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Neurobiology of Aversive States

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Abstract

Hoebel and colleagues are often known as students of reward and how it is coded in the CNS. This article, however, attempts to focus on the significant advances by Hoebel and others in dissecting out behavioral components of distinct aversive states and in understanding the neurobiology of aversion and the link between aversive states and addictive behaviors. Reward and aversion are not necessarily dichotomous and may reflect an affective *continuum* contingent upon environmental conditions. Descriptive and mechanistic studies pioneered by Bart Hoebel have demonstrated that the shift in the reward-aversion spectrum may be, in part, a result of changes in central dopamine/ACh ratio, particularly in the NAc. The path to aversion appears to include a specific neurochemical signature: reduced dopamine activity and increased ACh activity in “reward centers” of the brain. Opioid receptors may have a neuromodulatory role on both of these neurotransmitters.

Keywords

Behavior; Reward; Aversion; Stress; Drug Withdrawal; Opiate; Food Deprivation; Conditioned Taste Aversion; Conditioned Place Preference; Pain; Dopamine; Acetylcholine; Nucleus Accumbens; Striatum; Obesity; Eating Disorders; Alcohol

1. Introduction

Reward paradigms have been studied for decades using approach and self-stimulation measures. The state opposite of reward may be considered “aversion”, which is reflected in avoidance and stimulation escape measures [1]. The Merriam-Webster Dictionary defines *aversion* as: a) a feeling of repugnance toward something with a desire to avoid or turn from it; b) a settled dislike: antipathy; c) a tendency to extinguish a behavior or to avoid a thing or situation and especially a usually pleasurable one because it is or has been associated with a noxious stimulus. Although aversive states have been studied extensively in the psychological context [2–8], the neurobiology behind aversion has received far less attention. In part, this may be because the definition of aversion is seemingly ambiguous

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when applied to neurobiological pathways. Different criteria may apply to acute versus chronic aversion, perhaps reflecting neuro-mechanistic differences. This review will explore these differences with an emphasis on the work by Bartley G. Hoebel and others on implicated neurotransmitters.

2. Behavioral Measures

A number of protocols have been constructed to induce aversive states acutely in rodents, such as restraint stress, trauma to an extremity (tail or foot shock), administration of nausea-inducing agents (i.e. lithium chloride), intracranial electrode stimulation, or intraperitoneal acetic acid administration [9–12]. Behavioral measures (i.e., ultrasonic vocalizations and behavioral reactivity) can then be used to interpret the degree to whether the aforementioned stimuli are indeed aversive [9, 13]. Ultrasound vocalizations at 22 kHz are important components of the unconditioned defensive behavior repertoire in rats and a reliable measure of fear and aversion in laboratory animals [194]. Therefore, the frequency of the vocalization response is the important parameter that separates a reflex from a response indicative of an aversive state. Other researchers measure avoidance motivation in an aversive state [14], or use classic fear conditioning to determine how quickly an animal learns to respond with fear to a neutral stimulus which has been contingently paired with an aversive stimulus [15–17].

Conditioned place aversion (CPA) is also used to evaluate preferences for environmental stimuli that have been associated with aversive states. This procedure involves several trials where the animal is presented with a negative stimulus paired with placement into a distinct environment containing various cues (i.e. tactile, visual, and/or olfactory). When later tested in the normal state, withdrawals and the amount of time spent in compartments previously associated with negative stimuli serve as an indicator of preference and a measure of reward learning versus aversion [14].

Hoebel and colleagues have used electrical stimulation studies to explore reward and aversion [12, 18–26]. Electrical stimulation of the hypothalamus is known to be either rewarding or aversive depending on the location of the stimulation electrode [1, 25]. While electrode placement in the lateral hypothalamus (LH) is generally considered a positive reinforcer (promotes self-stimulation), more medial electrode placement causes signs of aversion and elicits stimulation-escape responses where an animal lever presses to stop stimulation [1, 12]. Therefore, self-stimulation and stimulation-escape are sometimes used to measure positive and negative reinforcers associated with appetitive and aversive states, respectfully.

