Review Articles

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From taste blunting to anhedonia: Remodeling of the taste-reward neural circuitry and receptor molecular mechanisms in depression

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ABSTRACT

Background Major depressive disorder (MDD) is a globally prevalent condition characterized by high heterogeneity. Anhedonia—the inability to experience pleasure—is a core symptom and a predictor of poor prognosis. Emerging evidence suggests that "taste blunting" (reduced taste sensitivity and pleasure) is a measurable sensory component of anhedonia, reflecting a potential disruption in the neural systems that translate sensory signals into hedonic experiences. **Methods** This review synthesizes current clinical and preclinical evidence to investigate the link between taste dysfunction and the brain's reward system in depression. We analyze neuroimaging data, molecular studies on taste receptors, and the impact of neuroinflammation and neurotransmitter dysregulation on the taste-reward neural circuitry. **Results** Clinical findings demonstrate that MDD patients exhibit significant reductions in taste intensity and pleasure, which correlate with symptom severity. Neurobiologically, this dysfunction is mapped onto a remodeled mesocorticolimbic reward circuit, involving the nucleus accumbens (NAc), ventral tegmental area (VTA), and prefrontal cortex (PFC). Molecularly, chronic stress leads to the downregulation of peripheral sweet taste receptors and 5-HT receptors in taste cells. Centrally, pro-inflammatory cytokines disrupt dopamine synthesis and corticostriatal connectivity. Furthermore, the activation of "anti-reward" systems, such as the κ-opioid receptor (KOR) system, and imbalances in glutamatergic signaling further exacerbate circuit dysfunction. **Conclusions** Taste blunting in depression is not a mere peripheral sensory deficit but an external manifestation of a profound disruption within the shared taste-reward neural circuitry. This perspective suggests that sensory assessment of taste may serve as a valuable translational marker for MDD subtypes. Future therapeutic strategies should move beyond monoamine-centric models to target this circuitry directly via glutamatergic modulators, KOR antagonists, and anti-inflammatory interventions.

1. Introduction

Major depressive disorder (MDD) imposes a significant global disease burden, characterized by a heterogeneous constellation of symptoms [1]. Among these, anhedonia—the diminished capacity to experience pleasure or interest in rewarding stimuli—stands as a core diagnostic feature and a significant predictor of poor treatment response and adverse outcomes [2][3]. While anhedonia encompasses deficits across social, physical, and sensory domains, growing clinical and preclinical evidence positions sensory anhedonia, particularly pertaining to taste and smell, as a compelling and measurable component of this complex symptom [4][5].

Historically, the link between depressed mood and alterations in taste perception has been clinically observed, with patients often reporting that food "tastes bland" or "has no flavor" [6]. This clinical phenomenology suggests a potential disruption in the neural systems that translate a basic sensory signal (taste) into a subjective hedonic experience (pleasure). The hedonic impact of palatable food is a fundamental form of reward, and its neural processing shares substantial overlap with the brain's mesocorticolimbic reward circuitry, which is centrally implicated in the pathophysiology of anhedonia [7][8]. Dysfunction within this circuitry, encompassing regions like the nucleus accumbens (NAc), ventral tegmental area (VTA), and prefrontal cortex (PFC), is considered a neurobiological substrate for the loss of pleasure and motivation seen in MDD[9][10].

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Therefore, investigating taste dysfunction in depression transcends a mere focus on a peripheral sensory deficit. It offers a unique translational window into the integrity of the brain's reward system. This review synthesizes current evidence to explore the hypothesis that taste blunting in depression is an external manifestation of a more profound disruption within the shared taste-reward neural circuitry. We will examine the clinical correlations between taste alterations and anhedonia, delineate the neurocircuitry that processes taste hedonics and is disrupted in depression, elucidate the molecular mechanisms—from peripheral receptors to central inflammation and neurotransmitter systems—that underlie this circuit dysfunction, and finally, discuss the therapeutic implications of targeting this axis for the treatment of anhedonic depression.

2. The clinical link between taste dysfunction and anhedonia in depression

Clinical studies provide direct evidence for altered taste perception in individuals with depression, which often correlates with the severity of anhedonic symptoms. Patients with MDD report subjective reductions in taste pleasure and intensity [6]. More objective assessments reveal measurable changes in taste function. For instance, individuals with late-life depression exhibit significant chemosensory anhedonia, defined as a diminished hedonic response to smell and taste, and this deficit correlates with both greater depressive symptom severity and cognitive impairment [4]. This suggests that the inability to derive pleasure from food is not just a subjective complaint but a quantifiable clinical feature linked to the core pathology of depression.

