

Electrophysiological correlates of enhanced vulnerability to cocaine self-administration.

MARINELLI M., COOPER D.C., WHITE F.J.

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ELECTROPHYSIOLOGICAL CORRELATES OF ENHANCED VULNERABILITY TO COCAINE SELF-ADMINISTRATION.

M. Marinelli, D.C. Cooper, F.J. White

Dept. of Cellular & Molecular Pharmacology. Finch University of Health Sciences/The Chicago Medical School. 3333 Green Bay Rd. North Chicago, IL.

It is well known that both differences between individuals (individual “traits”) and repeated exposure to drugs (drug-induced “states”) may participate in determining drug addiction. We have examined the role of individual traits, drug-induced states, and the interaction between the two in determining vulnerability to drugs. Using *in vivo* extracellular recordings, we examined the impulse activity of midbrain dopamine (DA) cells, as these neurons are considered one of the main neurological substrates mediating the reinforcing effects of drugs of abuse.

Individual traits. The concept of inter-individual differences mediating vulnerability to drug addiction started with the observation that there is considerable variation between individuals with respect to sensitivity to addictive drugs. It was hypothesized that certain “individual traits” would make some subjects vulnerable to the addictive properties of drugs, and others resistant. In animals, this individual propensity to develop drug self-administration (SA) can be predicted by drug-independent behavior, such as the level of motor activity during the exposure to a novel environment. Rats with high levels of locomotor activity in a novel environment (High Responders, HRs) show greater reactivity to psychostimulant drugs compared to animals with low levels of motor activity (Low Responders, LRs). Using this HR/LR model, it has been shown that HRs have higher DA levels in the nucleus accumbens compared to LRs. No studies have determined the origins of this difference. In our first experiments, we determined whether differences in DA neuron activity of HRs and LRs could underlie individual differences in vulnerability to drug SA. Animals screened for their response to a novel environment were tested for acquisition of cocaine SA and, in a separate experiment, for the impulse activity of midbrain DA neurons. Only HRs developed cocaine SA (175 µg/kg/infusion) and there was a positive correlation between locomotor response to a novel environment and cocaine intake (fig. 1a). Differences in cocaine SA were not due to differences in sampling because these behaviors did not differ in HRs and LRs self-administering a saline solution. HRs also showed enhanced impulse activity of DA neurons compared to LRs. Both the firing rate (fig. 1b) and the bursting activity ($46.0\% \pm 3.5$ vs $32.6\% \pm 3.3$ bursting action potentials; 7.6 ± 0.6 vs 5.0 ± 0.6 burst events/10 sec) were greater in HRs compared to LRs. In addition, inhibition of firing rate by the DA D2 class receptor agonist quinpirole was attenuated in HRs as compared to LRs, suggesting that increased impulse activity in HRs may, at least in part, be associated with functional sub-sensitivity of impulse-regulating DA autoreceptors.

Drug-induced states. Though vulnerability to drugs may be endogenously present in certain individuals, it may also be induced by exposure to psychostimulants. Repeated drug administration increases behavioral responses to drugs (i.e. behavioral sensitization), and increases drug SA. These heightened drug effects depend on drug-induced neuroadaptations. Concerning the activity of DA neurons, repeated exposure to psychostimulants transiently increases the impulse activity of midbrain DA cells and induces sub-sensitivity of impulse-regulating DA autoreceptors. We have argued that such neuroadaptations in the VTA may be necessary for the initiation of sensitization and increased vulnerability to drug addiction. However, these studies have been performed using non-contingent (experimenter delivered) drug injections; little is known about the effects of voluntary drug exposure. In addition, the consequences of autoreceptor sub-sensitivity on drug craving are unknown. In this second series of experiments, we studied impulse activity of DA VTA neurons following cocaine SA; in parallel, we studied the consequences of autoreceptor activation on drug craving. After stabilization of SA behavior (500µg/kg/infusion, average of 20 mg/kg/day for 7 days), we recorded the activity of DA neurons 1, 3, 10 and 30 days after withdrawal from SA. Rats that self-administered cocaine showed an increase in the firing rate of VTA DA neurons as compared to controls (naïve rats or animals that self-administered saline). This effect was greatest on withdrawal day (WD) 1, and decreased in a time-dependent manner on WD3, WD10 and WD30 (fig. 1c). The greater activity of VTA DA cells on WD1 may be related to decreased sensitivity of impulse-regulating DA autoreceptors, as the WD1 group required higher doses of quinpirole to suppress DA neuron activity compared to control rats. Instead, on WD 10, quinpirole-induced inhibition of firing was similar to that of controls. To determine if the functional activity of impulse-regulating DA autoreceptors could modify drug craving, we studied the effects of autoreceptor activation (by administration of autoreceptor-selective doses of quinpirole) on drug seeking behavior. On WD1 (when DA autoreceptors are sub-sensitive), quinpirole did not modify drug-seeking behavior. But on WD10, (when DA autoreceptors are normo-sensitive), quinpirole decreased drug-seeking behavior. This suggests that autoreceptors, by regulating neuronal activity, could participate in modulating craving and seeking behavior.