Precipitation of drug withdrawal, particularly opiate withdrawal, is another frequently used approach in inducing an aversive state that can be easily demonstrated through behavioral criteria and a well-defined physiological response [134]; and protocols of chronic food deprivation that induce significant weight loss can be quite useful in studying not only a prolonged aversive state but also the motivation to obtain a powerful reinforcer like food to reverse it [135].

3. Acute versus chronic aversion

A distinct incident of mild pain or stress can cause an acutely aversive state, which an animal will try to escape. Upon cessation of the aversive stimuli, the animal tends to recover from the aversive state, psychologically and neurochemically. However, repeated stressors can cause a chronic state of aversion, which has long-lasting ramifications, even after the stimulus has been removed. Examples of chronic aversion may include chronic food deprivation, obesity, bulimia nervosa, drug withdrawal, learned negative associations,

depression, and chronic pain. Clinical studies have shown that chronic pain patients present several psychological disturbances such as high levels of anxiety and depression [27, 28], stress [29, 30], or reduced sleep quality [31]. These disturbances are likely reflective of central monoamine aberrations. Moreover, chronically aversive states result in neuroanatomical alterations such as a decrease in grey matter density [32]. Acute versus chronic states of aversion may reflect distinct neurochemical phenomena, as discussed below.

4. Neurobiology

4.1 Dopamine

The majority of research on mesoaccumbens dopamine focuses on appetitively-motivated behaviors. Dopamine release in the nucleus accumbens (NAc), striatum, and medial prefrontal cortex is potentiated by rewarding stimuli, such as food intake [33–35], drugs of abuse [33, 36–38], and sexual behavior [39, 40]. However, mesolimbic dopamine is also involved in aversively motivated (i.e. “avoidance”) behaviors [41–44]

Acute states of aversion (i.e. immediate pain) have been shown to increase dopamine activity in mesolimbic areas traditionally associated with reward, although regional variations exist in degree and time course [45–53]. This increase in striatal dopamine release is supportive of other lines of investigation suggesting a role for striatal dopamine in the response to acute stress; for example, destruction of the dopaminergic neurons of the nigrostriatal bundle reduces the capacity of rats to respond appropriately to stress [54].

However, not all aversive states reflect an increase in dopamine activity. When intraoral saccharine infusions are repeatedly paired with lithium chloride (nausea-evoking agent), animals in the conditioned taste aversion group experience significant decreases in NAc dopamine when given the saccharine conditioned stimulus alone [55]. Because sweet taste (saccharine) is usually associated with reward (and enhanced dopamine), this demonstrates the ability of learned aversions to alter neurochemical responses.

Medial hypothalamic (MH) stimulation, which has been considered to cause a primarily aversive state [1, 12], causes a significant decrease in extracellular dopamine [25]. However, when rats can lever-press to escape MH stimulation, NAc dopamine increases instead. This is similar to findings from Cabib and colleagues that show that the NAc dopamine metabolite, 3-methoxytyramine, decreases when foot shock is inescapable and increases when animals are allowed to control the painful shock experience [56]. Inescapable foot shock may be analogous to learned helplessness or depression, which are more chronic conditions.

The seemingly dichotomous nature of dopamine responses to stressful stimuli may reflect different neurobiological factors contributing to acute versus chronic states of aversion. Although an acutely painful stimulus enhances dopamine activity globally in the brain, chronic pain stimuli seem to downregulate dopaminergic transmission [28, 53, 57–60]. Interestingly, fibromyalgia patients, who are arguably in a chronic state of aversion, do not experience the same increases in dopamine in response to acute pain stimuli as healthy controls [28]. However, the perceived rating of the pain is greater for these patients. Thus, it is possible that the enhanced dopamine response to acute stress discussed above may be a compensatory action in healthy individuals to dampen perception of the stressful stimulus. In chronic states of aversion, this adaptation is lacking.