Alterations extend to basic taste thresholds. Studies indicate that taste sensitivity is modulated by monoamine neurotransmitters, systems profoundly dysregulated in depression. Administration of agents that increase serotonin (5-HT) or noradrenaline (NA) can significantly lower detection thresholds for sweet and bitter tastes in healthy individuals, respectively [11]. Conversely, acute depletion of central serotonin in healthy volunteers enhances detection of salt and increases perceived intensity of bitter and sour tastes, while blunting the pleasantness of bitter stimuli [12]. These findings imply that the serotonergic and noradrenergic imbalances characteristic of depression could directly perturb the gustatory system, leading to distorted taste perception. Furthermore, anxiety levels, frequently comorbid with depression, positively correlate with bitter and salt taste thresholds, indicating a broader affective influence on taste processing [11].

The relationship may also have a genetic component. Taste sensitivity to bitter compounds like phenylthiocarbamide (PTC) has been explored as a potential marker for vulnerability to depression. One study found that individuals with the lowest sensitivity to PTC (non-tasters) reported significantly lower general hedonic capacity on the Snaith-Hamilton Pleasure Scale compared to supertasters, suggesting that genetically determined peripheral taste receptor function might be a peripheral risk factor for anhedonia [13]. While not all studies find that simple sweet taste tests differentiate depressed from non-depressed groups[14], the convergence of evidence points to a tangible disruption in the sensory-affective processing of taste in MDD. This disruption is particularly salient in melancholic depression, where anhedonia is a cardinal feature [1], and may serve as a specific marker to distinguish depression from other conditions like Alzheimer's disease in the elderly [15].

3. The neural circuitry of reward: a shared substrate for taste pleasure and motivational deficits

The experience of pleasure from a palatable taste is not generated solely on the tongue but is constructed within a distributed neural network known as the reward circuitry. This circuitry is critical for assigning hedonic value, generating motivation, and guiding goal-directed behavior—processes that are collectively impaired in anhedonia [16][17]. Key nodes include the NAc (particularly its shell region), the VTA, the ventral pallidum (VP), the amygdala, the hippocampus, and regions of the prefrontal cortex (PFC) such as the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and ventromedial prefrontal cortex (vmPFC) [7][18].

The NAc serves as a crucial hub, integrating sensory, emotional, and cognitive information to gate reward-related behavior. Pharmacological manipulation of the NAc can directly modulate hedonic taste reactivity in rodents [19]. Importantly, afferent inputs to the NAc determine specific aspects of reward. For example, optogenetic stimulation of ventral hippocampal (vHipp) inputs to the NAc shell enhances food palatability and is sufficient to condition flavor preferences, highlighting a pathway directly linking memory-related structures to hedonic valuation [19]. The VTA provides dopaminergic input to the NAc and PFC, a projection essential for reward anticipation, motivation, and reinforcement learning [20][21].

In MDD, neuroimaging studies consistently reveal dysfunction within this reward network. A core finding is blunted activation of the ventral striatum (which includes the NAc) during the anticipation of reward, a neural correlate of reduced motivation or "wanting" [22][25]. This hypofunction appears to be a trait-like marker, as it is observed in never-depressed individuals at high familial risk for MDD [22]. During the outcome or "liking" phase of reward, findings are more mixed but often show alterations in mesocorticolimbic regions [23][25]. Furthermore, depression is associated with decreased functional connectivity within corticostriatal reward pathways. Specifically, reduced connectivity between the ventral striatum and the vmPFC has been linked to greater anhedonia severity [24][26][27]. This disrupted communication between the striatum (reward valuation) and the vmPFC (value representation and decision-making) may underpin the inability to translate potential rewards into motivated action.

Crucially, this same circuitry is engaged during the pleasurable experience of tasting. Neuroimaging studies in healthy humans show that the taste of pleasant foods activates the OFC, amygdala, and striatum [28]. In depression, structural and functional alterations in these regions are evident. For instance, increased gray matter volume in the medial OFC (gyrus rectus) is found in anorexia nervosa and bulimia nervosa, and this volume predicts taste pleasantness ratings, directly linking structure to hedonic taste function [29]. The convergence of evidence strongly suggests that the neural machinery responsible for the pleasure of eating is the same machinery that malfunctions in depressive anhedonia, providing a circuit-level explanation for the clinical phenomenon of taste blunting see Figure 1.

