucleotide polymorphism in the 5′ region of the MME gene that provides a high activity of this enzyme and subsequently reduced endogenous opioid peptides by substantial inactivation. The resulting state-general "hypo-opioidergia," specific "hypo-endorphinergia" at delta/mu receptors, and "hypo-dynorphinergia" at kappa receptors (not shown in 4)-impairs opioid signaling. Additionally, individuals may carry the rs260997 C allele of Proenkephalin (PENK), which is associated with significantly reduced enkephalin synthesis across the BRC [30]. Moreover, Niikura., *et al*. [31] reported that there are epigenetic insults that reduce mRNA expression involving downregulation of mu receptor numbers or availability by chronic use/misuse of opiate analgesics like heroin or potent synthetic opioids like methadone, buprenorphine. Consistent with this, Nylander., *et al.* [32] observed reduced leu-enkephalin in the VTA of Sprague-Dawley rats after chronic morphine exposure.

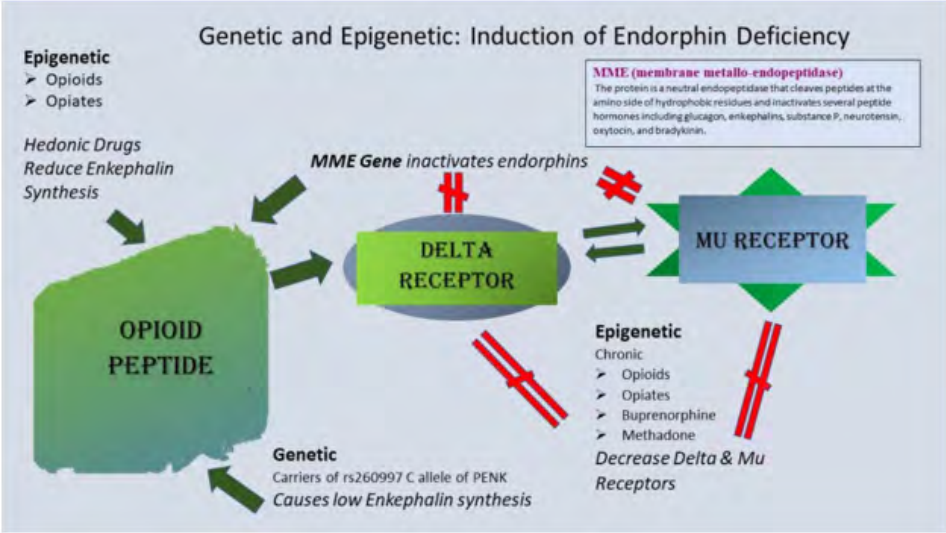

Figure 4: *Schematic of genetic and epigenetic induction of opioid peptide deficiency syndrome.*

Opioid Peptide Deficiency Syndrome (OPDS) may arise from genetic and epigenetic insults affecting the opioid-peptide components of the brain reward circuitry (endorphins, enkephalins, dynorphins). Genetic deficits may include polymorphisms in membrane metallo-endopeptidase (MME), a carboxypeptidase that inactivates endogenous opioid peptides. Comings et al. reported a 5′-region dinucleotide polymorphism in MME associated with increased enzymatic activity and greater inactivation of endogenous opioid peptides. Consequently, a general "hypoopioidergia," or a more specific "hypoendorphinergia" at delta or mu receptors and a "hypodynophinergia" at kappa receptors (not shown in figure 3), may result [red hatch sign]. Also, individuals carrying the Proenkephalin (PENK) rs260997 C

allele at birth may show significantly reduced enkephalin synthesis across the BRC [red hatch sign]. Moreover, Niikura., *et al.* described epigenetic insults-induced by chronic use/misuse of opioids (e.g. heroin, methadone, buprenorphine)-that reduce mRNA expression and downregulate mu-opioid receptor number/availability [red hatch sign]. Furthermore, Nylander et al. observed decreased leu-enkephalin in the VTA of Sprague Dawley rats after chronic morphine exposure [red hatch sign]. Dark green arrows indicate normal flow.

