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Review

Striatal ups and downs: Their roles in vulnerability to addictions in humans

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ABSTRACT

Susceptibility to addictive behaviors has been related to both increases and decreases in striatal function. Both profiles have been reported in humans as well as in animal models. Yet, the mechanisms underlying these opposing effects and the manner in which they relate to the behavioral development and expression of addiction remain unclear. In the present review of human studies, we describe a number of factors that could influence whether striatal hyper- or hypo-function is observed and propose a model that integrates the influence of these opposite responses on the expression of addiction related behaviors. Central to this model is the role played by the presence versus absence of addiction related cues and their ability to regulate responding to abused drugs and other rewards. Striatal function and incentive motivational states are increased in the presence of these cues and decreased in their absence. Alternations between these states might account for the progressive narrowing of interests as addictions develop and point to relevant processes to target in treatment.

Contents

1. Introduction 00
2. Preclinical studies in laboratory animals 00
3. Studies in humans: subjective and behavioral states 00
   3.1. Effects of cues 00
   3.2. Effects of drugs 00
   3.3. Effects of cues and cues + drugs in different subject populations 00
4. Subjects without addictions: striatal activations 00
   4.1. Effects of cues 00
   4.2. Effects of cues + drugs 00
   4.3. Age related differences: implications for development 00
5. Subjects at risk for addictions: striatal activations 00
   5.1. Effects of cues 00
   5.2. Effects of cues + drugs 00
6. Subjects with substance use disorders: striatal activations 00
   6.1. Effects of cues 00
   6.2. Effects of cues + drugs 00
7. Subjects with non-substance addictions – gambling and binge eating disorders: striatal activations 00
8. Conclusions: treating the striatum – boost or block? 00
   Acknowledgements 00
   References 00

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1. Introduction

Two frequently contrasted theories propose that the development of addiction related behaviors reflects the hyper- versus hypo-activation of limbic reward systems. The debate is not new (e.g., Wikler, 1948, 1973; Vogel et al., 1948). Nor are the positions irreconcilable. Recent evidence raises the possibility that the expression of hyper- versus hypo-active incentive motivational states might reflect, in significant part, the presence versus absence of addiction related cues (Leyton and Vezina, 2012; see also Anagnostaras and Robinson, 1996; Anagnostaras et al., 2002; Stewart and Vezina, 1988, 1991; Vezina and Leyton, 2009). The present review focuses on the evidence for these alternating states in humans, the possibility that individuals may differ in their susceptibility to them, and the role that addiction related cues play in their expression. Although considered in the human clinical setting, many of the ideas discussed here have been tested over the last thirty years in some detail in preclinical drug sensitization experiments. The processes identified in these studies could have particular bearing for our understanding of the role played by addiction related cues in the generation of subjective and behavioral states in humans. We thus begin with a brief review of this literature before turning to a systematic treatment of the evidence in humans.

2. Preclinical studies in laboratory animals

Psychostimulant drugs like amphetamine, cocaine, and nicotine have long been known to produce their behavioral activating and motivating effects by stimulating the mesoaccumbens dopamine (DA) system. Many preclinical studies, mostly in rodents, have studied the effects of repeated exposure to these drugs on biochemistry and behavior. Of the different consequences of drug exposure assessed, two have emerged that have particular relevance for our understanding of excessive drug taking: the development of sensitization to the behavioral stimulant and incentive motivational effects of drugs and the formation of conditioned associations between these drug effects and various environmental stimuli. Although separate phenomena, these two consequences of drug exposure are known to interact as outlined below. It is the nature of this interaction that may be particularly informative for understanding how addiction related cues can influence the generation of subjective and behavioral states in humans.

