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Mini Review

When the Brain Coordinates Life-Risk Behavior: A Rewarding Anorexia

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Abstract

Understanding how brain supports adapted (and adaptive) decisions when individuals deal with challenge of the environment (stressor) is critical as adapted decision-making (goal-directed behavior) is supposed to protect from disturbances including unexpected death. How does the brain can then trigger chronic consumption of drugs or persistent food restriction (anorexia) until the point of death? In the neurosciences field, most of studies report correlations between behavioral disturbances in the face of environmental challenges and deregulations of neural circuits. Even if causal relationship is less described, exploring these correlations in simpler animal models makes possible the study of molecular and behavioral phenotypes in isolation and has revealed the conservation of specific molecular mechanisms in humans. For instance, involvement of serotonergic system in eating behavior remains crucial as current investigations, consistent with several decades (79 years from 1940 to 2019) of studies, reveals the conservation of specific molecular underpinnings of eating behaviors in animals and humans with eating disorders, suggesting the robustness of identified effects. In this context, studies describe commonalities between restrictive food intake and addiction, as in the nucleus accumbens - a critical structure of the brain's reward system - activation of addictive signaling under the control of serotonin (5-HT, 5-hydroxytryptamine) 4 receptors (5-HT_4Rs) mediates reduction in motivation for food in food-deprived mice, and ties anorexia and motor hyperactivity; Two hallmarks of anorexia nervosa. Accordingly, the brain prevents the transition from transient to persistent hypophagia (anorexia) with a network governing goal-directed behavior against depressive-like behavior, under the control of 5-HT_4Rs localized in the medial prefrontal cortex. Food restriction at the onset following stress appears as an adapted behavior for managing stressors (as mediated by specific molecular changes related to depression resistance), but in the face of chronic stress, loss-of-control of the mPFC could imbalance the activity of the NAc and triggers persistent anorexia.

Keywords: Addiction; Anorexia; Stress; Food intake; Locomotion; Animal models; Brain; Nucleus accumbens; Medial prefrontal cortex; Serotonin 4 receptors

Abbreviations: cAMP: Cyclic Adenosine Monophosphate; CART: Cocaine- and Amphetamine-Regulated Transcript; KO: Knockout; mPFC: Medial Prefrontal Cortex; Nac: Nucleus Accumbens; Pka: Protein Kinase A; 5-Ht: 5-Hydroxytryptamine Or Serotonin; 5-Htrs: Serotonin Receptors; 5-Ht_4rs: Serotonin 4 Receptors; Sirna: Small Interference RNA

Introduction

All behavior appears to be the result of context-dependent brain functions; neuronal networks implement gradually over development during their interrelationships with environmental factors. This cerebral network likely becomes mature context-dependently and may gradually favor adapted (and adaptive) behavior as adapted decision-making (i.e., *goal-directed behavior*). Goal-directed behavior expresses motivation. For instance, when individuals feel hungry, they are motivated to obtain food under physiological circumstances. Feeling hungry then translates into the demand for energy. Hunger impels the organism to display goal-directed behavior to seek and consume foods and thus survive. However, individuals do not make the decision to feel hungry, but can decide to satisfy or not satisfy hunger. For some individuals, eating behavior can be chronically disordered and can include persistent food restriction and/or excessive intake despite negative consequences, suggesting disturbances of motivation, and of goal-directed behavior. Food is a basic primary reward, requiring motivation to obtain it ("wanting") [1]. Some investigators

assimilate excessive consumption of foods, regardless of whether it is associated with obesity (Corwin RL, et al.) [2], to addiction [3]. However, whether binge eating represents a kind of addiction remains unclear [2]. Here, we describe common molecular mechanisms between anorexia and addiction.

Towards Critical Implication of 5-HT Volume Transmission

The rewarding effect of anorexia has been described in humans at the onset of anorexia nervosa symptoms [4]. Is it the result of excess synapses (*fixed brain*) that maintain food restriction until the point of death? As the prospect of receipt of a positive reward is capable of inducing risky, and potentially lethal behavior, impairments in the neural underpinnings of persistent food restriction until lethal point could be included in those of dependence.

