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Review

Dual role of dopamine D_2-like receptors in the mediation of conditioned and unconditioned fear

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ABSTRACT

A reduction of dopamine release or D_2 receptor blockade in the terminal fields of the mesolimbic system, particularly the amygdala, clearly reduces conditioned fear. Similar D_2 receptor antagonism in the neural substrates of fear in the midbrain tectum attenuates the processing of unconditioned aversive information. However, the implications of the interplay between opposing actions of dopamine in the rostral and caudal segments of the dopaminergic system are still unclear. Previous studies from this laboratory have reported the effects of dopaminergic drugs on behavior in rats in the elevated plus maze, auditory-evoked potentials (AEPs) recorded from the midbrain tectum, fear-potentiated startle, and conditioned freezing. These findings led to an interesting framework on the functional roles of dopamine in both anxiety and fear states. Dopamine D_2 receptor inhibition in the terminal fields of the mesolimbic dopamine system generally causes anxiolytic-like effects, whereas the activity of midbrain substrates of unconditioned fear are enhanced by D_2 receptor antagonists, suggesting that D_2 receptor-mediated mechanisms play opposing roles in fear/anxiety processes, depending on the brain region under study. Dopamine appears to mediate conditioned fear by acting at rostral levels of the brain and regulate unconditioned fear at the midbrain level, likely by reducing the sensorimotor gating of aversive events.

1. Background

Aversive stimuli that underlie aversive or stressful situations can be divided into two categories: unconditioned and conditioned stressors. Unconditioned aversive stimuli, such as pain, asphyxia, and innate fear-inducing stimuli (e.g., snakes and tigers), evoke unconditioned reflexive freezing and escape responses. Conditioned aversive stimuli are neutral stimuli that have acquired aversive properties because they have been previously paired with a noxious or aversive event. A third category, general stressors, can also be included as stimuli of an aversive nature that activate the general alertness system. The latter has been represented by the activating reticular ascending system, and different brain structures subserve each of the defense reactions that are triggered by unconditioned and conditioned stressors [17,28,8,6,7].

When applied to periventricular structures, such as the dorsal periaqueductal gray (dPAG) and medial hypothalamus, electrical stimulation is well known to elicit escape behavior [5]. An important step toward understanding the processes and mechanisms that underlie this defensive response was the demonstration that such periventricular stimulation induced an aversive effect. Animals that received such stimulation readily learned to switch off the stimulation whenever it was given the opportunity to do so [43]. In the mid 1980s, the superior colliculus and inferior colliculus (IC) in the mesencephalon were also shown to be part of this system, which has since been known as the encephalic aversion system (EAS; [11,10,2]. From this time onward, substantial evidence has been obtained to support the notion that defense reactions that are elaborated at the level of the EAS are mediated by multiple mechanisms (Fig. 1). Indeed, γ-aminobutyric acid (GABA), excitatory amino acid, neuropeptide (e.g., neurokinin), opioid, and serotonin systems are now known to act together to neurochemically mediate the neural substrates of aversion in this

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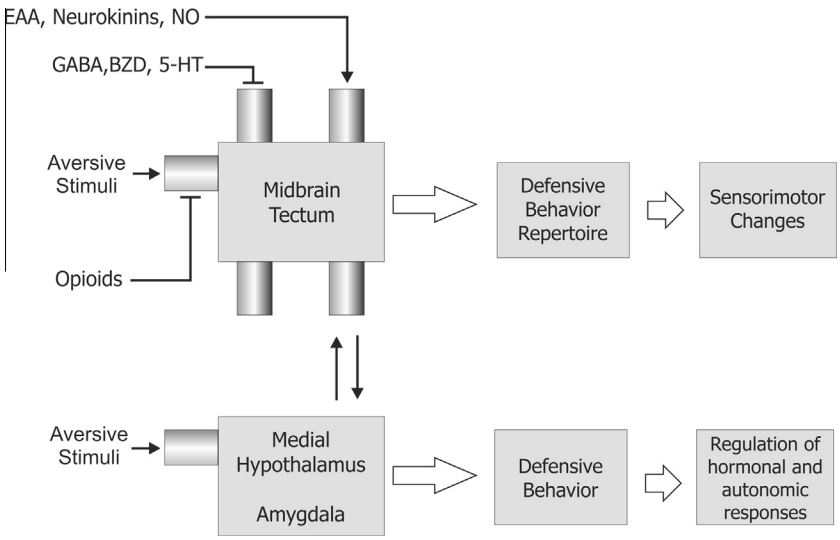

