Commentary

Euromediterranean Biomedical Journal
*for young doctors*
(formerly: Capsula Eburnea)

# THE ROLE OF THE DOPAMINERGIC SYSTEM IN GRATIFICATION PROCESSES.

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**SUMMARY**

Gratification is one of the functions necessary for the satisfaction of basic needs geared towards welfare and reproduction, which evolved in higher animal species. Over the years, several studies on the mechanisms through which gratification exerts its effects on the nervous system and is associated with feelings of pleasure have shown that the dopaminergic system is the most important circuit acting as a biological basis for gratification. This article will review the current knowledge on the response of the midbrain dopaminergic system to appetitive and aversive stimuli, as well as the role played within this context by the Lateral Habenula, a structure that has attracted great interest among researchers in the recent years.

**Introduction.** Gratification is an emotional state of fulfillment that follows the achievement of an aim or the occurrence of a pleasing event. It is one of the functions necessary for the satisfaction of basic needs geared towards welfare and reproduction, which evolved in higher animal species.

Over the years, several studies on the mechanisms through which gratification exerts its effects on the nervous system and is associated with feelings of pleasure have shown that the dopaminergic system is the most important circuit acting as a biological basis for gratification. These studies have used several scientific approaches, including selective electrical stimulation of different areas of the dopaminergic system (1), their selective inhibition by destruction (2; 3; 4), or a generalized activation or inhibition of the system through the infusion of agonists or antagonists (5). Furthermore, it has also been shown that the activation of the dopaminergic system occurs not only through natural rewards, necessary for the survival of the species, such as sex, food or drink (6), but also through stimulation by substances of abuse (7; 8; 9).

**The dopamine neurons and their responses to appetitive and aversive stimuli.** The classic electrophysiological studies indicate that gratification is encoded by dopaminergic neurons through a variation in their discharge frequency. In-depth studies have shown that these cells encode the error (positive or negative) associated with the prediction of a reward. In fact, their discharge frequency and the number of bursts increase in conjunction with an unexpected rewarding stimulus or a stimulus which predicts gratification (10; 11; 12), while they are reduced (compared to baseline) in the absence of an expected reward (10). Similarly, their discharge activity also changes if the animal receives a reward greater or lesser than expected: in the first case they get excited, while in the second they are inhibited (10). On the contrary, their activity does not significantly change when the animal receives an awaited reward or another type of unforeseen gratification.

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***Received**: March 15th, 2013 — **Revised**: April 9th, 2013 — **Accepted**: May 11th, 2013*

In this regard, "reinforcement learning", i.e. reward-related learning (in other words, learning new behavioral responses which lead to receiving a prize), is related to the above-mentioned changes in the activity of dopamine neurons (10; 13).
This relationship was confirmed by a study involving neurophysiological recording of the dopaminergic areas in monkeys. When the monkeys were given juice as a reward after a visual signal, these areas were activated; after many repetitions, however, the monkey learned that the visual signal was followed by juice, and the dopaminergic system did not become excited at the arrival of the reward, but at the time of the visual signal (14).
The inhibitory response of dopaminergic neurons occurs not only when an expected reward is omitted, but also as a result of negative stimuli, such as an electrical stimulus. Recently, research on this subject produced data that undermine the general theory that dopaminergic neurons are uniformly inhibited by nociceptive stimuli (10; 15; 16; 17). According to these most recent theories, a single area of the dopaminergic system may be constituted by different neuronal subpopulations capable of responding differently to the same stimulus: for example, Brischoux et al. showed that different neuronal groups within a single mesencephalic area (the Ventral Tegmental Area, VTA) of anesthetized rats responded to a small electric shock on a leg with one group becoming excited and the other inhibited (18). The different responses to the same stimulus may result from the different afferents (excitatory or inhibitory) that each dopaminergic subpopulation receives. Among these, an important role is played by the afferents from one epithalamic structure: the Lateral Habenula (LHb).

**The role of the Lateral Habenula in signal encoding to the dopamine neurons of the midbrain.** Damage involving the LHb results in an increase of the dopaminergic transmission in the VTA, and, conversely, electrically stimulating this structure results in a decrease of the transmission. This evidence indicates that the LHb has a tonic inhibitory effect on the dopamine system (19). Since the neurons of the LHb are glutamatergic, such inhibition must necessarily be mediated by other neurons: the GABAergic interneurons of the Rostral Mesopontine Tegmentum (RMTg), which constitutes the most posterior portion in the VTA, and therefore is also called tail-VTA (20).
Both the neurons of the LHb and the RMTg are among the few encephalic structures that have an opposite response, compared to the dopaminergic areas, to rewarding and aversive stimuli: in fact, they are inhibited by the former and excited by the latter (21; 22, 23).
In addition, the LHb is at least in part responsible for the reduction of the dopaminergic activity that occurs in the event of a reward prediction error, i.e. failure to receive an expected reward, when positive feedback is omitted after a correct behavioral response. This has been demonstrated by Matsumoto and Hikosaka, who implanted electrodes in the dopaminergic *substantia nigra* (SNc) and the LHb of primates who learned that making saccadic eye movements towards a certain direction would result in receiving a reward (21).
Hence the role of the LHb is to encode negative environmental stimuli related to rewards ("negative reward-related signals"), namely firing when stimuli with a negative value arise, and when an expected reward is omitted (24), thus inhibiting the dopaminergic mesencephalic system, at the level of VTA and SNc; this inhibition may lead to behavior suppression, through mechanisms of synaptic plasticity, such as long-term depression (LTD) (25; 26). For this reason, the LHb would seem to be implicated in the learning processes that ensue from errors, as well as in the adjustment of the behavioral strategies that follow.

**Conclusions.** In view of what discussed above, it is clear that further research is needed to fully understand the influence of the LHb on the mesencephalic dopaminergic system, in order to learn more about diseases that cause reward mechanism alterations and addiction.

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