Some investigators examine the activity of neural centers involved in the recognition of rewards and the development of habits [5]. A report described goal-directed decision-making as a complicated process and argued that reward-based decisions depend on the *habit* and *goal-oriented systems* [6]. The *habit system* "stores" stimulus-response associations based on past rewards and the *goal-oriented system* selects one action by anticipating the positive and negative outcomes [6]. Indeed, "*Addiction is a form of learning and relapse is a persistent memory of the drug experience*" [7]. As neural bases of learning and memory appears the result of synapse function, as mainly demonstrated by studies of Eric Kandel; Does neural communication, as the serotonin (5-hydroxytryptamine, 5-HT) *volume transmission*, serve to avoid *habits* for conferring the most *instant flexibility* to better adapt to environmental changes [8]?

The existence of the synapse was critically challenged until 1954; and, in 1975, Descarries L, et al. [9], described that 5-HT binds receptors (5-HTRs), more often located at 100 µm than at 20 nm (*synaptic transmission*), introducing the *volume transmission* (Descarries L, et al.) [9], from the site of 5-HT release. The preponderant 5-HT volume transmission extends the ubiquitous distribution of the serotonergic system, supporting its multiple functions; all physiologically interrelated, from habituation, memory, moving etc., to protecting survival, likely in order to critically contribute to adaptive and adapted eating responses to stress. The phylogenetically old serotonergic system then appears as a *continued red line* underlying crucial functions, which appear sophisticated to the point of a 5-HT-independent action of some 5-HTRs to evoke constitutive activity, such as the 5-HT_4 receptors (5-HT_4Rs), in eating behavior [10].

Serotonergic System in Brain Serves to Reduce Food Intake and Motivation to eat

In mammals, the serotonergic neuronal cell bodies assemble in the raphe nuclei (reviewed in [11]). Among nine nuclei, the dorsal and median raphe nuclei (DR, MR) send axons to the whole forebrain [11]. In particular, the serotonergic axons in the cerebral cortex mainly arise from the DR (Figure 1a). 5-HT binds 18 G-protein coupled receptors (5-HTRs) and commonly mediates reduction in food intake [8].