Depression and learned helplessness are other forms of chronic aversion marked by decreased dopamine activity. Clinical studies have demonstrated increased levels of

dopamine transporter (DAT) in depressed patients [61], which results in greater reuptake and shortened dopamine signaling, and medications which raise dopamine levels have anti-depressant effects [62–64]. In animals, behavioral depression can be inferred using the forced-swim test, which measures swimming escape efforts vs. passive floating [65]. In the forced-swim test, a rat gives up trying to escape on the second day, demonstrating learned helplessness, and extracellular dopamine in the NAc subsequently decreases [21, 66]. Park and colleagues found that they could induce learned helplessness in mice by prolonged exposure to dopamine [67], suggesting that repeated stressors (which acutely release dopamine) may cause neuroadaptations that result in a downregulated dopamine system.

Similarly, drugs of abuse, which repeatedly release excess dopamine in central reward regions, may trigger a chronic aversive state as the brain compensates by decreasing basal dopaminergic activity. Numerous studies have demonstrated diminished dopamine neurotransmission during withdrawal from addictive substances [68–74]. In cases of pharmacologically induced withdrawal, dopamine also decreases [71, 75] and the threshold for brain-stimulation reward rises [76].

In the past decade, Bartley Hoebel's work has demonstrated that certain patterns of binge eating on sugar can cause an aversive state with dopaminergic similarities to drug addiction [21, 77–82]. While intermittent bingeing on sugar repeatedly releases dopamine in the NAc [82], the resulting state of obesity is marked by decreased dopamine activity [83–85]. Other changes in the dopamine system, such as increases in D1 receptor binding, decreases in D2 receptor binding, and increases in D3 receptor mRNA, are also common to aversive states that follow sugar bingeing [79, 80, 86–88] or drug withdrawal [86, 89–91]. Furthermore, "sugar-dependent" rats experience somatic signs of withdrawal, such as teeth chattering, forepaw tremor, and head shakes when withdrawal is precipitated with an opioid antagonist (naloxone), or when sugar is removed [79]. Electrical stimulation studies have also produced evidence of an aversive state following overeating. Lateral hypothalamic electrode placement, which usually produces self-stimulation, instead results in escape responding after overeating [12].

Like overeating, undereating can also trigger an aversive state with changes in the dopamine system. Restricted eating with weight loss decreases extracellular dopamine in the NAc and significantly alters dopamine response to amphetamine, morphine, and food intake [92]. Chronic food deprivation and subsequent weight loss increases drug-seeking behavior and voluntary drug intake in animals [93–96] and individuals with Anorexia Nervosa (AN) have been found to have higher rates of substance abuse [97, 98]. Clinical studies also demonstrate decreased dopaminergic transmission in AN [99–101].

Overall, aversive stimuli seem to enhance dopamine activity in the acute sense. Over time though, the brain adapts to counteract these dopamine surges by downregulating dopaminergic transmission. The decreased dopaminergic neurotransmission secondary to its activation may be a consequence of prolonged excitatory stimulation of dopamine-containing neurons by opioids (discussed later in this paper), which results in depletion of dopamine stores and/or depolarization blockade in excitability of dopamine cells [53]. Other events such as receptor internalization, upregulation of D2-Short autoreceptors, decreased transmitter synthesis, increased reuptake, or a combination of the above could also contribute to a compromised dopamine system.

4.2 Acetylcholine

Acetylcholine (ACh) may interact with dopamine to modulate approach and avoidance behaviors in the reward-aversion spectrum. Hoebel and colleagues (2007) suggest that the dopamine/ACh balance in the NAc may affect motivation (and motivational disorders)

analogous to movement (and movement disorders) where dopamine enables a person to start moving, while ACh acts as a control to prevent over-responding and facilitate stopping [21]. Other studies support a counter-regulatory role of dopamine and ACh. In the striatum, dopamine excites while ACh inhibits GABA/dynorphin output via a predominance of D1-type receptors and dopamine inhibits while ACh excites GABA/enkephalin output cells via D2-type receptors [102, 103].

