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COMMENTARY

Where's the Excitement in Psychostimulant Sensitization?

Repeated psychostimulant exposure produces sensitized behavioral responses that persist into withdrawal and are thought to model increased drug craving in psychostimulant abusers (Post and Rose 1976; Robinson and Berridge 1993; Stewart 1983). A potential mechanism for inducing behavioral sensitization could involve a transient increase in AMPA glutamate receptor-mediated excitability in ventral tegmental area (VTA) dopamine neurons (White et al. 1995; Zhang et al. 1997). Previously, this hypersensitivity was thought to involve transient increases in AMPA (and NMDA) receptor subunits after multiple drug or stress-related treatment regimens known to induce behavioral sensitization (Churchill et al., 1999; Fitzgerald et al. 1996).

However, a study by Lu, Monteggia, and Wolf published in this issue of Neuropsychopharmacology directly challenges the idea that psychostimulant-induced hypersensitivity in VTA dopamine neurons involves an increase in the actual amount of glutamate receptors. In this study, multiple treatment regimens with amphetamine and cocaine, known to induce behavioral sensitization, and identical to protocols used in previous studies, all failed to increase AMPA subunits in the VTA and neighboring substantia nigra. Such discrepancies in the drug abuse literature usually are attributed to differences in dose, chronicity, withdrawal time, self- versus passive drug administration, or other methodological considerations.

The study by Lu et al. (1999, 2001) used quantitative immunohistochemical and reverse transcriptase–polymerase chain reaction methods to measure GluR1-4 levels throughout the rostral-caudal extent of the VTA and substantia nigra, whereas increases in AMPA subunits previously were detected in immunoblots of VTA tissue. After a series of experiments to verify epitope and sequence specificity of the GluR1 antibody and RNA probe, respectively, the authors conducted an exhaustive and thorough search for the precise anatomical site in VTA where the elusive upregualtion in GluR1 subunits was thought to occur. They found no evidence for upregulation of AMPA subunits at the mRNA or protein level in any region of VTA and substantia nigra, whether at 16 and 24 h or 3 and 14 days after multiple chronic treatment regimens with amphetamine and cocaine. Other studies have also failed to find evidence for upregulation in mRNAs for AMPA GluR1 or NMDA NR1 subunits, suggesting that reported increases in GluR1 and NR1 protein may not involve changes in GluR1 gene expression (Bardo et al., 2001; Ghasemzadeh et al., 1999). However, the present study also failed to find increases in GluR1 protein. One potential caveat to the immunohistochemical method used by Lu et al. is that GluR1 antibodies could recognize other endogenous proteins containing GluR1-like epitopes that dilute changes in GluR1 subunits themselves in native tissue slices; this problem was circumvented in previous studies in which GluR subunits were isolated by standard SDS PAGE techniques before immunolabeling. However, the authors note that their immunohistochemical method is capable of detecting changes as small as 15% in other brain regions. What may be apparent from this and other studies is that relatively similar chronic drug treatments produce markedly different effects on AMPA subunits in VTA across several laboratories (see Table 1).

In the present study, Lu et al. conclude that transient increases in GluR1 protein cannot account for transient increases in AMPA-mediated electrophysiological responses associated with the induction of behavioral sensitization, and they suggest phosphorylation or membrane trafficking of AMPA receptors as alternative hypotheses. There is considerable evidence for phosphorylation and membrane trafficking as important events in AMPA receptor plasticity in long-term potentiation (LTP) and long-term depression (LTD) (Carroll et al. 2001; Scannevin and Huganir 2000). Indeed, a recent

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Table 1. Differential Alterations in Glutamate Receptor Subunits and Tyrosine Hydroxylase (TH) in VTA at Early and Late Psychostimulant Withdrawal

	GluR1		GluR2/3		NR1		TH	
Chronic Cocaine	**mRNA**	**Protein**	**mRNA**	**Protein**	**mRNA**	**Protein**	**mRNA**	**Protein**
Early withdrawal ⩽ 3 days	No Δ (Bardo et al. 2001; Lu et al. 2001)	↑ (Fitzgerald et al. 1996; Churchill et al. 1999)	No Δ (Bardo et al. 2001)	No Δ (Fitzgerald et al. 1996; Churchill et al. 1999, 2001; Lu et al. 2001)	—	↑ (Fitzgerald et al. 1996; Churchill et al. 1999; Loftis and Janowsky, 2000)	↑ (Vrana et al. 1993)	↑ (Beitner-Johnson et al. 1991; Sorg et al. 1993; Vrana et al. 1993)
		No Δ (Lu et al. 2001)				No Δ (Lu et al. 1999)	No Δ (Sorg et al. 1993)	No Δ (Schmidt et al. 2001[a])
Late withdrawal > 3 days	No Δ Ghasemzadeh et al. 1999; Bardo et al. 2001)	No Δ (Churchill et al. 1999; Lu et al. 2001)	No Δ (Ghasemzadeh et al., 1999) Bardo et al. 2001)	No Δ (Churchill et al. 1999; Lu et al. 2001)	No Δ (Ghasemzadeh et al. 1999)	No Δ (Churchill et al. 1999; Lu et al. 1999)	No Δ (Sorg et al. 1993)	↑ (Masserano et al. 1996)
						↑ (Loftis and Janowsky, 2000)		No Δ (Sorg et al. 1993; Schmidt et al. 2001[a])
								↓ (Trulson et al. 1987)

[a]Indicates intravenous cocaine self-administration.

study found that a single injection of cocaine produces both behavioral sensitization and LTP in VTA dopamine neurons independent of detectable AMPA receptor upregulation (Ungless et al. 2001), thereby implicating other possible trafficking and/or phosphorylation alterations. However, others have found that "synaptic" concentrations of AMPA receptors actually do increase after LTP in the hippocampus, and such subanatomical changes may not be detected in tissue slices or crude tissue homogenates (Heynen et al. 2001).

It is clear from these studies that drug-induced neuroadaptations in the VTA differ widely across research laboratories, even when drug regimens and withdrawal times are taken into account. Several studies on psychostimulant regulation of glutamate receptor subunits in the VTA are listed in Table 1, along with regulation of VTA tyrosine hydroxylase levels, which also differ among studies and psychostimulant treatment regimens. It is important to consider that several methodological variables differ between these studies, such as rat strains and vendors and whether animals received drug treatments in their home cages or in specific drug-associated test chambers. Drug-induced neuroplasticity is profoundly altered by certain contextual or other experience-related factors (e.g., Bell et al. 2000; Schmidt et al. 2001), and the potential influence of these factors should not be underestimated.

Results from behavioral studies are sometimes encumbered by the fact that certain effects clearly and easily obtained in one laboratory are difficult to repeat in another. Even when animal strains are held constant and procedures are carefully controlled, different, and even opposite, results can be found (Crabbe et al. 1999). The findings of Giorgetti and colleagues (Gioergetti et al. 2001), when taken in view of previous studies, highlight the fact that neurobiological studies can suffer a similar dilemma. However, in scientific research, these discrepancies serve well to remind us that a single study cannot, and should not, ever be considered definitive. Scientific progress benefits from both convergent and divergent lines of evidence, and discrepant findings such as these ultimately help to illuminate intricate facets of neural and behavioral plasticity that may have important implications for drug addiction research and treatment.

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