Fig. 1. Schematic diagram that shows the various neurotransmitters that are known to mediate (↑) or regulate (⊤) defensive behavior in the midbrain tectum, medial hypothalamus, and amygdala, structures that belong to the encephalic aversion system (EAS). EAA, excitatory amino acids; GABA, γ-aminobutyric acid; BZD, benzodiazepine; 5-HT, 5-hydroxytryptamine (serotonin); NO, nitric oxide.

system [12,13,6,7]. Endocannabinoids, nitric oxide, and corticotrophins also play a role in mediating the EAS [4,37,38]. An excellent review that was published at the beginning of this century proposed that dopamine can also function as a mediator of conditioned fear in terminal areas of the mesocorticolimbic system [33].

2. Dopamine in conditioned fear

In parallel with studies on the function of the EAS, the last two decades also witnessed a large number of studies that sought to elucidate the neural substrates that elaborate behaviors related to the rewarding and pleasurable effects of stimulating certain brain areas, such as the ventral tegmental area (VTA), nucleus accumbens, and other rostral brain areas [16]. Many of these studies reported the essential involvement of long ascending fiber systems (e.g., dopaminergic fibers). Today, this system is referred to as the reward system. A turning point in the role of dopamine in the modulation of brain function was the postulation that dopaminergic systems that arise from the VTA mediate conditioned fear responses. In fact, many studies have reported the involvement of dopamine in aversive conditioning using diverse conditioned fear paradigms, such as the contextual fear test, fear-potentiated startle with the use of a context or light as conditioned stimuli, and the two-way active avoidance test [39]; for review, see [33].

Despite the widely accepted notion that dopamine is involved in the regulation of anxiety, no agreement has been reached on whether dopamine enhances or diminishes anxiety. The former hypothesis is largely based on earlier experiments in which the effects of drugs that non-selectively act on brain dopamine systems were measured in animals that were subjected to tests of fear conditioning [3,34,40,41,46,31,1,23]. With regard to dopamine's mediation of conditioned fear, an increase in dopamine metabolism in the mesolimbic system is correlated with conditioned fear, and a decrease in dopamine activity in the basolateral amygdala (BLA) reduces the expression of conditioned fear [18,19,20]. In fact, intraperitoneal injections of low doses of the D_2 receptor agonist quinpirole act at autoreceptors on VTA neurons, slowing dopamine release at their terminals and causing a reduction of conditioned fear responses [23,21]. Therefore, the fear response to a light (conditioned stimulus [CS]) appeared to depend on the activation of mesolimbic dopaminergic connections and could be specifically modulated by manipulating these projection neurons. One possibility that cannot be discarded is that the pathway that connects the VTA with the amygdala promotes resistance to the aversive effects of unconditioned stimuli (USs), suggesting that the interplay between neural systems that are responsible for processing conditioned and unconditioned fear stimuli may exist at this level.

3. Dopamine in unconditioned fear

The EAS consists of the dorsal periaqueductal gray (dPAG), superior and inferior colliculi, and the hypothalamus and is responsible for the elaboration and expression of defense reactions to unconditioned or innate aversive stimuli. The behavioral and autonomic changes that are associated with defense reactions are likely to be expressed as an aversive emotional-motivational state. Activation of the dPAG motivates switch-off behavior, inhibits antecedent behavior, facilitates escape from electric footshock, and acts as an aversive US in Pavlovian conditioning and place aversion procedures [17,28,6,7]. Considering that conditioned and unconditioned fear may somehow overlap, one unresolved issue remains. Substantial experimental evidence implicates the mesocorticolimbic dopamine system in anxiety, but the functional role of dopamine in the midbrain tectum associated with fear is still unclear. Some reports associated dopamine in the midbrain tectum with prepulse inhibition, catalepsy, and the modulation of auditory signals from the IC to medial geniculate thalamus [42,32,44,27]. We present evidence that dopamine modulates the neural substrates of fear in the EAS.

Unclear is the role of dopamine in unconditioned fear, particularly in the EAS. No study approached this issue until 2004, when a study conducted in our laboratory showed that dopamine facilitated unconditioned responses in rats in the light switch-off test [36]. One year later, another study showed that systemic administration of the selective dopamine D_2 receptor antagonist sulpiride caused proaversive effects in rats in the elevated plus maze [26].