Contrary to dopamine, which typically fosters approach and states of reward, ACh release in the nucleus accumbens correlates with the onset of acute and maintenance of chronic aversive states. Further studies on the effect of cholinergic receptor antagonism in the nucleus accumbens on the expression of such states would illustrate as to whether this is a causal relationship. However, regional variations may exist based on the nature of the stressor (acute versus chronic). Restraint stress or foot-shock immediately stimulates ACh release in the hippocampus, but not in the NAc [104–106]. ACh release in the NAc may be more involved in slower onset states of “aversion”, reflecting changes in reward evaluation. For example, ACh in the NAc has a role in the onset of satiation, with extracellular increases in the NAc towards the end of a meal [81, 107]. While the increase in dopamine during feeding signals food “reward”, the increase in NAc ACh may code for the aversive aspects of gastric distention. This increase in ACh is attenuated with sham feeding where food drains from a gastric fistula after ingestion [81]. Thus, the food-induced dopamine release goes unopposed in sham-feeding, which may be analogous to purging in Bulimia Nervosa.

Other studies also indicate that enhanced NAc ACh may reverse hedonistic eating and contribute to food aversion. Endogenous appetite suppressants, such as hypothalamic dopamine, serotonin, and CCK, act via the NAc by releasing ACh [108] and synthetic appetite-suppressant drugs also release ACh in the NAc [109]. This indicates that the rewarding aspects of food intake may become aversive as satiation is reached through mechanisms that increase ACh. Likewise, if food intake becomes aversive by pairing the food with lithium chloride-induced nausea, the taste of that food significantly increases ACh in the NAc [11]. Thus, food (in particular, sweet taste), can release dopamine or ACh depending on the learned physiological consequences. Moreover, elevated ACh is sufficient by itself to cause a taste aversion [110]. This effect may be mediated by enhanced ACh acting at M1 receptors that oppose dopamine’s D2 receptor effects on the indirect GABA output pathway for behavior inhibition [111, 112].

Further evidence that aversive states are marked by increased ACh comes from drug-seeking and drug withdrawal studies. Drugs that increase NAc ACh inhibit cocaine self-administration [109, 113, 114], and block cue-induced heroin seeking [115] and conditioned place preference, which is reversed by selective ablation of ACh neurons [116]. Naloxone-precipitated drug withdrawal, a classic state of aversion, causes dopamine to decrease and ACh to be released instead [71, 75, 117, 118]. Nicotine and ethanol withdrawal are also marked by a significant decrease in dopamine and increase in ACh [72, 73]. Similarly, aversive hypothalamic stimulation increases the level of extracellular ACh in the NAc. Animals increase lever pressing to escape this ACh-mediated state [24]. Acute administration of drugs that directly stimulate dopaminergic reward pathways (i.e. nicotine, amphetamine, cocaine) increases NAc ACh, but has a larger effect on dopamine than ACh, in terms of percent increase. This suggests that the dopamine/ACh ratio may be the key factor, rather than absolute levels, in creating a rewarding versus aversive state.

In states of depression, as measured by escape efforts in the forced swim test previously described, basal ACh levels remain elevated while dopamine decreases when behavior is depressed [119]. Antidepressants are known to restore escape swimming [120], and thus, Hoebel and colleagues hypothesized that an antidepressant drug (i.e. serotonin enhancer)

should also lower ACh. They confirmed this hypothesis and found that the serotonin-1a receptor is one of the relevant receptors mediating this effect [111, 121]. Because local bilateral injection of a muscarinic agonist (arecholine) depresses swimming behavior, and the M1 antagonist, pirenzepine, increases escape efforts [112], ACh may be working through the M1-type receptor to influence depression [21]. Notably, this is not a locomotor effect because these manipulations do not cause hyperactivity in an open field test [112].

In summary, it appears that high ACh, especially when central dopamine is low, may generate an aversive state [21] and regional variations in ACh may reflect differences in chronic or slower-onset stressors versus acute stressors.