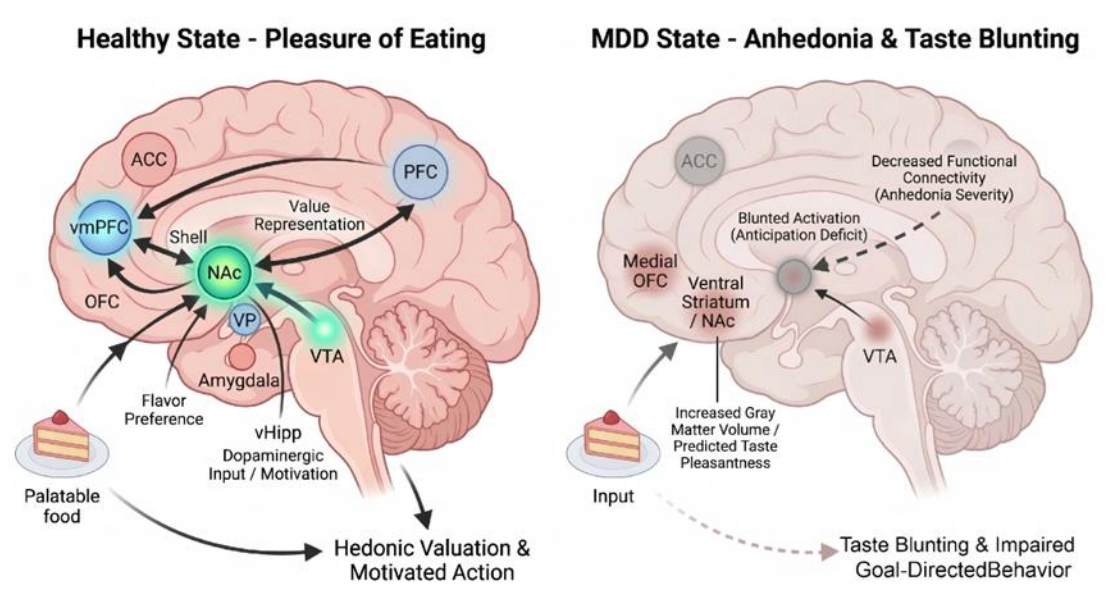

Fig.1 -

Comparison of taste-reward neural circuitry between the healthy state and Major Depressive Disorder (MDD).

