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Neural systems recruited by drug- and food-related cues: Studies of gene activation in corticolimbic regions

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Abstract

In order to survive, animals must acquire information about the reward value of stimuli in their environment. This process partly depends on the ability of the organism to make associations between the environmental context and the internal representation of value. While this type of learning probably evolved in order to promote behaviors that increase fitness (e.g. ingestive and sexual behavior), neuropsychological research utilizing addictive drugs, which are potent artificial reinforcers, has led to a deeper understanding of reinforcement mechanisms. Through these associations, sensory cues can acquire emotional salience and motivational properties. Exposure to drug-related cues in human addicts results in drug craving and localized activation of central circuits that are known to mediate cue-induced reinstatement of drug-seeking behavior in animal models of relapse. Similar regional activation patterns occur in humans in response to cues associated with foods. Furthermore, drug- and food-related cues not only activate common neuroanatomical regions but also result in similar activity-regulated gene expression programs within these shared areas. Here we discuss recent studies from our laboratory that investigate gene expression patterns elicited by exposure to palatable food- or drug-related cues. These studies suggest that the central nervous system stores and utilizes information about 'natural' and drug reinforcers in similar ways, both neuroanatomically and biochemically. These considerations may have important implications for the pharmacological and cognitive-behavioral treatments of substance use disorders, addiction, eating disorders, and obesity.

Keywords: Addiction; Relapse; Craving; Reinstatement; Nicotine; Morphine; Eating disorders; Obesity; Classical conditioning; Pavlovian conditioning; Immediate early gene; Cue exposure; Extinction; c-*fos*; *arc*; *NGFI-B*; Prefrontal cortex; Cue reactivity

There is a growing realization that the neural pathways underlying motivation for food and those affected by drugs of abuse share many commonalities [1]. Highly palatable food and rewarding drugs both stimulate specific neurotransmitter systems in cortico–striatal–hypothalamic circuits. Contextual cues associated with rewarding food or drugs can exert powerful effects on emotions and behavior, eliciting a motivational state of craving and "wanting" [2,3]. It is theorized that such cues can play an important role in relapse to drug use, and possibly also in non-homeostatic eating (food intake not driven by energy deficit) [4]. There is evidence that sensory cues associated with rewarding states activate prefrontal circuits, which may then engage subcortical brain regions controlling behavioral actions. We have recently investigated a model in rats where environmental cues are repeatedly paired with drug (morphine, nicotine) or food (chocolate, fat), and gene expression is analyzed in prefrontal cortex and other regions [5]. In this paradigm, rats are administered drugs (morphine or nicotine) or provided with palatable food (chocolate chips or chocolate Ensure), and the drug or food is always paired with a particular environment (paired group). A control condition is carried out in which the same animals receive the drug or food in yet another environment (unpaired group). In this way, all rats received the same amount of treatment and thus any changes observed are likely to be solely due to exposure to reward-related cues rather than long-term adaptive effects

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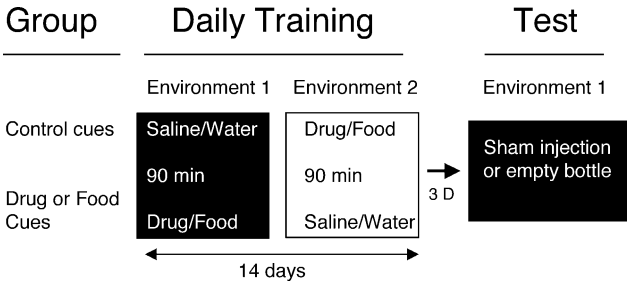

Fig. 1. A schematic diagram of the conditioning protocol used in recent studies described in the text (e.g. Ref. [5] and unpublished findings). Animals are given the palatable food or drug in one environment, and the control condition in another. Pairings are carried out for 10–14 days. All animals receive the same treatment throughout the experiment. On the final test day, half the rats in the experiment are placed in the reward-related environment (Environment 1) and half are placed in the control environment (Environment 2). The brains are then processed for in situ hybridization for detection of mRNA and semi-quantitative measurement of gene expression.

of the drug or food (see diagram of behavioral protocol in Fig. 1). On the test day (usually 3–5 days following the end of treatment), animals are placed in the distinctive environments; half are placed in the reward-paired environment and half in the control environment. About 1 h later, rats are sacrificed and their brains processed with either immunohistochemistry or in situ hybridization for detection of immediate early genes, transcription factors, and effector genes regulating synaptic plasticity.