A range of human activities trigger the production of endorphins or enkephalins. Laughter increases pain tolerance and stimulates endorphin release [33], and vigorous aerobic exercise elevates β-endorphin [34,35]. Endorphins are released by pleasurable behaviors such as eating chocolate (contains TIQs), sex, orgasm, eating, yoga, meditation, and listening to music [36,37].

Enkephalins are abundant in the brain, especially in the hippocampus and prefrontal cortex. Stressors modulate these neuropeptides and signaling at metabotropic enkephalin G-protein-coupled receptors (delta-opioid and mu receptors) [38,39]. Other endogenous opioid ligands such as dynorphins bind to kappa receptors, while endorphins primarily bind to mu receptors [40,41].

In the mesolimbic reward pathway, enkephalins binding to μ-receptors inhibit GABA release, thereby increasing dopamine production and release [42]. Endorphin or opioid deficiency weakens inhibitory control over GABA and, via raphe interactions at the substantia nigra-VTA junction, reduces dopamine release at the NAc. This resulting hypodopaminergia increases addiction vulnerability.

It is well known now that the interaction of at least seven neurotransmitter systems (serotonin, opioid peptides, cannabinoids, GABA, Glutamate, acetylcholine, and dopamine) and associated second messengers play a role in reward processing in the brain of *Homo sapiens*. The Brain Reward Cascade (BRC) that culminates in dopamine release (illustrated in figure 1) is the basis of pleasures from everyday natural rewards. Balanced neurotransmission supports well-being and stress reduction, whereas BRC impairment can produce hypodopaminergia. For example, if an individual carries a polymorphism in the OPM1 (rs1799971-A118G) that reduces mu-opioid receptor function, this reduction can drive over-expression of GABAergic signaling and significantly reduce the net preferential-neuronal release of Dopamine at the NAc. Also, there could be epigenetically induced methylation that can cause a reduced mRNA expression for at least two generations [43]. Having an antecedent opioid/endorphin deficiency may predispose an individual to uncontrolled dependence once exposed to a powerful opioid like Oxycontin. This risk underscores the challenges the entire scientific community has in the face of the worst opioid epidemic ever seen in America [44].

Understanding obesity as a hypodopaminergia

Another example of specific RDS behavior is obesity. Affecting more than 300 million people worldwide, obesity remains difficult to manage with popular weight-loss tactics. Managing the obesity problem seems within reach, as our understanding of genomic influences on drug/nutrient responses develops. Strategies indicated by this understanding of nutriepigenomics and neurogenetics in the treatment and prevention of metabolic syndrome and obesity include modulating mRNA expression by DNA methylation and inhibiting histone deacetylation. Based on an individual's genetic makeup, deficient metabolic pathways can be targeted epigenetically, for example, with dietary supplementation containing phytochemicals, vitamins, and functional amino acids. Also, the chromatin structure of imprinted genes that control nutrients during fetal development may be modified. Pathways affecting dopamine signaling, molecular transport and nervous system development are implicated in these strategies. Obesity is a subtype of Reward Deficiency Syndrome (RDS) and these new strategies in the treatment and prevention of obesity aim to improve dopamine function. It is not merely a matter of gastrointestinal signaling linked to hypothalamic peptides but also finding novel ways to improve ventral tegmental area (VTA) dopaminergic function and homeostasis.

Obesity is impacting on the lives of more than 300 million people worldwide [45] and maintaining a healthy weight using popular weight loss tactics remains a very difficult undertaking. Managing the obesity problem seems within reach, as a better understanding of the function of our genome in drug/nutrient responses develops.

The literature is rife with research and reviews related to the role of dopamine and other neurotransmitters and their neurological interactions within the reward circuitry [46-59]. Indeed, following their first genetic study that found that severe alcoholism associated with the Taq A1 allele of the dopamine D2 receptor gene (D2R) [60], Blum., *et al*. [61] delineated "Reward Deficiency Syndrome (RDS)". RDS is the result of a malfunction of "Brain Reward Cascade" neurotransmission [59]. This dysfunction directly links to abnormal craving and reduced executive function (decision making), involving multiple reward-gene and second-messenger deficits across prefrontal and mesolimbic systems. In contrast, the functional collaboration of dopamine with other neurotransmitters such as serotonin and opioids (neuropeptides), supports a sense of well-being and is relevant even in cocaine abuse contexts [62-66].