4.3 Opioids

As with dopaminergic transmission, mu-opioid transmission is acutely enhanced by stressful stimuli [13, 122, 123], while chronic states of aversion result in a downregulation of mu-opioid activity [57, 124–126]. This is likely a result of desensitization due to repeated release of endogenous endorphins from aversive events, such as chronic pain [122, 123, 127]. Common pharmacological treatments for chronic pain result in further stimulation of the opioid system, specifically at mu-opioid receptors. An interesting phenomenon in chronic pain patients is the diminished abuse potential of common analgesics, such as morphine and other μ -opioid agonists [57, 128, 129]. Some studies suggest activation of the endogenous kappa-opioid-dynorphin system by aversive stimuli may result in the suppression of the development of rewarding effects produced by morphine and drugs of abuse [57, 130–134]. Unlike activation of mu-opioid receptors that results in euphoria, activation of kappa-opioid receptors is associated with dysphoria [135, 136] and many of the aversive effects of stress are blocked by kappa-opioid receptor antagonists [135, 137, 138].

Dynorphin is the primary endogenous kappa opioid receptor ligand, and, as a co-transmitter in one of the GABA output pathways, can inhibit dopamine neurons [131–134, 139]. Excessive levels of dynorphin are linked to depression, possibly due to decreased dopaminergic transmission [139–141]. Aversive states associated with chronic stress [137] and learned helplessness [142] increase dynorphin expression, and thus, dynorphin may be a therapeutic target to attenuate states of aversion.

Contrary to kappa-opioid activation, sustained sadness conditions are associated with a significant deactivation in μ -opioid neurotransmission, demonstrating dynamic changes in μ -opioid activity in response to experimentally induced negative affective states [143–145]. Women with Major Depressive Disorder (MDD) also demonstrate a reduction in mu-opioid binding potential at baseline (in the absence of an emotional challenge) [143]. Thus, depressive states may reflect an opioid imbalance in which the kappa-opioid system is overactive while the mu-opioid system is underactive.

Other aversive states are also associated with changes in opioid neurotransmission. Although binge-eating, particularly of palatable foods, stimulates mu-opioid receptors [146–149], individuals with BN have lower levels of β -endorphin [150] and decreased μ -opioid receptor binding in the insular cortex [151], suggesting desensitization. Furthermore, the mu-opioid antagonist, naloxone, reduces the consumption of sweet high-fat foods in obese and lean female binge-eaters [152]. In binge eating rats, Kelley and colleagues have demonstrated a decrease in enkephalin gene expression in the NAc [153]. On the other end of the eating spectrum, Demitrack et al. (1993) found a decrease in β -endorphin levels in underweight anorexic individuals [154], reflecting that aversive states resulting from both under- and overeating may have diminished opioid functioning.

The state of aversion that results from repeated use of drugs of abuse is also partially mediated by opioidergic alterations. Whether directly or indirectly, nearly all addictive substances are associated with the release of endogenous opioids [155–160]. In cocaine-dependent [161] and alcohol-dependent subjects [162], drug abstinence is associated with an upregulation of mu-opioid receptor binding that is proportional to drug craving. This may reflect a hyper-sensitization of receptors to compensate for decreased endogenous opioid transmission resulting from repeated drug assault. For example, acute alcohol intake in animals increases beta-endorphin levels [160], while habitual alcohol consumption leads to lowered beta-endorphin levels [163]. Dynorphin expression is also induced in the NAc and related striatal regions after exposure to drugs of abuse, an effect that seems to be mediated by the gene transcription factor CREB (cAMP response element binding protein) [164]. This could also contribute to the dysphoric states associated with drug addiction.