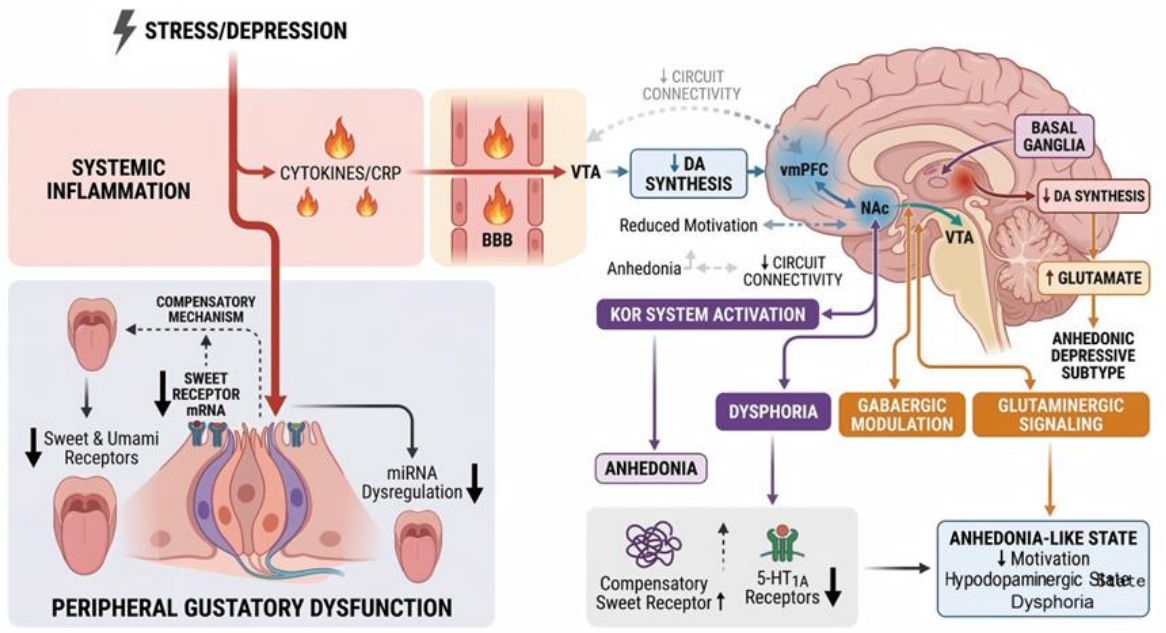

Fig. 2 - Molecular and neurobiological mechanisms underlying taste-reward circuit dysfunction in depression.

4. Molecular mechanisms underlying circuit dysfunction: From inflammation to neurotransmitter systems

The dysfunction within the taste-reward circuitry is driven by a cascade of molecular events, ranging from peripheral taste receptor changes to central neurochemical and inflammatory disturbances.

At the peripheral gustatory level, chronic stress and depression models in animals show altered expression of taste receptors. Stress can downregulate mRNA for sweet (T1R2, T1R3) and umami taste receptor subunits in circumvallate papillae [30][31], potentially diminishing the initial sensory signal for palatability. Conversely, in some stress-susceptible models, an upregulation of sweet taste receptors has been observed, possibly as a compensatory mechanism for increased energy expenditure or altered central processing [32]. Serotonin signaling within taste cells may also be involved, as stress-induced anhedonia in rats is accompanied by decreased expression of 5-HT1A receptors in taste cells [33]. MicroRNA dysregulation, which can induce an anhedonia-like state in animal models, may represent another layer of molecular control over hedonic valuation [34].

Centrally, inflammation has emerged as a key pathophysiological pathway linking stress to anhedonia and reward circuit dysfunction [35][36]. A

significant subset of MDD patients exhibits elevated peripheral inflammatory markers, such as C-reactive protein (CRP) and pro-inflammatory cytokines [35]. This inflammation can access the brain and disrupt reward processing. Inflammatory cytokines can reduce the synthesis, release, and availability of dopamine in the striatum, a neurotransmitter critical for motivation and reward learning [36][37]. Neuroimaging studies confirm that higher inflammation in MDD is associated with decreased functional connectivity in corticostriatal reward circuits (e.g., between ventral striatum and vmPFC) and with greater anhedonia and psychomotor slowing [26][27][38]. Furthermore, inflammation can increase brain glutamate levels, and the combination of high CRP and high basal ganglia glutamate defines a depressive subtype with prominent anhedonia and disrupted local brain network integrity [38].

Dopaminergic dysregulation is central to reward deficits. The mesolimbic dopamine pathway, projecting from the VTA to the NAc, is crucial for incentive salience and effort-based decision-making [20][21][39]. Preclinical and clinical data suggest a hypodopaminergic state in anhedonic depression, contributing to reduced motivation [40]. Other neurotransmitter systems are intricately involved. The κ-opioid receptor (KOR) system, activated by the endogenous dynorphin peptide, is considered an "anti-reward" system that produces dysphoric and anhedonic states[41][42]. Stress induces dynorphin release, and KOR antagonists show antidepressant and anti-anhedonic effects in animal models [42][43]. The GABAergic system, particularly GABA_B receptors, also modulates reward and depression, with antagonists often exhibiting antidepressant-like properties [41]. Finally, glutamatergic signaling, especially through NMDA receptors, is fundamental for synaptic plasticity within the reward circuitry. The rapid antidepressant effects of agents like ketamine are believed to involve a cascade ultimately leading to enhanced glutamatergic and dopaminergic transmission in the mesolimbic circuit [44][45] see Figure 2.

5. Therapeutic implications: Targeting the taste-reward circuitry in depression

The reconceptualization of anhedonia as a reward circuit disorder, with taste blunting as a potential peripheral marker, opens avenues for novel therapeutic strategies. Traditional first-line antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), have demonstrated limited efficacy in treating anhedonia and may even have a pro-anhedonic effect in some individuals [2][3][46]. Therefore, treatments that more directly target the dysregulated neurobiology of reward are needed.