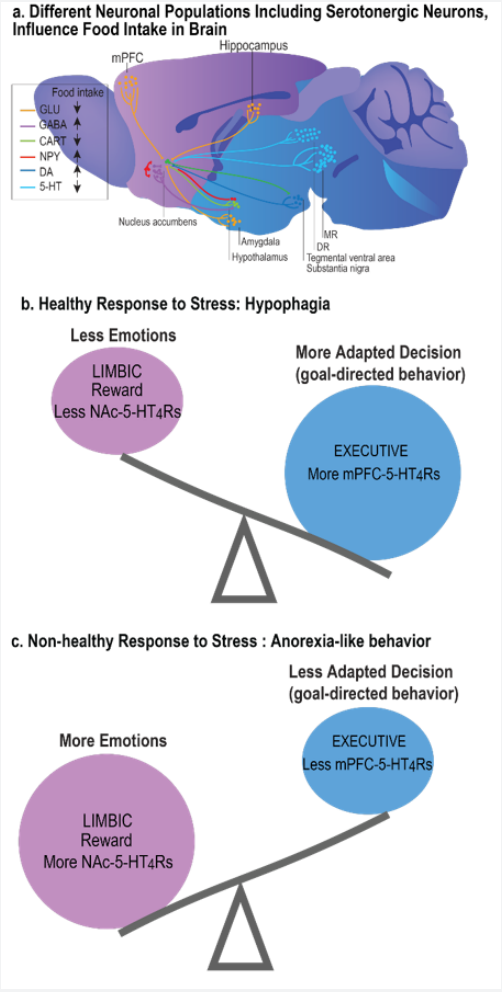

Figure 1: A working hypothesis: A predominance of a cortical (medial prefrontal cortex: mPFC control could reflect an adaptive process to prevent depressive-like behavior when facing an acute stress at the onset of anorexia nervosa; limits of this adaptive process could "submerge" cortical control and "release the influence of the subcortical areas" such as the nucleus accumbens (NAc). (a) Numerous biological systems influence food intake including serotonergic neurons in brain; In the mPFC, 5-HT neurons mainly arise from the DR and send axon collaterals to the NAc [33]. In the mPFC, 60% of pyramidal efferent neurons express both 5-HT_4Rs and 5-HT_{1A}R mRNA [34]. In the mPFC, 5-HT_4R mRNA are mainly expressed by GLU-expressing efferent neurons [35]. In the NAc, 5-HT_4Rs are localized on GABA-expressing efferent neurons to the lateral hypothalamus [14]. From the mPFC, 5-HT_4Rs serve to increase the firing activity of DR 5-HT neurons in rodents [18,36,37]. From the DR and mPFC, 5-HT_{1A}R exert a negative feedback on DR 5-HT neurons [22,38-40]. We found that mPFC-5-HT_4Rs overexpression induced (i) decreases in the levels of plasma membrane 5-HT transporter (SERT), (ii) increases in the 5-HT release, which (iii) activates DR 5-HT_{1A}R that prevent the transition from a transient to persistent hypophagia, i.e., "early anorexia", introducing an antidepressant effect of anorexia [5-HT accumulation resulting from 5-HT_{1A}R desensitization and SERT reduction [15]. (b) When the mRNA levels of mPFC-5-HT_4Rs are enhanced following acute stress, the mRNA levels of NAc-5-HT_4Rs is reduced [15], suggesting that mPFC-5-HT_4Rs serve to reduce NAc-5-HT_4Rs expression following acute stress. Stimulation of NAc-5-HT_4Rs provokes both anorexia and motor hyperactivity [14,19]. These both behavioral responses are addictive signaling pathway-dependent (cAMP/PKA/CART) [14,19]. (c) Following up these studies, we posit that following chronic stress reduced activity of the mPFC-5-HT_4Rs (among many other factors) could favor a subcortical influence, i.e. an autonomous control without adaptive decisional control irrespective to requirement for energy, with "more 5-HT_4Rs in the NAc", which may favor a dependent-anorexia [41].

Hoebel and Leibowitz's groups in 1976 and 1986 reported, in series of studies, that 5-HT volume transmission commonly serves to reduce food intake, *i.e.* hypophagia, and to enhance satiety, in the hypothalamus. Following up these findings, decades of reports have described hypophagia following stimulation of 5-HT_{1B} and 5-HT_{2C} receptors (5-HT_{1B}R, 5-HT_{2C}R), whereas 5-HT_{1A}R and 5-HT_{2B}R can exceptionally serve to enhance feeding [12]. In 2004, 5-HT volume transmission has also been reported to favor less motivation for food in food-deprived mice, mediating anorexia-like behavior through the activation of addictive signaling (cAMP: cyclic adenosine monophosphate / PKA: protein kinase A / CART: cocaine- and amphetamine-regulated transcript), in the NAc [13,14]. In 2017, causal relationships between the activity of the serotonergic system and hypophagia in response to external stress were identified in a network governing goal-directed behavior [15]. This network consists of the ascending serotonergic inputs from the DR to the mPFC and is controlled by 5-HT_4Rs [15].

In sum (reviewed in Compan V. [8]), under basal conditions, specific 5-HTRs located in an automatic executive system (the hypothalamus) serve to stabilize usual food intake, whereas in response to external stressors, other 5-HTRs; 5-HT_4Rs located in a more adaptive-decisive system, including the mPFC and the NAc, favor rewarding effects of food restriction [14-19]. Such dual organization of 5-HTRs could promote decisional processing and dampen autonomic input, resulting in dysfunctional eating irrespective to requirements for energy. When food intake varies temporarily to the baseline, survival is not compromised, and restrictive food intake may well be adapted (and adaptive with beneficial effects on longevity), but when eating response to stress persists, as seen in anorexia nervosa, survival is compromised [20]. The predominance of cortical control could reflect adaptive processes to prevent "negative emotions" as neural commonalities exist between anorexia and antidepressant effect (Jean A, et al.) [15], (Figure 1); while, hypothalamic events could represent an executive system, which became autonomous as learned during long conserved evolutionary processes. It results the hypothesis formulated above: The low number of 5-HT cortical synapses (30%) could serve to prevent habits (do not have to be memorized) for conferring the most *instant flexibility* to better adapt to environmental changes [8].