Given that the EAS does not function only as an output center for defense reactions, certain structures of the midbrain tectum may also be involved in processing aversive information [45,9]. For example, aversive stimulation of the IC at the escape threshold

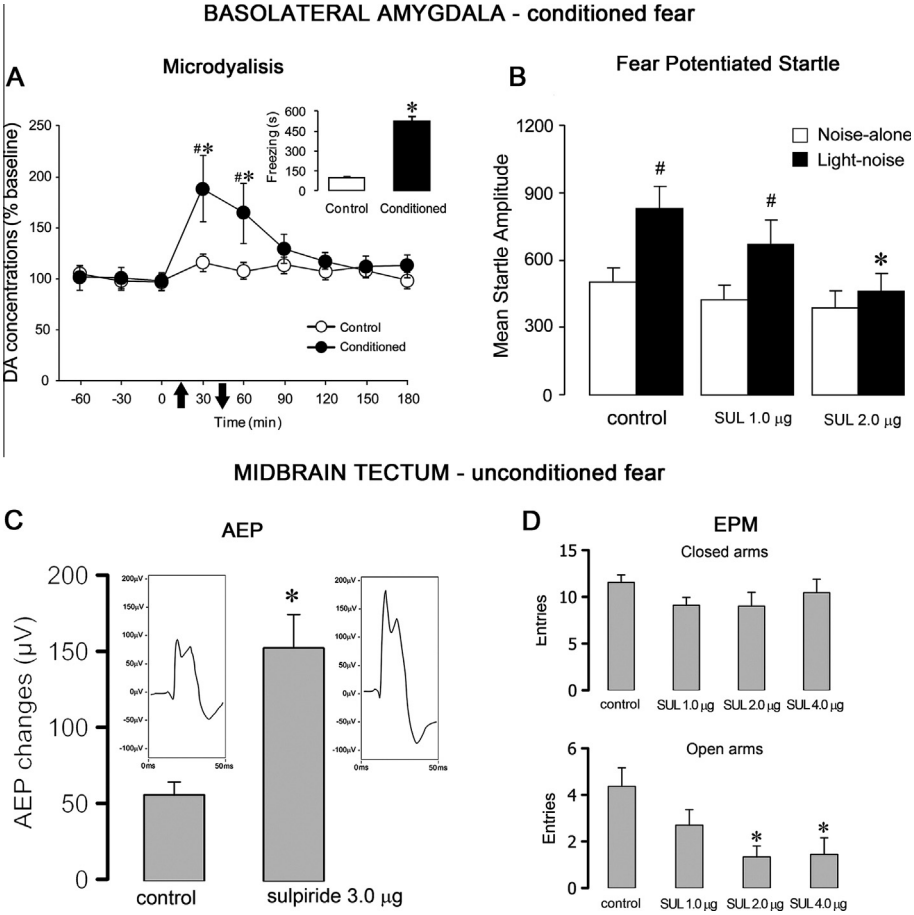

Fig. 2. (A) Dopamine levels in the basolateral amygdala during conditioned fear. Extracellular levels of dopamine (DA) in the BLA in rats that were previously subjected to paired (conditioned) or unpaired (control) exposure to light and footshock and exposed to the light-CS in the fear conditioning test. (Inset) Conditioned freezing behavior during the 20 min period of the light-CS test session without footshock. $^{\#}P < 0.05$, different from baseline (−60, −30, and 0 min); $^{*}P < 0.05$, different from control group (Newman–Keuls *post hoc* test). Arrows indicate the start and end of the conditioned fear test. (B) Effects of injections of the D_2 receptor antagonist sulpiride in the basolateral amygdala on fear conditioning (fear-potentiated startle). The figure shows the mean startle amplitude in rats that were treated with sulpiride (1.0 and 2.0 µg/0.2 µl) before the test session. $^{\#}P < 0.05$, compared with noise-alone; $^{*}P < 0.05$, compared with light-noise in the saline group (Newman–Keuls test). (C) Effects of intra-inferior colliculus (IC) injections of vehicle or 2.0 and 3.0 µg/0.2 µl sulpiride on the amplitude of auditory-evoked potentials recorded in the IC in response to presentations of a loud noise. $^{*}P < 0.05$, compared with control group (Newman–Keuls test). (D) Effects of intra-IC injections of vehicle or 1.0, 2.0, and 4.0 µg/0.2 µl sulpiride/0.2 µl on exploratory behavior in rats in the elevated plus maze. The figure shows the number of entries into the closed and open arms. $^{*}P < 0.05$, compared with control group (Newman–Keuls test). Further details can be found in De Oliveira et al. [20,22] and Muthuraju et al. [35].