In our opinion there are a number of important strategies to overcome obesity. For example: 1) further investigate hypothalamic energy regulation and how metabolic hormones affect VTA dopamine neurons; 2) identify neurobiological mechanisms shared between food and drug addiction; 3) expand neuroimaging on dopamine in food addiction, brain metabolism, and addiction transfer following bariatric surgery, and probe the role of non-coding miRNAs in drug addiction and the epigenetics of metabolic syndrome; 4) detect early-life chromatin modifications of imprinted genes that regulate nutrients during fetal development; 5) develop treatments that epigenetically target deficient metabolic pathways, including dietary supplementation with phytochemicals, vitamins, and functional amino acids.

However, to appreciate the role of the neural reward circuitry and dopamine regulation in obesity, we must revisit gut-hypothalamic mechanisms.

Gut-hypothalamic homeostatic energy regulation

The first reported connection between the ventromedial hypothalamus (VMH) and obesity came from Hetherington and Ranson who in 1940 found that lesions of the VMH resulted in hyperphagia (overeating) and obesity in rats [67]. The lesioning was extensive, involving the ventromedial (VMN) and arcuate (ARC) nuclei [68,69]. The importance of the ARC subsequently became an intense focus. The regulation of energy (glucose homeostasis) was linked to the Proopiomelanocortin (POMC) and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons within the ARC [70]. In contrast, profound anorexia and weight loss were produced when Anand and Brobeck created extensive lesions of the lateral hypothalamic area (LHA). The hypothalamic "dual-center" hypothesis with the "satiety center" located in the VMH and the "feeding center" at the LHA site proposed by Stellar was initially dominant [71]; however, a distributed-control view now appears more parsimonious. Grill., *et al*. [28] emphasized that energy control is distributed across a network of sites. Lesions in one part of the brain can shift body weight and adiposity [72].

The set point dilemma

Keely and others suggested that VMH and LHA lesions provided evidence that weight "set point" might depend on external and internal environments (neural substrates) [73] and that a parsimonious feedback signal likely monitors peripheral metabolic status to regulate energy homeostasis. Kennedy [74] proposed a "lipostatic" hypothesis in which adipose stores supply a negative-feedback signal. Kennedy suggested that a negative-feedback system signals in proportion to adipose tissue mass to regulate intake or expenditure and maintain body fat within a predetermined set point (See figure 2) [74].

The hormone leptin, secreted in proportion to fat mass, was eventually found [75]. The idea of a "set point" (preserved body weight) is still controversial, with articles supporting [76] and opposing it [77-79]. Interestingly, researchers have found that in certain rodent strains and most humans that become obese the "preserved" body weight can be readily driven upward, while efforts to move below an elevated set point fail in ~90% of individuals [80-85]. This set point dilemma continues to be a central focus of weight loss researchers and may have some relationship to a similar set point observed in the drug abuse literature [86].

Homeostatic systems

The hypothalamus integrates the hormonal, autonomic, and somatomotor regulation of nutrient levels in the body by orchestrating neuroendocrine homeostatic responses [84]. The networks that control central system energy homeostasis are distributed, interconnected neural circuits [87-90]. Two neuronal types that control energy balance are the hypothalamic anorexigenic POMC neurons, and the orexigenic NPY/AgRP neurons [91,92]. Trans-synaptic GABA neurons can modulate POMC neuronal activity indirectly via inputs arising from NPY neurons [93-95]. ARC POMC and NPY neurons project widely into several hypothalamic and extra-hypothalamic sites that shape consumption [96]. Outputs from the paraventricular nucleus (PVN) to endocrine, autonomic, and somatomotor systems [97-99], as well as the pre-autonomic brain stem and spinal cord [100,101], are involved in feeding and energy balance regulation.

