On the origins of a selective vulnerability to opioid addiction.

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Abstract

The origins and neural bases of the current opioid addiction epidemic are unclear. Genetics plays a major role in addiction vulnerability, but cannot account for the exponential recent rise in opioid abuse, so environmental factors must contribute. Individuals with history of early-life adversity (ELA) are disproportionately affected, yet whether ELA directly influences brain function to cause opioid vulnerability is unknown. We simulated ELA in female rats, which provoked a profound, selective opioid-addiction phenotype. This was characterized by resistance to extinction, increased relapse-like behavior, and, as in addicted humans, dramatic increase in economic demand. By contrast, seeking of natural rewards was unaffected. These discoveries provide novel insight into the origins and nature of reward circuit malfunction that drives opioid abuse.

Main Text

The devastating epidemic of opioid addiction in the U.S is enormously costly, both economically and in human life[1]. Genetics plays a major role in addiction vulnerability, but cannot account for this recent rise in opioid abuse, so environmental factors must contribute[2,3]. Indeed, opioid use is more prevalent among those who experienced early-life poverty and trauma, most notably women[4,5]. However, it is yet unclear whether early-life adversity actually *causes* opioid use disorder.

In humans, separating influences of ELA from the roles of genetics and other contributing factors is complex[6]. Therefore, we simulated resource scarcity in rats during a short, defined postnatal sensitive period, by limiting bedding and nesting materials in the cage (LBN)[7,8]. This leads to aberrant maturation of brain circuits underlying reward and stress[8], which are crucially implicated in addiction to a range of abused drugs.

Surprisingly, we did not previously find evidence for augmented risk of addiction to the psychostimulant cocaine after ELA[9]. Here, we tested whether ELA instead directly promotes the use, seeking, and addiction to opioid drugs and examined the nature of alterations in specific functions of the reward circuitry.

We found strikingly augmented addiction-like behaviors for two distinct classes of opioid drugs, heroin and remifentanil, in adult female rats raised under ELA conditions (**Fig. 1**). Although total heroin self-administration did not vary between control and ELA rats (**Fig. 1A**), the ELA group resisted extinction once heroin was withdrawn (**Fig. 1B**), a robust indicator of compulsive seeking[10,11]. Moreover, when the ELA rats were re-exposed to either small priming doses of heroin itself or heroin-associated cues (risk factors for craving and relapse to drug use in humans attempting to quit[12,13]), they reinstated their seeking of heroin to a far greater degree than controls (Fig. 1C,D).

In humans, drug addiction is characterized by high demand for drug that is insensitive to escalating financial, social, and health costs. This phenomenon, termed 'demand inelasticity,' is characteristic of economic demand for a wide range of essential commodities, and is a hallmark of compulsive drug seeking in people with substance use disorders[14,15]. Therefore, we tested demand elasticity for the synthetic opioid remifentanil in control and ELA rats, using an established and sensitive assay of microeconomic demand[9,16].

Remarkably, rats reared in simulated poverty exhibited features similar to human addicts when given the opportunity to self-administer remifentanil. Specifically, they were willing to pay a significantly higher price to obtain the drug compared to controls—their demand became in-elastic and relatively insensitive to cost (**Fig. 1E**). The selectivity of this addictive-like behavior was striking: no changes were observed in the preferred intake of remifentanil by the LBN group when the drug was essentially "free" (i.e. in the hedonic set-point, **Fig. 1F**). Notably, in a canonical assay of natural reward/pleasure versus anhedonia, the sucrose preference test[17-19], ELA rats were indistinguishable from those reared in control lab conditions (**Fig 1G-I**). Coupled with our prior demonstration of preserved demand elasticity of cocaine[9], these observations highlight the remarkable selectivity of ELA-induced addictive-like behaviors to opioids.

Together, these findings indicate that, in a preclinical experimental system where genetics and prior existing conditions can be controlled, poverty-like rearing during sensitive developmental periods[23,24] can directly provoke vulnerability to the addictive effects of opioid drugs. Indeed, the findings suggest that critical developmental periods—defined for sensory circuits—apply also to developing reward circuitries, and potentially to other cognitive and emotional brain systems[8,9,25,26]. The specific aspects of early-life adversity that cause these effects and the mechanisms by which ELA generates addiction-like behavior remain to be explored. Our prior work demonstrated that ELA (using our naturalistic LBN model) is characterized by chaotic, unpredictable maternal signals to the developing pups[20], and converging evidence from both humans and rodents shows that such unpredictable, fragmented early-life environments profoundly impact brain function later in life[21]. We propose that these long-term negative outcomes, including opioid addiction risk, result from aberrant maturation of specific brain circuits, a finding emerging with the use of translatable methods such as structural magnetic resonance imaging[8].