enhanced dopamine release in the prefrontal cortex [15,30] and intracollicular injections of the non-selective dopamine receptor antagonist haloperidol enhanced auditory-evoked potentials (AEPs) that were recorded directly from the IC in rats that were subjected to loud sounds as the US [35]. These results support previous studies from our laboratory that showed that systemic injections of sulpiride enhanced escape responses in rats that in the switch-off procedure [36] and increased the frequency of ultrasonic vocalizations during the training sessions in a fear conditioning test [14]. These data are in sharp contrast to other studies on the association between enhanced dopamine transmission and conditioned fear. For example, such studies reported that intra-amygdala injections of sulpiride attenuated the expression of conditioned fear [18,19,20,21,22]. We thus hypothesize a dual role for dopamine in defensive behavior that may explain some of these conflicting results.

4. Integrated view

In an attempt to integrate the above findings, we propose the following. The neurobiological function of dopamine in anxiety has been investigated in several laboratories. The current general idea is that the activation of dopamine pathways that arise from the VTA increases learned anxiety. The functional role of dopamine pathways that connect the VTA to the BLA in the mediation of conditioned fear/anxiety has been suggested by many studies from several laboratories [3,34,40,41,46,31,1,23]. In one of these studies from our laboratory [20], in vivo microdialysis was performed to measure dopamine levels in the BLA in Wistar rats that were subjected to footshock (US) that was associated with a neutral stimulus (CS). When these rats were exposed to the CS alone without footshock, freezing was the most prominent behavioral response, accompanied by the significant release of dopamine in the BLA (Fig. 2A, arrows). In this study, fear-potentiated startle (i.e., a common conditioning model of anxiety in animals) was used to assess the way in which dopamine mechanisms are activated during conditioned fear. The animals were subjected to the pairing of light + footshock. The next day, they were subjected to a session that consisted of 60 trials, half with loud noise and half with loud noise + light (CS). Fear-potentiated startle was evident when startle in response to light + noise was higher than to noise alone. The difference between the magnitude of the startle response under both conditions reflects the state of conditioned fear of the animals and has been utilized as a reliable measure of anxiety in

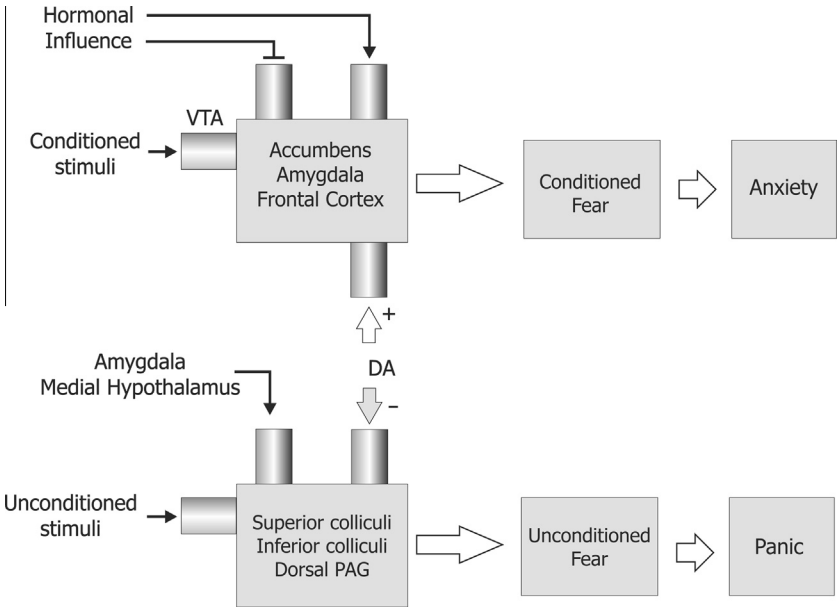

Fig. 3. Schematic diagram that shows the generation and organization of conditioned and unconditioned fear responses in response to respective conditioned and unconditioned stimuli that target the mesocorticolimbic system and encephalic aversion system, respectively. Hormonal factors may inhibit (⊤) or activate (→) defense reactions. VTA, ventral tegmental area. Dopamine has opposite actions on these systems (+, –).

animals. Intra-BLA injections of sulpiride before the test sessions attenuated fear-potentiated startle, indicating that D_2 receptors in this amygdaloid nucleus mediate conditioned fear responses (Fig. 2B). Thus, these data support the hypothesis that dopamine may plan an anxiogenic role in rostral brain structures, such as the hippocampus, amygdala, and prefrontal cortex, which are activated by CSs.

