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Review

# The mesoaccumbens dopamine in coping with stress

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ABSTRACT

Mesoaccumbens dopamine (DA) is involved in the stress response. Although neural mechanisms involved in stress are of paramount importance for both clinical and preclinical research, the results of studies on the stress response by mesoaccumbens DA have received little attention. Therefore, we aimed to review these results and propose a role for mesoaccumbens DA in coping with stress.

The data reviewed support the view that fluctuations of tonic levels characterize the mesoaccumbens DA stress response. Stress-induced increase of tonic DA levels in nucleus accumbens (NAc) supports expression of responses aimed at removing and avoiding the stressor through activation of DA D2 receptors, whereas inhibition of DA is associated with cessation of active defensive responses.

In novel unescapable/uncontrollable stressful conditions tonic levels of DA in NAc show an initial increase followed by a decrease below pre-stress levels that lasts as long as the stressful situation. This biphasic response fits with the dynamics of the primary and secondary appraisal of a stressor that cannot be removed, escaped or controlled by the organism. In fact, NAc DA fluctuations are controlled by the medial pre-frontal cortex, which is involved in stress appraisal.

We propose that enhanced mesoaccumbens DA supports expression of active coping strategies against an event appraised as a stressor and that inhibition of DA is required for passive coping with stressful situations appraised as unescapable/uncontrollable.



**Contents**

1. Introduction ..... 80
2. Coding stress in the brain ..... 80
   2.1. Stress, stressors and stress responses ..... 80
   2.2. Stress response in DA neurons ..... 81
   2.3. Conclusions ..... 82
3. Changes in NAc DA release in the course of stressful experiences ..... 82
   3.1. Enhanced DA release ..... 82
   3.2. Inhibition of DA release ..... 83
   3.3. Conclusions ..... 83
4. Regulation of accumbens DA in novel uncontrollable stressful conditions ..... 83
   4.1. Enhanced DA release ..... 83
   4.2. Inhibition of DA release ..... 84
   4.3. Conclusions ..... 84
5. Mesoaccumbens DA in coping with stress ..... 84
   5.1. Coping with stress ..... 84
   5.2. Coping with unpredictably variable environments ..... 85
6. General conclusions ..... 86
   Acknowledgements ..... 86
   References ..... 86

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## 1. Introduction

Evidence for a stress response by the mesoaccumbens dopamine (DA) system is compelling. Stress-induced changes in DA metabolism within the nucleus accumbens (NAc) were first reported in the late seventies (Fadda et al., 1978) and eighties (Robinson and Becker, 1986; Dunn and Berridge, 1987; Antelman et al., 1988; Cabib et al., 1988; Kalivas and Duffy, 1989). Data collected using intracerebral microdialysis and voltammetry in vivo confirmed the view that stressors modulate DA release in the NAc (Abercrombie et al., 1989; Imperato et al., 1991; Puglisi-Allegra et al., 1991; Doherty and Gratton, 1992; Rossetti et al., 1993; Pothos et al., 1995). Finally, DA transmission in NAc has been shown to modulate the behavioral responses to stress (Rossetti et al., 1993; Ventura et al., 2002; Scornaiencki et al., 2009).

The brain is the key organ of stress reactivity, coping, and recovery processes and brain mechanisms involved in the stress response are responsible for the outcomes of stressful life events in terms of resilience or pathology (Mancini and Bonanno, 2006; Rutter, 2006; Krishnan et al., 2007; Taylor and Stanton, 2007; Feder et al., 2009; Ganzel et al., 2010; McEwen and Gianaros, 2010). Altered NAc DA transmission has been consistently implicated in psychopathology (Lipska, 2004; Everitt et al., 2008; Goto and Grace, 2008; Robinson and Berridge, 2008; Carlezon and Thomas, 2009; Floresco et al., 2009; O'Sullivan et al., 2009). Therefore, mesoaccumbens DA is likely to be a major mediator of the stress outcomes.

Despite these considerations, the role of the mesoaccumbens DA response in stress has been generally neglected in the debate on the role of NAc DA and in the literature on the brain mechanisms involved in stress response. This could be because of the strong association between mesoaccumbens DA, reward and seeking that seemed at odds with its involvement in stress reactions normally involving aversion and avoidance. Another obstacle in identifying a role for mesoaccumbens DA in stress response is the direction of changes in NAc DA release observed in animals exposed to stress. In fact, although most studies report enhanced DA release (Horvitz, 2002, for review), some report stress-induced inhibition of DA (Puglisi-Allegra et al., 1991; Rossetti et al., 1993; Cabib and Puglisi-Allegra, 1994; Pothos et al., 1995; Rada et al., 1998; Mangiavacchi et al., 2001; Ventura et al., 2001, 2002; Pascucci et al., 2007).