Opioid agonists and antagonists alter the dopamine/ACh balance, which may be one way they influence states of euphoria versus dysphoria. As mentioned previously, states of aversion/avoidance are associated with greater increases in ACh and states of reward are associated with greater dopamine release. While the mu-opioid agonist, morphine, acutely increases the release of NAc dopamine and decreases ACh, the mu-opioid antagonist, naloxone, results in decreased dopamine and increased ACh [165]. Similarly, opiate antagonists can attenuate ethanol-induced increases in NAc dopamine release [166, 167], while causing a significant rise in NAc ACh [73].

One mechanism for these dopaminergic effects could be via mu-opioid inhibition of GABA inhibition (i.e. disinhibition) of dopamine cells in the ventral tegmental area in rewarding states [131, 168, 169] and dynorphin-mediated activation of GABA (thus, inhibition of dopamine) cells in aversive states [131, 133, 141, 170, 171]. Conversely, central ACh is elevated by striatal dynorphin infusion [172] and decreases with acute mu-opioid stimulation [170, 173, 174].

Overall, although acutely aversive stimuli globally activate the opioid system, chronic states of aversion seem to be marked by decreased mu-opioid transmission and increased kappa-opioid transmission via dynorphin, which has implications for the central dopamine/ACh balance.

5. Implications for reward seeking

It is well-established that individuals in a chronic aversive state, such as depression, chronic pain, or eating disorder, are more likely to have co-morbid addictive disorders [97, 98, 175–178]. This underscores the overlapping systems implicated in reward and aversion. In particular, brain dopamine decreases observed after prolonged/repeated exposure to aversive stimuli are in line with the “reward deficiency hypothesis” of addiction, whereby an individual seeks out rewarding stimuli to compensate for diminished dopamine [179–183]. Drug addicts demonstrate a decreased sensitivity of reward circuits, similar to that seen in obesity and depression [85, 179–181, 184–189], and thus, these individuals may require more of a substance (i.e. food or drug) to achieve normal mood elevations. Consequently, attempts to mitigate the unpleasantness of aversive states often involve the original aversive stimuli (i.e. drug use, binge eating) and perpetuate the problem. For example, substance abusers return to drug use to escape the unpleasant effects of withdrawal [190] or obese and bulimic individuals may binge eat to avoid feelings of depression [190–192]. Ultimately, though, these behaviors reinforce the neurobiological imbalances indicative of aversion.

Although the aversive states discussed in this paper have different behavioral manifestations, the degree of symptom cross-over and the similar neurotransmitter

involvement suggest that the underlying neurobiology can be generalized to different conditions. A common theme in these conditions appears to be a central reward deficit that makes the individual more vulnerable to addictive behaviors.

6. Conclusion

Reward and aversion seem to be mediated by overlapping neural systems. Although they are often known as students of reward states, Bartley Hoebel and colleagues have made significant advances in understanding the neurobiology of aversion and the link between aversive states and addictive behaviors. These two dichotomous states may reflect an affective *continuum* contingent upon environmental conditions. For example, lateral-hypothalamic stimulation may be perceived as rewarding to a food-deprived animal, yet aversive to an overfed animal [1]. Similarly, the taste of sucrose solution that is initially rated as “pleasant” shifts to “unpleasant” after a large meal of sucrose [193]. With drugs of abuse, initial intake causes euphoria, while repeated exposure triggers dysphoria and anhedonia [139].

Descriptive and mechanistic studies pioneered by Bartley Hoebel and others have demonstrated that the shift in the reward-aversion spectrum may be, in part, a result of changes in central dopamine/ACh ratio, particularly in the NAc. The path to aversion appears to be reduced dopamine activity and increased ACh activity in “reward centers” of the brain and kappa- and mu-opioid receptors may have a neuromodulatory role on both of these neurotransmitters.

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Highlights

- Hoebel and colleagues advanced the study of behavior and neurobiology linked to acute and chronic aversive states.
- Reward and aversion may reflect an affective *continuum* contingent upon environmental conditions.
- Descriptive and mechanistic studies have demonstrated that the shift in the reward/aversion spectrum may reflect changes in mesolimbic dopamine/acetylcholine ratio.
- Reward deficits associated with aversive states may predispose to addictive behaviors.