Common Signaling Pathway Between Anorexia and Addiction under the Control of Serotonin 4 receptors

The cerebral distribution of 5-HT_4Rs is conserved from rodents to humans, with one of the highest levels in the NAc [21,22]. Four 5-HT_4Rs splice variants were described in mice (10 in humans) called 5-$HT_{4(a)}$R, 5-$HT_{4(b)}$R, 5-$HT_{4(e)}$R, 5-$HT_{4(f)}$R [23]. Stimulation of 5-HT_4Rs reduces deficits of associative learning in olfactory discrimination task (Bockaert J, et al. [24]), and, 5-HT_4Rs favor long-term (but not short-term) memory [25]. In humans, stimulation of 5-HT_4Rs also favors memory [26]. The 5-HT_4Rs may therefore have conserved functions such as feeding from mice to humans. Indeed, stimulation of 5-HT_4Rs reduces food intake in rodents [14-16,19]. And, the concentration of 5-HT_4Rs is low when patients with Alzheimer's disease overeat, but not in individuals with Alzheimer who did not display hyperphagia [27]. Importantly, 5-HT_4Rs (and apparently not the other 5-HTRs) in the NAc serve to a rewarding effect of restrictive food intake, as stimulation of 5-HT_4Rs mediates anorexia-like behavior through activation of an addictive signaling pathway [cAMP/PKA/CART] [14,19], (Figure 1). Indeed, in neurons of the NAc, activation of a cAMP signaling is a means of transforming an immediate reduction of drugs' rewarding effect into a durable dependence [28]. Cocaine triggers counteracted adaptive responses as an increased activity of cAMP/PKA signaling in the NAc [28]. The resultant phosphorylation of the cAMP-responsive element binding (pCREB) dampens rewarding effects [29]. The sensitivity to subsequent drug exposures then decreases (tolerance) with increased activity of reward pathways (dependence) to the point that drugs removal triggers declines in motivation, mimicking depression, leading to maladaptive decision [28]. Considering the involvement of CART in motivational properties of cocaine (Rogge G, et al.) [30], these findings evidence commonalities between addiction and anorexia, consistent with the rewarding effect of anorexia seen at the onset of symptoms. Food restriction is initially highly rewarding because the individual feels to cope with difficult-to-manage stressors during adolescence and adulthood [31]. Indeed, the brain can implement food restriction until death, as the result of maladaptive decision-making. As deep brain stimulation in the NAc or the anterior cingulate cortex (that is homologous to the rodent mPFC) in patients with anorexia nervosa led to an overall improvement, our studies conducted in animal models may have critical clinical significance [32]. Accordingly, mPFC-5-HT_4Rs serve to prevent persistent food restriction by controlling the ascending 5-HT inputs from the DR to the mPFC under stressful conditions [15], (Figure 1). We predict that deregulation of 5-HT_4Rs could play a vital role in pathological appetitive decision as NAc-5-HT_4R levels are abnormal in overweight humans, which could be related to the capacity of 5-HT_4Rs to reshapes excitatory synaptic connections (Evgeni Ponimaskin, submitted), consistent with less dendritic spines in the NAc in 5-HT_4R knockout (KO) mice [8].

Conclusion

The neuronal network underlying eating behaviors is part of a larger network implicating reward and decision-making systems that react to environmental cues. Accordingly, environmental changes (i.e., stressors) associated with biological predisposition could alter motivation and adaptive decision-making, including persistent food restriction. Adaptive responses to stress depend on the serotonergic system – and, here, adaptive feeding response to stress depends on 5-HT_4Rs - eating disorders could emerge when serotonergic neurons reach the limit of their adaptive capacities. We suggest that a predominance of a cortical control reflects an adaptive process to prevent depressive-like behavior when facing an acute stress at the onset of anorexia nervosa (Figure 1). Numerous studies have to be conducted to test whether in the face of chronic stress, limits of this adaptive process could "submerge" cortical control and "release the influence of the subcortical areas"

such as the NAc (autonomous control without adaptive decisional control), in which uncontrolled oscillating changes in common molecule levels (cAMP, CREB: all controlled by G-protein coupled receptors, here by 5-HT_4Rs) could lead to an anarchic consumption of foods (from anorexia to bulimia and/or binge eating).

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Conflict of Interest

The author declares no competing financial interests.

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