In this review we propose that fluctuations of tonic levels of DA within the NAc have a role in sustaining different coping strategies in stressful situations. The first section of the review is dedicated to discussing differences between stressors and stimuli endowed with negative hedonic value in theoretical terms and in terms of the response they can elicit in DA neurons. In the second section we review data on the dynamics of DA outflow in the NAc of experimental animals exposed to stressful experiences. These dynamics will be evaluated in relation to the behavioral responses expressed by the stressed organisms. In the third part we describe the brain mechanisms that regulate fluctuations of DA in NAc during experiences with a novel, unavoidable/uncontrollable stressor. In the final part of the review we will present our hypothesis based on the reviewed data, the general concepts of coping and appraisal, and recently proposed roles of mesoaccumbens DA.

## 2. Coding stress in the brain

### 2.1. Stress, stressors and stress responses

Historically, research on stress and stress-associated phenomena has been hindered by ambiguous definitions. Indeed, the term stress has been used to indicate both a response (or a set of responses) and the stimuli that promote the response (Huether et al., 1999; Ursin and Eriksen, 2004). To avoid confusion, in the present review we explicitly refer to "stress responses" and use the terms "stressors" or stressful stimuli, conditions, situations and events to indicate whatever promotes the stress responses.

Stressors are usually identified with stimuli (or conditions) able to promote classical stress responses, such as activation of hypothalamus–pituitary–adrenocortical (HPA) axis. There is, however, general agreement that two distinct classes of stressors exist. The first class includes systemic stressors, such as marked changes in cardiovascular tone, respiratory distress, visceral or somatic pain, and signals of infection or inflammation, which represent homeostatic challenges recognized by somatic, visceral or circumventricular sensory pathways (Herman et al., 2003; Anisman and Matheson, 2005). By contrast, the class of psychogenic/neurogenic stressors requires appraisal, which involves higher order cortical areas and the limbic systems (Lazarus, 1993; Huether et al., 1999; Herman et al., 2003; Ursin and Eriksen, 2004; Anisman and Matheson, 2005; Day, 2005). The present review deals with responses elicited by the latter class of stressors.

Psychogenic stressors are challenges appraised by the organism as demanding beyond its actual means (Folkman et al., 1986; Lazarus, 1993). Homeostatic response mechanisms are the organism's primary means of responding to challenges, therefore stressors are stimuli or conditions that overwhelm these mechanisms (Herman et al., 2003; Day, 2005). Moreover, organisms deal with challenges by means of well-established behavioral and cognitive strategies. Therefore stressors are stimuli or conditions that defy expectancies about response-outcome relationships (Ursin and Eriksen, 2004). Based on these considerations, we can conclude that stressors are not just aversive stimuli nor only stimuli generally considered aversive. Indeed the list of stressful life events includes some events considered "positive" such as marriage (Paykel, 1997).

Stress responses have major adaptive value because they support the organism in the difficult process of developing ways to deal with challenges appraised as stressful. Indeed, a stressful experience cannot be sustained as such (McEwen, 2007); therefore, the organism needs to develop effective coping strategies. These, in turn, require major physiological and psychological changes. In other words, a stressful experience invariably leads to adaptation, which can be either healthy or pathogenic (Rutter, 2006; Maier and Watkins, 2010; Krishnan et al., 2007; McEwen, 2007; Taylor and Stanton, 2007; Kempton et al., 2009; Mitra et al., 2009).

Physiological stress responses, including increased release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and corticosterone/cortisol, have profound preparative and modulating effects on peripheral systems and foster changes within these systems (for a review, see McEwen, 2007). They also influence behavioral changes by modulating memory consolidation (de Kloet et al., 1999; Ferry et al., 1999; de Quervain et al., 2009) and orienting learning strategies (Dias-Ferreira et al., 2009; Packard, 2009; Schwabe et al., 2010). Indeed, adaptation to stressful conditions involves physiological allostasis and learning (Maier and Seligman, 1976; Ursin and Eriksen, 2004; McEwen, 2007; Ganzel et al., 2010; Maier and Watkins, 2010).

Psychological stress responses are crucial for the development of coping strategies able to terminate the stressful experience. Emotional alarm and distress orient and focus attention and reset organism's priorities (Ursin and Eriksen, 2004). Behavioral responses target the stressful stimuli or condition to remove, avoid or control them (Folkman et al., 1986; Vitaliano et al., 1990; Huether et al., 1999; Austenfeld and Stanton, 2004; Ursin and Eriksen, 2004; Anisman and Matheson, 2005; Taylor and Stanton, 2007). Cognitive elaboration monitors external and internal outcomes of these actions to determine whether the situation is controllable (Huether et al., 1999; Phan et al., 2004; Olff et al., 2005; Paul et al., 2005; Veissier and Boissy, 2007; Wager et al., 2008). Appraisal of controllability supports stabilization of the successful coping strategy,