Ventral tegmental area (VTA) dopamine neurons are modified by metabolic hormones, such as leptin and ghrelin. Leptin suppresses VTA dopaminergic activity, and the hyperphagia of leptin-deficient mice is reduced when dopamine signaling is absent [102-105]. Conversely, the direct introduction of ghrelin into the VTA enhances feeding [106,107].

Feeding behavior regulation by dopaminergic systems

Given the complexity of dopamine signaling across brain regions described in this review, we highlight differences in the sensitivity and regulation of dopaminergic function. The tuberoinfundibular dopaminergic (TIDA) neurons link the hypothalamus to the pituitary (hormonal regulation, nurturing, pregnancy, sensory processes), while the nigrostriatal pathway connects the substantia nigra to the striatum (motor control); the mesolimbic and mesocortical reward circuits originate in the VTA.

As early as 1984, Moore's group [108] reported differences in dopamine-mediated receptors between the nigrostriatal/mesolimbic systems and the hypothalamic TIDA neurons. Moore [109] further emphasized that anatomically distinct dopaminergic systems subserve diverse functions-maintaining postural reflexes, modulating basic psychic processes, and controlling pituitary hormone secretion linked to food intake. Each system is regulated by mechanisms appropriate to its function. Annunziato [110] showed that dopamine receptors in the anterior pituitary are more sensitive to agonists and antagonists than those in the striatum. Moreover, Demarest and Moore [111] noted that dopamine synthesis regulation in terminals of nigrostriatal, mesolimbic, and tuber hypophyseal nerves differs from tuberoinfundibular nerves, which lack an autoreceptors regulatory mechanism. Thus, dopaminergic responses vary by system and location-an essential consideration when explaining relationships between food and drugs.

Most animals and humans override homeostatic satiety when faced with highly palatable foods rich in sugar and fat [112]. Hedonic stimuli engage reward circuits mediating "liking" (pleasure) and "wanting" (motivation) [113]. VTA dopamine neurons play a significant role in obesity [114,115]. The mesolimbic pathway links the hippocampus and VTA to medial prefrontal cortex, nucleus accumbens, and amygdala.

Food and drug addiction identification of common neurobiological mechanisms

The idea that food and drugs share neurobiological and neurogenetic mechanisms was articulated by Hoebel over 30 years ago [115] and brought to mainstream attention by Gold, Avena, and colleagues [116-130]. Clinically, permitting candy in treatment settings may facilitate "addiction transfer" from alcohol, opiates, or cocaine to glucose. Current estimates suggest that roughly twenty percent of individuals undergoing lap-band surgery develop new-onset drug addiction post-surgery. This phenomenon of substituting drugs for food has been studied in both human and animal clinical trials. It is plausible that variants in reward-circuit genes reduce dopamine function and heighten craving for both glucose and alcohol. Conversely, during protracted (>3 weeks) abstinence from alcohol and other substances, some individuals may enter a "hyperdopaminergic," epigenetically influenced state characterized by elevated extracellular DA levels [131].

Regarding RDS, it is noteworthy, that both substance and non-substance addictive behaviors like food (glucose), opiates, alcohol, nicotine, internet gaming, gambling, music, and sex all trigger dopamine release in the nucleus accumbens. This acute release of dopamine leads to feelings of well-being in the very short term, especially in individuals who, through gene polymorphisms (variants), environmental factors, or both, have compromised dopaminergic function. The environmental compromise of dopaminergic function can be mediated epigenetically via expression of many genes; for example, DNA methylation (reduced expression) or inhibition of histone deacetylation (increased expression) within chromatin [131]. The core concept is the formula, Phenotype equals Genetics plus Environment [P = G + E]. This reflects a complex set of interactions involving many polymorphic genes and their subsequent interaction with the environment. Thus, if the hypodopaminergic effect of specific genetic reward polymorphisms is compounded by an unsatisfactory environment, further decreasing dopamine function, the affected person may attempt to boost brain dopamine. They may self-medicate to obtain a transient dopamine "fix" via behaviors (e.g. food, drugs, or sex that cause the acute release of dopamine**)** [132-135].