Interaction between individual traits and drug-induced states. The above findings show that increased activity of DA neurons is associated with vulnerability to drugs, either endogenously present in certain individuals (HRs), or induced

by repeated exposure to cocaine. In these studies, we tried to determine whether there is an interaction between these two conditions. In this last series of experiments, we studied the activity of DA neurons in HRs and LRs following SA of cocaine (500 µg/kg/infusion for 7 days). In these experiments, HRs and LRs had similar drug intake. In fact, at higher drug doses, both groups of animals acquire SA behavior. Despite similar drug intake, HRs and LRs developed differential neuroadaptations following cocaine SA. Both HRs and LRs showed increased firing rate on WD1, however, LRs showed recovery of DA firing by WD3, whereas HRs maintained increased firing until WD10 (fig. 1d). It is unknown whether this is due to a more efficient normalization process in LRs, or whether it is linked to a system that maintains increased activity in HRs.

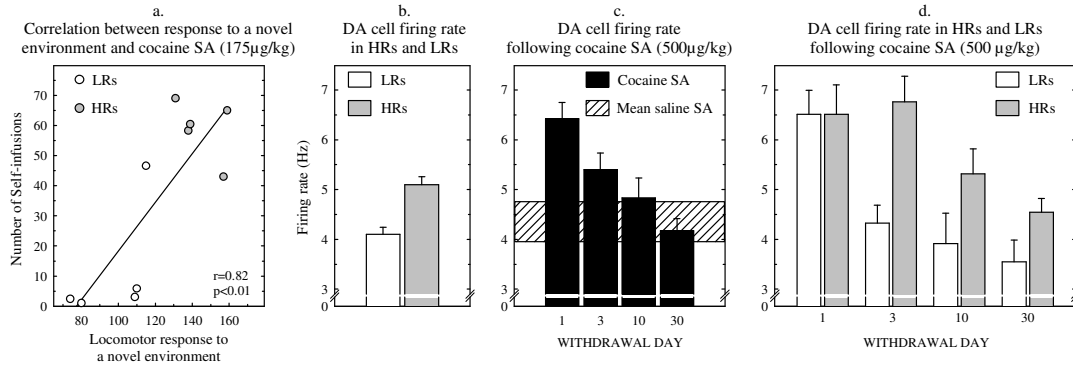


Figure 1. a) There was a positive correlation between response to a novel environment and cocaine SA (average over 7 days). b) HRs had greater firing rate of VTA DA neurons compared to LRs. c) Following cocaine SA, rats showed an increase in DA firing rate on WD1, which returned to baseline values in a time-dependent manner. d) HRs and LRs showed differential neuroadaptations following cocaine SA.

Conclusions. Overall, these results show that enhanced impulse activity of DA neurons is associated with increased vulnerability to drugs. In fact, hyperactivity of DA neurons was present in spontaneously vulnerable subjects (HRs), and following voluntary repeated exposure to drugs. This suggests that both “individual traits” and drug-induced “states” converge at the level of DA neurons to modulate vulnerability to drugs. The increased activity of DA neurons is associated with decreased functional activity of impulse-regulating DA autoreceptors and these changes within the VTA may participate in modulating craving and drug-seeking behavior.

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