Pharmacologically, drugs with dopaminergic or glutamatergic mechanisms show promise. Bupropion, a norepinephrine-dopamine reuptake inhibitor, is often cited for its potential benefit on motivation and energy [46]. The combination of dextromethorphan (an NMDA receptor antagonist and sigma-1 agonist) with bupropion (which also increases dextromethorphan bioavailability) represents a synergistic approach. This combination (Auvelity®) has demonstrated rapid (within 2 weeks) and sustained antidepressant efficacy, with high rates of remission, and is thought to act via glutamatergic modulation [47][49]. Ketamine, a rapid-acting antidepressant, exerts profound effects on the reward system. It reverses stress-induced deficits in dopamine function, increases reactivity in the mesolimbic reward circuitry (including the VTA and ventral striatum), and is associated with rapid reductions in anhedonia [44][45][50][51]. Its molecular effects involve a cascade leading to increased synaptic plasticity in reward-related brain regions [52].

Novel targets are also under investigation. κ-opioid receptor antagonists like aticaprant and navacaprant have generated interest due to their ability to block the dysphoric and anhedonic effects of stress-induced dynorphin release. Early clinical trials suggest aticaprant may improve depressive symptoms, particularly in patients with prominent anhedonia, when used as an adjunctive therapy [43][53][55]. Anti-inflammatory strategies represent another avenue. Since inflammation can dampen dopaminergic signaling, interventions that reduce inflammation (e.g., cytokine inhibitors, lifestyle changes) or that bypass its inhibitory effects on dopamine (e.g., with dopaminergic agents) could be beneficial for the inflammatory subtype of anhedonic depression [35][36].

Neuromodulation techniques can directly influence the reward circuitry. Repetitive transcranial magnetic stimulation (rTMS) targeting the left dorsolateral PFC, which is connected to deeper reward structures, has shown efficacy in improving depressive symptoms, including anhedonia [46]. Other techniques like transcranial direct current stimulation (tDCS) and transcutaneous auricular vagus nerve stimulation (taVNS) are also being explored [46].

Finally, psychotherapeutic and behavioral interventions remain cornerstone approaches. Behavioral Activation (BA) therapy is explicitly designed to counteract anhedonia and avoidance by systematically increasing engagement with potentially rewarding activities [2]. Mindfulness-based strategies and savoring techniques can help patients re-engage with and amplify positive experiences, including those related to food and taste[46].

6. Conclusion and future perspectives

The journey from a bland taste on the tongue to the profound emptiness of anhedonia in depression is mapped onto a complex neural and molecular landscape. Converging evidence strongly supports the model that taste dysfunction is not an isolated sensory deficit but a salient clinical manifestation of a broader disruption within the brain's mesocorticolimbic reward circuitry. Peripheral alterations in taste receptor expression and sensitivity may represent the initial point of a pathological cascade that involves central inflammatory processes, dopaminergic and glutamatergic dysregulation, and ultimately, dysfunctional communication between key nodes like the striatum and prefrontal cortex.

This integrated perspective has significant implications. It argues for the routine clinical assessment of sensory anhedonia, including taste and smell, as it may provide valuable insights into the reward deficit profile of a patient [3]. Therapeutically, it underscores the need to move beyond monoamine-centric approaches and embrace treatments that directly target the reward circuitry, whether through novel pharmacotherapies (KOR antagonists, glutamatergic modulators), neuromodulation, or targeted psychotherapy. The identification of an inflammatory-anhedonic subtype, characterized by specific neural and molecular signatures, paves the way for biomarker-guided, personalized treatment strategies [26][35][38].

Future research must bridge several gaps. There is a need for more sophisticated translational models that better capture the multifaceted nature of anhedonia, distinguishing between deficits in "wanting" and "liking" [39][56]. Longitudinal studies are required to determine whether treating taste-perception deficits or circuit-based dysfunction can prevent the onset or improve the prognosis of depression. Furthermore, clinical trials for novel agents should employ an experimental therapeutics approach, directly testing target engagement in the reward circuitry to understand mechanisms of action and predictors of response [22]. By continuing to unravel the intricate connections between the tongue and the brain's reward centers, we move closer to developing more effective,

precise, and holistic interventions for one of depression's most debilitating core symptoms.

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