Although, addiction to food is not the source of all cases of obesity, research has shown that obesity produces alterations in behaviors and brain structures similar to those alterations seen in drug addiction. Might it be presumed that a considerable number of people no longer eat to survive, but rather survive to eat; are we serving up enough dopamine for dinner?

Within the framework of the brain's reward system with regard to food consumption, the "thrifty gene hypothesis" (a survival gene linked to famine and fat metabolism) and the commonality between food and drug addictions [136,137] are important. Food and drug consumption engage both homeostatic and hedonic reinforcers, activating connections within overlapping neural circuits [138-142]. Several regions of the brain are involved in the reinforcement of both drug and food intake [143-146], and numerous neurotransmitters and hormones have been examined in these and related regions [147-149]. Extensive literature supports these commonalities, including work by Avena's group [150-152] and by Blum., *et al.* [153].

In clinical situations, reciprocal comorbidity of food and drug addictions typically appears in the literature. This overlap warrants intensive investigation [154-157]. Have a common phenotype and treatment been identified for these seemingly distinct conditions?

Recent changes in the nomenclature of addictions indicate a significant shift in the conceptualization of addictions, where non-substance behaviors may also be classified as addictions. Extensive data provide empirical evidence that there are overlaps of different types of addictive behaviors in etiology, phenomenology, and in the underlying psychological and biological mechanisms. One study by Kotyuk., *et al*. [158] reported an epidemiological analysis carried out as part of the Psychological and Genetic Factors of the Addictive Behaviors (PGA) Study, collecting data from 3,003 adolescents and young adults (42.6% males; mean age 21 years). Addictions to psychoactive substances and behaviors were rigorously assessed. They reported lifetime occurrences of the assessed substance uses, their co-occurrences, the prevalence estimates of specific behavioral addictions, and co-occurrences of different substance use and potentially addictive behaviors. Associations were found between (i) smoking and problematic Internet use, exercising, eating disorders, and gambling; (ii) alcohol consumption and problematic Internet use, problematic online gaming, gambling, and eating disorders; and (iii) cannabis use and problematic online gaming and gambling. The results suggest a large overlap between the occurrence of these addictions and behaviors and underscore the importance of investigating the possible common psychological, genetic, and neural pathways. These data further support concepts such as the Reward Deficiency Syndrome and the component model of addictions that propose a common phenomenological and etiological background of different addictive and related behaviors.

Although overeating may have significant neurochemical associations with drug abuse [159], regarding other eating disorders such as bulimia [160] and anorexia [161,162] less is known. Nonetheless, evidence is accumulating that similar gene polymorphisms confer risk across food- and drug-related phenotypes. Common risk alleles like the A1 form of the dopamine type 2 receptor (DRD2) gene, found to associate with eating disorders such as binge eating disorder, bulimia, and anorexia also associate with substance abuse in genetic studies.

Utilizing sophisticated neuroimaging, especially positron emission tomography (PET), Gene-Jack Wang, Nora Volkow, Peter K. Thanos, and others have contributed to the field with valuable insights regarding the molecular role of dopamine function and obesity [163-193]. This line of work began with a PET study showing an inverse relationship between Body Mass Index (BMI) and dopamine in obese humans. The same group found that the availability of dopamine D2 receptor was reduced in obese individuals and inversely related to BMI. Dopamine moderates reward and incentive circuits and thus, dopamine deficits in obese individuals may prolong disordered eating to balance the reduced stimulation of these circuits. In a recent study, Thanos., *et al*. [194] provided strong evidence from animal studies that dopamine D2 gene expression can impact behaviors throughout an entire lifespan. They found that both locomotor activity and body weight were moderated by an enriched environment and that mice from an enriched environment showed greater behavioral variability between genotypes compared to mice from a deprived environment.