While numerous aspects of addiction vulnerability we have discovered here require further investigation, the present work defines specific and selective alterations of the functions of the reward circuitry. Importantly, it creates for the first time a direct causal link between ELA and opioid addiction, and establishes a new framework for testing mechanisms across species, ultimately enabling the development of predictive biomarkers and prevention.

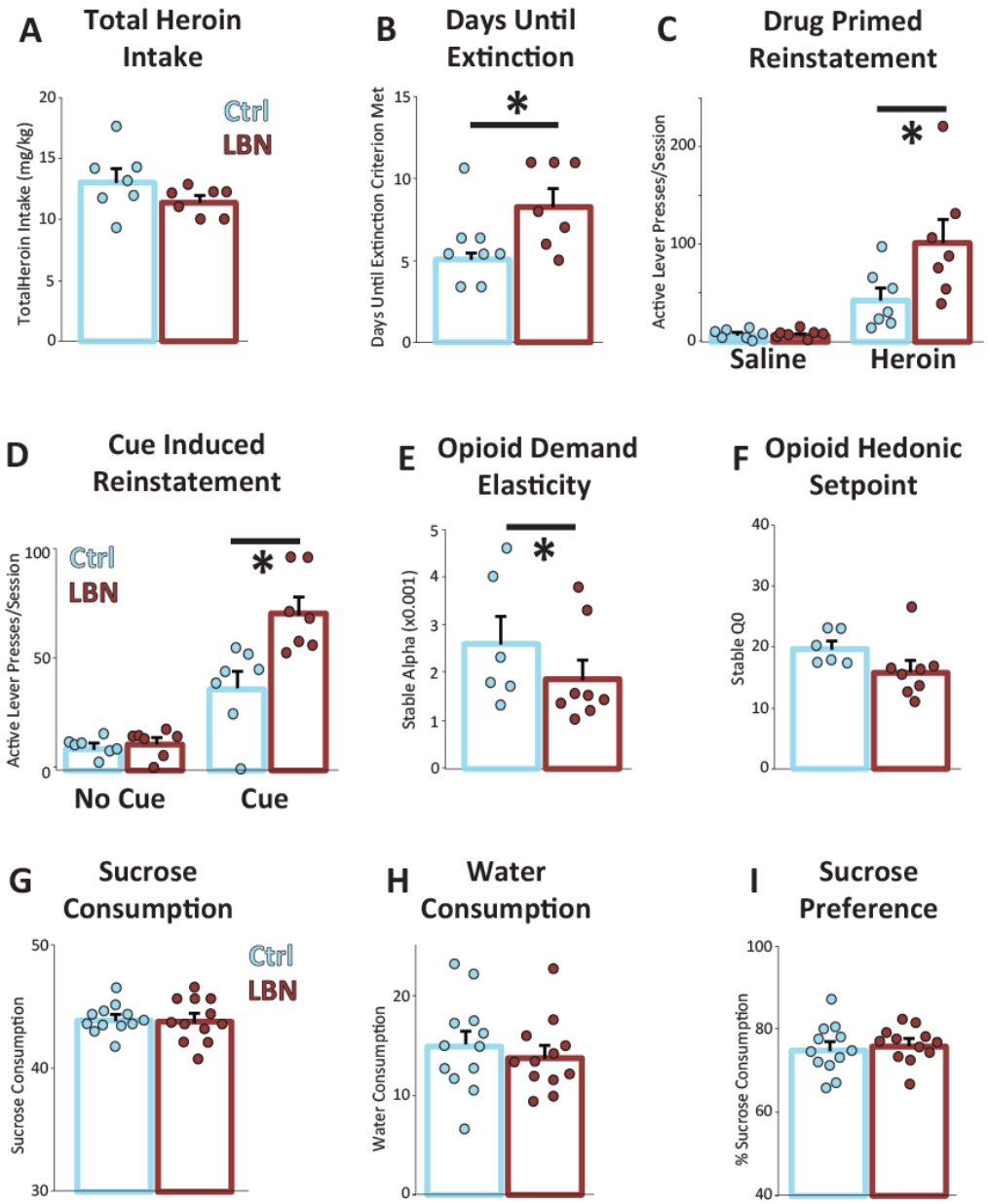

Figure 1: Early-Life Adversity Induces Specific Vulnerability to the Addictive Effects of Opioid Drugs: Whereas heroin self-administration of ELA-experiencing and control female rats did not differ appreciably (A), the early-life adversity (LBN) group was more resistant to extinction (B). Relapse-like behaviors triggered by small doses of heroin itself (C) or by heroin-associated cues (D) were augmented in the LBN group, and sensitivity of remifentanil intake to price was reduced (i.e., decreased demand elasticity) (E). No changes in the hedonic set-point for remifentanil (F) was observed, nor were there changes in the intake of the natural rewards sucrose (G) or water (H). Thus, sucrose preference, a standard measure of pleasure, reward, and anhedonia was unaffected by ELA (I).

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