Our earlier work using an immunohistochemical approach had examined the effects of repeated administration of morphine, nicotine, or chocolate chips on expression of the immediate early gene c-*fos* in selected brain regions [6–8]. We found that contextual cues associated with drug administration induced conditioned motor activity, and strongly activated Fos expression in widespread corticolimbic regions, but particularly strong effects were found in prefrontal and cingulate areas, in agreement with human neuroimaging experiments in which addicts are exposed to drug-related cues [9–11]. In other studies in animals, palatable food similarly activated Fos. This pattern of findings suggests that conditioned stimuli activate common neuromolecular substrates whether linked to past experience with drugs or rewarding food.

We recently extended this hypothesis by examining how nicotine, morphine, and palatable food-related contextual conditioning alter transcription factors in addition to c-Fos (*NGFI-B*, *zif268*) as well as effector genes such as *arc* and *homer 1A*. These genes have been implicated in neural plasticity and learning. For example, *arc* is upregulated during learning and memory tasks [12]; *homer 1A* has been shown to regulate AMPA receptor function [13]. In accordance with our hypotheses, we found marked upregulation of all of these genes when animals were exposed to the environment associated with drug or highly palatable food (chocolate Ensure). Figs. 2 and 3 show examples of these findings. Confirming earlier work, strong upregulation was found in prefrontal regions, although other cortical and limbic regions (striatum, amygdala, sensorimotor cortex) were also recruited. The remarkable similarities between conditioned gene activation following exposure to food- or drug-related cues suggest that addictive drugs induce neuroadaptations in brain circuits normally subserving learning and memory for motivationally salient stimuli. However, it is important to note that differences between food- and drug-related conditioned activation may also exist

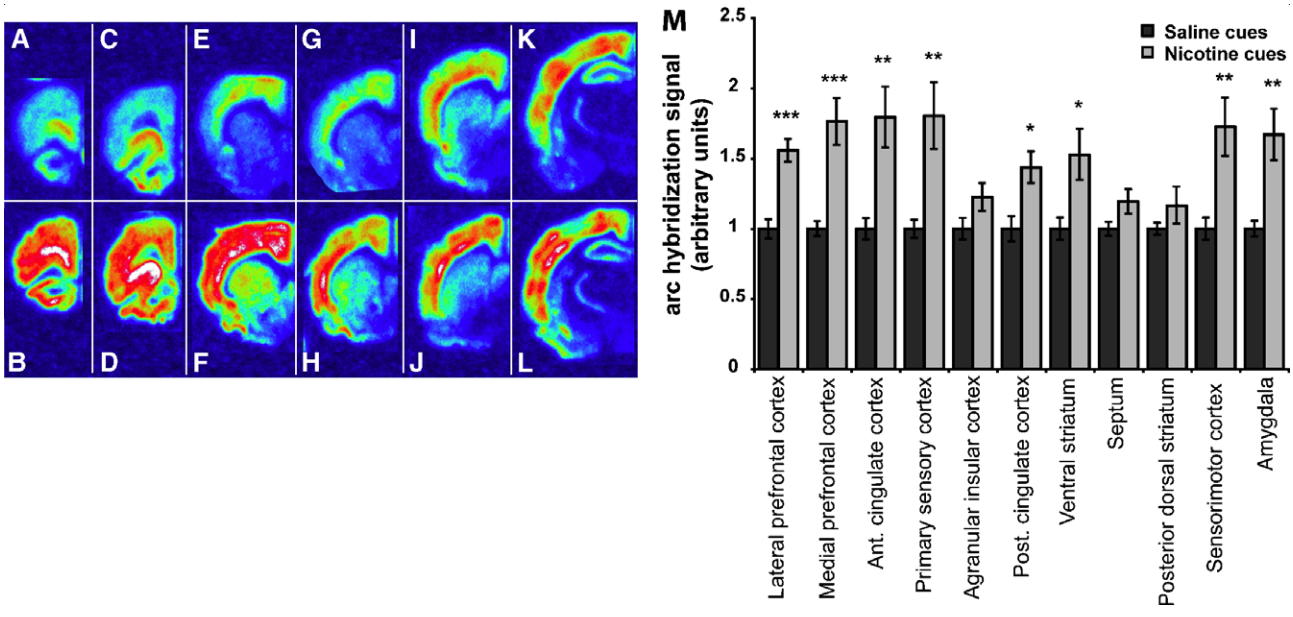

Fig. 2. Exposure to nicotine-associated cues strongly upregulates the expression of the early response gene *arc* in widespread corticolimbic regions. Top row shows representative cross-sections from rat brain in animal exposed to the saline-paired environment and bottom row shows equivalent sections from animal exposed to nicotine-related context. The right-hand graph shows the percentage increase in gene expression based on optical density image analysis. From Ref. [5], with permission.