An extensive preclinical literature now indicates that repeated intermittent exposure to psychostimulant drugs enhances not only the locomotor and brain DA activating effects they produce but more importantly the amount of work animals will emit to obtain and self-administer the drug (Mendrek et al., 1998; Vezina, 2004; Vezina et al., 2007). These effects are persistent (they are observed weeks to months after drug exposure in rodents; Hamamura et al., 1991; Paulson et al., 1991; Suto et al., 2004; Vezina et al., 2002), there is evidence that they increase in magnitude with the passage of time (Vanderschuren and Kalivas, 2000; Vezina, 2007), and they are observed following intermittent exposure (Robinson and Becker, 1986; Zimmer et al., 2012), a pattern often associated with initial exposure to the drug and initiation of drug use. Together, these findings support the proposal that sensitization of mesoaccumbens DA neuron reactivity may underlie the transition from sporadic experimentation to more frequent drug use and substance related problems (Robinson and Berridge, 1993, 2003).

An equally longstanding preclinical literature supports the importance of conditioned associations between stimulant drug effects and environmental contextual stimuli in drug seeking and self-administration (Stewart et al., 1984). The ability of drug paired stimuli to elicit conditioned locomotion (Stewart and Eikelboom, 1987) and forebrain DA release (Aragona et al., 2009; Di Ciano et al., 1998; Duvauchelle et al., 2000; Ito et al., 2000) is well established. Importantly, environmental stimuli previously paired with a psychostimulant drug slow extinction of responding for the drug (Tran-Nguyen et al., 1998) and reinstate drug seeking (de Wit and Stewart, 1981) in a manner that parallels their effects on DA transmission in the nucleus accumbens and amygdala (Weiss et al., 2000). The ability of these stimuli to reinstate drug seeking is long-lasting (Ciccocioppo et al., 2004) and becomes more intense with time (Grimm et al., 2001).

Because repeated systemic drug injections are administered in the presence of multiple environmental stimuli, the conditions are ripe for the simultaneous development of sensitization and conditioning of stimulant drug effects and for these two forms of plasticity to interact. While sensitization is known to develop non-associatively (Singer et al., 2009; Vezina and Stewart, 1990), there is evidence that its expression can come to be controlled by environmental stimuli previously paired or unpaired with the drug (Anagnostaras and Robinson, 1996; Anagnostaras et al., 2002; Stewart and Vezina, 1988, 1991; Vezina and Leyton, 2009). Thus, rats previously exposed to the drug in one environment exhibit sensitized behavioral responses in this environment while rats previously exposed to the drug elsewhere do not. Indeed, rats that previously received the drug elsewhere show levels of responding on tests for sensitization that are comparable to those of rats administered the drug for the first time. This control over the expression of behavioral sensitization may be mediated, at least for contextual stimuli, by activity in a ventral hippocampus - nucleus accumbens – ventral pallidum – ventral tegmental area neuronal loop that regulates DA neuron firing in the latter site (Lodge and Grace, 2008).

Much of the evidence for the ability of environmental stimuli to control the expression of sensitization comes from experiments measuring locomotion (above references) although similar effects have been reported for drug-induced nucleus accumbens DA overflow (Guillory et al., 2006; Reid et al., 1996). Importantly, such conditioned environmental stimuli have also been shown to control the expression of enhanced amphetamine self-administration and drug-induced reinstatement in rats previously exposed to nicotine (Cortright et al., 2012), again underscoring the critical role these stimuli play in the expression of enhanced drug self-administration and drug seeking.

The above preclinical findings notwithstanding, there has been some debate as to their generalizability to the human clinical arena. For example, no change or even reduced rather than augmented striatal responses to drugs have been reported in a number of influential studies of psychostimulant exposure conducted in drug self-administering non-human primates and addicted human subjects (e.g., Bradberry, 2007; Volkow et al., 1997). This has led to the proposal that increased DA reactivity associated with drug sensitization is of limited value to the human condition as a mechanism for drug abuse and other forms of pathology. We assess the merits of this argument below by reviewing the results of a large number of studies aimed at deciphering the effects of drugs and drug associated cues in humans. A number of factors emerge that may have potential importance for understanding how motivated behaviors are generated. Central among these is the presence versus absence of addiction related cues and their ability to regulate responding to abused drugs and other rewards. This factor in particular can facilitate the integration of a previously disparate group of findings in the animal and human literatures alike.

3. Studies in humans: subjective and behavioral states

3.1. Effects of cues

In substance abusers, exposure to stimulant drug associated cues elicits a wide range of subjective, behavioral and physiological

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