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Behavioral control blunts reactions to contemporaneous and future adverse events: Medial prefrontal cortex plasticity and a corticostriatal network

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ABSTRACT

It has been known for many years that the ability to exert behavioral control over an adverse event blunts the behavioral and neurochemical impact of the event. More recently, it has become clear that the experience of behavioral control over adverse events also produces enduring changes that reduce the effects of subsequent negative events, even if they are uncontrollable and quite different from the original event controlled. This review focuses on the mechanism by which control both limits the impact of the stressor being experienced and produces enduring, trans-situational "immunization". The evidence will suggest that control is detected by a corticostriatal circuit involving the ventral medial prefrontal cortex (mPFC) and the posterior dorsomedial striatum (DMS). Once control is detected, other mPFC neurons that project to stress-responsive brainstem (dorsal raphe nucleus, DRN) and limbic (amygdala) structures exert top–down inhibitory control over the activation of these structures that is produced by the adverse event. These structures, such as the DRN and amygdala, in turn regulate the proximate mediators of the behavioral and physiological responses produced by adverse events, and so control blunts these responses. Importantly, the joint occurrence of control and adverse events seems to produce enduring plastic changes in the top–down inhibitory mPFC system such that this system is now activated by later adverse events even if they are uncontrollable, thereby reducing the impact of these events. Other issues are discussed that include a) whether other processes such as safety signals and exercise, that lead to resistance/resilience, also use the mPFC circuitry or do so in other ways; b) whether control has similar effects and neural mediation in humans, and c) the relationship of this work to clinical phenomena.

1. Introduction

There are large differences in how individuals react to seemingly the same adverse life events, with some being strongly impacted (vulnerable) while others either show little impact (resistant) or recover quickly (resilient). This has led to intensive investigation of factors that modulate how organisms react to adverse events (here called "stressors" for convenience), factors that are either contemporaneous with the stressor being experienced (e.g., the presence of safety signals), or historical and predispose how organisms react to adverse events in the future (e.g., early handling). It is not at all clear how to categorize or classify these processes. Some of these are non-experiential, such as genetic polymorphisms and changes in the microbiome. Others are experiential, with some being physical/physiological (e.g., elevated carbon dioxide) and some involving how the organism processes the adverse event (e.g., cognitive/behavior therapy). Clearly, these are not distinct categories and there are factors that induce resistance or resilience that are a mixture. For example, exercise could have beneficial effects because it confers a sense of efficacy, or because exercising muscles release a substance that enters the nervous system and directly alters neural function. It would be highly unlikely that all of these would modulate vulnerability and resistance/resilience by the same mechanisms, and this will indeed be one conclusion of this review.

Our laboratory has been interested in psychological variables, that is, variables that involve how the organism processes a stressor. In order to implicate a psychological factor it is necessary to vary the factor while at the same time holding the physical aspects of the stressor constant, and we have developed paradigms to do so (see below). In humans, how adverse events are appraised and viewed is key (Southwick et al., 2005), as is the individuals assessment of her ability to cope (Dicorcia and Tronick, 2011). These

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are the types of processes that we have set out to understand at a neural circuit and neurochemical level. Perceived behavioral control over an adverse event is at the core of coping, and this is what we have studied in animals where neural processes can be explored in detail. The paradigm that we employ involves triads of subjects, typically rats. Each of the subjects is placed in a small box with a wheel located on the front wall, and its tail extends from the rear of the chamber and is affixed with shock electrodes. Two of the rats receive periodic tailshocks, with each tailshock beginning at the same time for both rats. For one of the shocked rats, turning the wheel at the front of the chamber terminates each shock. If the subject does not turn the wheel each shock persists to an experimenter defined limit. Thus, this rat has an instrumental escape response (escapable shock, ES) and has behavioral control over the duration of each of the tailshocks. This rat cannot avoid a tailshock, but it can reduce its duration. For the second shocked rat each tailshock is yoked to its ES partner and terminates whenever the ES subject turns the wheel. For this rat turning the wheel has no consequence, and this subject does not have control over the shock durations. That is, the shocks are inescapable (IS). Thus, the physical aspects of the tailshocks (intensity, durations, temporal distributions, etc.) are identical for the ES and IS subjects, but ability to exert behavioral control over an aspect of the adverse event differs. The third rat is not shocked, and with this paradigm it is possible to determine whether any behavioral, neurochemical, endocrine or other consequence of the tailshock stressor is modulated by control.