As mentioned above, the EAS is a multifaceted neural circuit that involves several neurotransmitters (GABA, serotonin, excitatory amino acids, and neurokinins, among others) and plays a role in modulating the organization, elaboration, and expression of defense reactions. However, the use of tests of unconditioned fear has generated experimental results that do not always fit the hypothesis of dopamine's anxiogenic role [36,14,22,35]. Studies that used aversive USs that decisively activate brainstem structures, such as the IC, to elicit defensive behavior in rats has led to the suggestion that dopamine exerts an antiaversive action in this brain region [35,22]. Thus, the ascending dopamine pathway that originates in the VTA and innervates the amygdala and frontal cortex has been suggested to facilitate conditioned fear, whereas the periventricular pathway that innervates the dPAG and IC inhibits innate fight/flight reactions to impending danger. These latter studies showed, in contrast to animal models of anxiety, that D_2 receptor antagonism at the level of the midbrain tectum in rats that are exposed to unconditioned aversive stimuli increases defensive reactions in the elevated plus maze and in response to the presentation of repetitive loud noises (100 dB). Indeed, sulpiride injections in the IC increased AEPs that were recorded directly from electrodes implanted in the IC during the presentation of repetitive loud noise (Fig. 2C) and enhanced avoidance of the height and openness of the open arms of the elevated plus maze (Fig. 2D). Supporting these results, a substantial concentration of dopamine has been found in the midbrain tectum, particularly in the IC [29]. We also showed that the same pattern of responses emerged when sulpiride was injected into deep layers of the superior colliculus. Sulpiride injections in the dPAG caused proaversive effects in rats in the elevated plus maze (manuscript in preparation).

Altogether, the extant evidence suggests that the activation of dopamine pathways that arise from the VTA increases learned anxiety, with possibly an opposite action on innate fear. The results support our hypothesis of a dual role of dopamine-mediated mechanisms in unconditioned and conditioned fear and that these different responses to aversive stimuli can be neurally dissociated from each other. This new approach to associating dopaminergic mechanisms with anxiety has led to some intriguing questions. Benzodiazepine anxiolytics supposedly decrease dopamine release in the frontal cortex [24,25], and neuroleptics that are known for their ability to decrease dopamine neurotransmission in limbic structures exert antipsychotic rather than anxiolytic effects. The proposal presented herein opens a window on further discussions on the implications of dopamine's mediation of the multiple facets of anxiety disorders.

5. Concluding remarks

The present review provides evidence of the opposing actions of dopamine-mediated mechanisms in fear/anxiety processes. Depending on the type of threatening condition (i.e., conditioned or unconditioned), dopamine D_2 receptor antagonists may reduce or heighten the aversiveness of the situation. Intra-BLA injections of these compounds clearly reduce conditioned fear in rats that are subjected to animal models of anxiety [20,21,14,23]. To test the hypothesis that dopamine plays a modulatory role in the neural substrates of fear in periventricular structures, we microinjected dopamine receptor antagonists into the IC to inhibit D_2 receptor-mediated mechanisms. This treatment impaired exploratory behavior in rats in the elevated plus maze and enhanced AEPs that were recorded in the IC in response to loud sounds [35,22]. Thus, dopamine appears to mediate conditioned fear by acting at rostral levels of the brain, and dopamine in midbrain areas appears to regulate unconditioned fear, likely by reducing the sensorimotor gating of aversive events. Thus, the reduction of dopamine activity enhances unconditioned fear, likely by acting at the midbrain level, opening sensory gating for aversive events, and reducing conditioned fear by acting at more rostral levels of the brain (Fig. 3). Further studies are needed to clarify the differential roles of dopamine in conditioned and unconditioned fear to shed more light on the neurobiological complexity of mental disorders.

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