Summary

Genetic researchers have asked whether some individuals possess genetically fragile opioid systems that could implode when exposed to exogenous opioids. The genetic addiction risk score (GARS) predicts vulnerability to opioid dependence [195]. These findings argue that Endorphinergic Deficiency Syndrome, a subset of RDS [196], rather than a generalized opioid deficiency syndrome, underlies the opioid epidemic. Gold's work on concurrent inhibition of the locus coeruleus by alpha-2 adrenergic systems supports novel pharmacological therapies like clonidine and lofexidine [197], facilitates rapid and slow nonopioid detoxification, and suggests possible new treatments for craving and anxiety. The current emphasis on opioid replacement in opioid use disorders (OUD) rests on an unproven disease model. Oddly, the most efficacious treatments for OUDs promote compliance [198], are pharmacologically close to abused opioids, and can lead to dependence on the treatment itself, making discontinuation unlikely [199]. The brain does not exhibit a specific "opiate/opioid deficiency" phenotype per se.

However, methadone and buprenorphine treatments remain first-line for most, if not all, patients with OUDs [200]. As in early methadone maintenance, opioid replacement is often analogized to insulin for diabetes, yet dosing targets receptor saturation/blockade of exogenous reinforcement rather than endogenous opioid physiology [201]. Dose escalation in medication-assisted treatment (MAT) may further compromise the patient's ability to ever recover from an underlying Endorphinergic Deficiency Syndrome. Relatively opioid naïve OUD patients may develop an iatrogenic endorphin deficiency. Exogenous opioids can induce Dopamine Deficiency Syndrome (DDS), also a subset of RDS, as well as depression and anhedonia, potentially driving continued opioid seeking, misuse, and overeating [202].

Most guidelines around the world recommend psychosocially assisted agonist maintenance therapy, rather than medication alone, as a treatment for OUD. During the pandemic, access to this support was often limited, leading some patients to drop out, and others to adopt telemedicine and technology-assisted behavioral therapies while continuing their MATs.

The finding that dopamine neurons and their location can show different responses to the same substance must be considered when explaining the relationship between food and drugs. In one pharmacological example, Syvälahti [203] showed that the antipsychotic activity of neuroleptic drugs yields distinct pathway effects. Both nigrostriatal (induce extrapyramidal symptoms) and tuberoinfundibular mechanisms (increases prolactin levels) may co-occur while the mesocortical effects (reduced symptoms of schizophrenia) of antipsychotic drugs are sought after. Thus, we must account for these differences, especially when considering therapeutic targets and shared mechanisms between food and drugs.

While the Hypothalamic-Gut Axis plays a major role in nutrient selection, therapeutic targets to prevent food addiction include Pro-Dopamine Regulation (See figure 1). Converging support from fMRI in humans and animal research supports the theory that distributed neurobiological circuits are disturbed in addiction, metabolic syndrome, and obesity. Altered dopamine reward circuits contribute to

pathologic food consumption behaviors. For example, Chen., *et al*. [204] reported that, compared with the dopamine D2 TaqA2 allele, there is a high correlation of high percent body fat with the D2 TaqA1 allele (See figure 5 and other associations involving the DRD2 A1 allele). Given the commonality of neuro mechanisms between drug and glucose addiction, and evidence from neuroimaging and epigenetic studies, dopamine-agonist treatment strategies that epigenetically target disrupted dopamine pathways-rather than current antagonist approaches-may succeed.

Figure 5: *Schematic of DRD2 A1 allele and associations with RDS behaviors.*

Pathways that affect dopamine signaling, molecular transport, and nervous system development are implicated in these approaches. Obesity is a subtype of RDS, and emerging prevention/treatment strategies target improved dopamine function. Neurogenetic evidence supporting pro-dopamine regulation appears sound [205].

Balanced dopaminergic activity that supports resting-state functional connectivity in the mesolimbic system may promote healthier choices and reduced craving [206]. Accordingly, novel approaches that balance dopamine and enhance well-being are encouraged to

treat and prevent obesity. Pursuing this therapeutic direction may help shift addictions to food, drugs, and other behaviors. Beyond gastrointestinal-hypothalamic peptide signaling, the aim is to improve ventral tegmental area (VTA) dopaminergic function and homeostasis (see figure 1).