Since exposure to potent stressors is known to produce a variety of changes in subsequent behavior often summarized as either anxiety-like or depression-like, it is not surprising that IS has been found to alter a broad range of behaviors for a number of days. Exposure to IS has been shown to lead to failure to escape shock in a new situation such as a shuttlebox (the "learned helplessness effect"), reduced aggression, reduced social dominance, immobility, neophobia, exaggerated fear conditioning, impaired fear extinction, anxiety on standard measures such as juvenile social investigation, hyper-vigilance as indicated by eaxaggertated attention to external cues, reduced food and water intake, etc. (Maier and Watkins, 1998 for review). Importantly, none of these occur following exactly equal ES. That is, the presence of control blocks all of these behavioral changes. Importantly, the presence of control does more than blunt the behavioral impact of the stressor being controlled. In addition, it alters the organism in such a way that the behavioral and neurochemical effects of **later** experiences with uncontrollable stressors are **blocked**, a phenomenon coined "immunization" (Maier and Seligman, 1976; Williams and Maier, 1977). Physically identical IS does not reduce the impact of subsequent uncontrollable stressors, and indeed, often exacerbates them. Thus, it is not the prior occurrence of the stressor that is immunizing, but rather **the experience of control** over the stressor. Several features of ES-induced immunization are noteworthy here. First, Such immunization effects can be quite **long lasting**. For example, the experience of ES in adolescence was shown to block the behavioral effects of IS in adulthood (Kubala et al., 2012). Second, immunization is **trans-situational**. Thus, ES in one environment/apparatus can block the effects of IS in a very different apparatus/environment. For example, Amat et al. (2010) demonstrated that exposure to ES blocked the behavioral and neurochemical effects of social defeat occurring 7 days later. Social defeat and ES are very different physically, were administered in very different apparati, and even on different floors of the building by different experimenters to minimize common cues.

The purpose of this review is to summarize the research that we have conducted directed at understanding the neural mechanisms by which the experience of control blunts the behavioral impact of the stressor being controlled, here tailshock, as well as subsequent uncontrollable stressors occurring in the future. However, this research will be difficult to understand without at least a brief summary of some of the mechanisms by which IS produces the behavioral changes that it does.

2. The dorsal raphe nucleus (DRN)

How could IS produce all of the diverse behavioral outcomes that follow? As a starting point we used the work on conditioned fear as a model. The central nucleus of the amygdala had been shown to serve as a final common efferent structure, sending projections to regions of the brain that are the proximate mediators of the wide ranging responses that occur during fear. Thus, for example, the central nucleus projects to the periaqueductal gray (PAG) thereby producing the freezing response that is part of fear, the hypothalamus thereby leading to the cardiovascular changes that are part of fear, etc. The central nucleus is activated during fear, and the diverse array of behavioral and physiological changes that constitute fear occur because the central nucleus projects to the relevant controlling structures.

It seemed to us that the changes produced by exposure to IS could be summarized as inhibited fight/flight and exaggerated fear/anxiety. The dorsal PAG (dPAG) was known to be critical for mediating fight/flight (Brandao et al., 1994), while the amygdala was known to be critical for fear/anxiety (LeDoux, 2003). It was also known that the dorsal raphe nucleus sends serotonergic (5-HT) projections to both structures, and that 5-HT facilitates amygdala function and inhibits dPAG function (Graeff et al., 1997). Thus, if IS, relative to ES, were to selectively activate the DRN, this would recapitulate many of the behavioral changes that are produced by IS. Moreover, the DRN projects to the striatum, a structure important for instrumental learning such as escape learning. Indeed, IS proved to produce a much more intense activation of 5-HT neurons in the mid to caudal regions of the DRN than does ES, the region of the DRN that projects to regions such as the amygdala (Hale et al., 2012). Thus, IS was found to induce Fos in 5-HT labeled neurons (Grahn et al., 1999) and to produce large increases in extracellular 5-HT in both projection regions such as the amygdala (Amat et al., 1998a), and within the DRN itself (Maswood et al., 1998), likely from axon collaterals (Tao et al., 2000).

The fact that DRN 5-HT neurons are only activated if the stressor is uncontrollable does not imply that activation of these cells is either necessary or sufficient to produce the behavioral sequelae of IS. To examine whether DRN 5-HT activity is necessary, DRN 5-HT activation has been blocked by microinjection of a variety of pharmacological agents during exposure to IS. In all cases, blockade of 5-HT activation within the DRN blocked the occurrence of the behavioral changes normally produced by IS (Maier et al., 1993, 1995b, 1994). Moreover, pharmacological blockade of 5-HT receptors in target regions of the DRN blocked the behaviors altered by IS that are mediated by those structures. For example, blockade of 5-HT2C receptors in the basolateral amygdala prevented the anxiety-like changes such as reduced juvenile social investigation (Christianson et al., 2010), while blockade of 5-HT2C receptors in the striatum prevented the shuttlebox escape learning deficits (Strong et al., 2011). In addition, simply activating DRN 5-HT neurons pharmacologically, in the absence of any stressor at all, produced the behavioral consequences that are produced by IS (Maier et al., 1995a).

However, IS-induced increases in DRN 5-HT activity continue for only a few hours beyond the termination of IS, yet the behavioral effects of IS persist for a number of days, and blockade of 5-HT receptors at the time of later testing blocks the behavioral effects. These findings suggest that perhaps the intense activation of DRN