Based on this seminal research, and unlike other existing genetic tests, The USA and Foreign patented GARS test is, to our knowledge, the first validated Genetic Addiction Risk Severity test with important clinical benefits, including personalized medicine and assessment of RDS risk severity (e.g. alcoholism), as first suggested by our group. The test will also include the cytochrome P450 system of genetic variants that influence how individuals metabolize opioids. Our laboratory continues to develop other specific genetic tests for obesity, ADHD, and PTSD. As discussed, early identification of genetic antecedents will inform targeted systems therapeutics [207,208].

Policy implications and real-world recommendations

The scientific rationale for pro-dopamine regulation is compelling, but its translation into practice requires more than laboratory evidence. The policy landscape is largely shaped by pharmaceutical paradigms, which often leave little room for innovations such as nutraceuticals. A practical path forward involves setting baseline quality safeguards, developing payer mechanisms that allow access beyond boutique markets, and embedding these supports in a way that complements-not replaces-existing treatments.

All nutraceuticals, sometimes referred to as "neutraceutical" when they target brain-specific pathways, are already required under U.S. law to be produced in facilities compliant with Good Manufacturing Practices (GMP). This baseline, however, does not guarantee public confidence. Voluntary third-party certifications, such as those offered by USP, NSF, or ISO, can provide additional assurance of identity, purity, and consistency. These certifications should be understood not as additional regulatory hurdles, but as complementary trust-building measures. Encouraging the use of USP-grade raw materials would further enhance quality and reliability without imposing the heavy burdens of a pharmaceutical approval pathway.

Equally important is how these supports are paid for. If nutraceuticals remain confined to cash-pay boutique models, access will be inequitable and limited to the privileged few. Instead, coverage mechanisms should be explored through demonstration projects and value-based payment models. For example, CMMI pilots could integrate nutraceuticals into bundled care alongside medication-assisted therapy, behavioral counseling, and lifestyle interventions. In this model, reimbursement would hinge not on the capsule itself but on measurable outcomes such as reduced craving, improved adherence, fewer relapses, stabilized weight, and patient-reported well-being. Private insurers could follow suits where quality standards are met, and real-world data suggest cost savings through reduced hospitalizations or improved function. Until such coverage mechanisms mature, philanthropic and patient-assistance programs may serve as interim bridges, but the long-term goal must be payer-integrated access to ensure equity.

The research agenda must also adapt. Pharmaceutical randomized controlled trials will remain the gold standard for drugs, but nutraceuticals can be evaluated effectively through pragmatic trials, registries, and observational studies that capture outcomes in real-world contexts. Independent replication is desirable, but policy should not erect barriers that prevent safe, evidence-supported products from being tested in practice. Transparency is essential: label claims should be tied to available evidence, and registries should make outcomes public. Nutraceutical use must always remain voluntary, patient- and clinician-driven, and accessible across socioeconomic groups.

Within this broader category, pro-dopamine regulators represent a particularly promising direction. KB220, the most extensively studied prototype, illustrates how such formulations can be investigated and applied responsibly across preclinical, imaging, and clinical

contexts. It should not be subjected to retrospective regulatory hurdles; rather, it serves as a reference point for how future products might aspire to meet both scientific and clinical expectations. Policy ought to recognize KB220 as an exemplary, while ensuring that any similar entrants meet at least the baseline of GMP compliance and are encouraged to pursue complementary third-party certification. This approach safeguards patients without stifling innovation and sets a trajectory where trust is built on transparency, quality, and real-world outcomes.

In sum, the challenge is not to force nutraceuticals through the same regulatory funnel as pharmaceuticals, but to establish pragmatic standards that protect patients, foster innovation, and encourage equitable access. GMP compliance, complemented by voluntary third-party verification, offers a credible quality baseline. Coverage mechanisms that reward outcomes rather than ingredients can make these supports accessible to broader populations. Research structures adapted to real-world practice can build the evidence base further. And exemplars such as KB220 demonstrate that decades of responsible investigation can chart a course for others. By grounding policy in these real-world recommendations, it is possible to align innovation with patient safety, payer confidence, and societal equity.

Conclusion

Clinically, the future is here, and the treatment of chronic addiction depends on scientifically sound, evidence-based early genetic risk determinations that enable personalized patient care rather than fictional, hypothetical, or theoretical practices.

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