Associative Mechanisms and Drug-Related Behavior

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This special issue of the *International Journal of Comparative Psychology* is based on presentations delivered at the Focus Session of the 2004 Winter Conference on Animal Learning and Behavior (WCALB) held in Winter Park, Colorado. The *Associative Mechanisms and Drug-Related Behavior* Focus Session began with an invited address by Shepard Siegel titled *The Ghost in the Addict: Drug Anticipation and Drug Addiction.* He described an impressive body of research showing that conditioning mechanisms underlie drug tolerance and withdrawal. Siegel's address underscored the important contribution of associative mechanisms to drug-related behavior and set the stage for the six papers presented in this issue.

Siegel began by describing his landmark study that first demonstrated the "situational specificity of tolerance" (Siegel, 1975). In that study, tolerance to morphine was only observed when rats were injected with morphine in an environment where they had previously experienced morphine. In contrast, no tolerance to morphine was observed when rats were injected in a novel environment. This result demonstrated that environmental factors might be as important, or even more important, than pharmacological factors in the expression of tolerance to drugs. Siegel pointed out that these results were anticipated by Subkov and Zilov (1937) who demonstrated conditioned tolerance of epinephrine-induced tachycardia.

Siegel hypothesized that this situational specificity of tolerance was mediated by conditioned compensatory responses (CCRs) that counteracted the analgesic effects of morphine. According to this conditioning account of tolerance, the environmental stimuli present before and during morphine (the unconditioned stimulus or US) administration should act as Pavlovian conditioned stimuli (CSs). Through these pairings, the CSs come to elicit a conditioned response (CR) that opposes the direct effects of morphine. Therefore, since morphine itself produces analgesia, the environmental CSs that are paired with morphine come to elicit hyperalgesia. These oppositional processes then summate to produce a zero net effect, which manifests itself as tolerance, when morphine is administered in the presence of cues previously paired with morphine.

A critical prediction of the CCR analysis of tolerance is that an effect opposite to the direct effects of morphine (e.g., hyperalgesia) should be observed if the morphine-paired CSs are presented without the morphine (e.g., saline injection

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is substituted for morphine). This is because the full expression of the CCR should be elicited with nothing to counteract them. Siegel (1975) showed that hyperalgesia is indeed observed when previously morphine-paired stimuli are presented in the absence of morphine to morphine-tolerant rats. He has called these unopposed CCRs "withdrawal symptoms" (Siegel, 1999). Thus, for Siegel, tolerance and withdrawal are both manifestations of a CCR—tolerance is observed when the CCR is elicited in the presence of the drug and withdrawal symptoms are observed when the CCR is elicited in the absence of the drug (Siegel, 1999; 2002).

Siegel proceeded to review numerous studies conducted over the past 30 years supporting the view that drug tolerance reflects the processes of classical conditioning. Principally, this evidence comes from studies showing that tolerance is affected by learning contingencies in the same way that other nondrug Pavlovian CRs are affected by these contingencies. This reveals generality of process through "functional contiguity" (Sidman, 1960). These learning phenomena include, but are not limited to, extinction, external inhibition, latent inhibition, partial reinforcement effects, blocking, sensory preconditioning as well as electrophysiological and pharmacological manipulations (Siegel, 1975, 1989, 1991; Siegel & Larson, 1996; Dafters et al., 1983; Siegel et al., 2000).

So where is the ghost in Siegel's address? In describing his experience with opium addiction, Jean Cocteau wrote "the dead drug leaves a ghost behind. At certain hours it haunts the house" (Cocteau, 1958, p. 60). Siegel materializes the ghost by reframing it in terms of Pavlovian conditioning. For Siegel, the 'ghost' refers to the CRs elicited by drug-associated CSs resulting from extended drug experiences. The candidates for conditioned stimuli can be numerous and include the complex of stimuli present when drugs are taken, such as people, places, sounds and smells. He also posited that the CSs may be interoceptive in nature.

Siegel presented his recent research on interoceptive drug-associated cues that logically extend his research on Pavlovian conditioning of exteroceptive cues. This work essentially shows that interoceptive cues can indeed acquire CS functions in ways similar to exteroceptive cues. He considered two types of interoceptive cues, those associated with self-administration and drug onset cues. Self-administration cues are stimuli arising from the active administration of the drug (such as movement of the body and other proprioceptive stimuli). Evidence was presented that self-administration cues contribute to tolerance and symptoms of withdrawal (Weise-Kelly & Siegel, 2001; MacRae & Siegel, 1997). Siegel then described research demonstrating the CS function of drug onset cues. In a prototypical experiment, rats receive chronic injections of a large dose of morphine (50 mg/kg). On test days, a much smaller dose (e.g., 5 mg/kg) is given. The small dose of morphine precipitated opiate withdrawal as evidenced by the behavioral and thermic data. This finding is expected if the interoceptive stimulation produced by the small dose was similar to the early drug-onset cues associated with the administration of the large dose. In other words, the early drug-onset cues are analogous to exteroceptive morphine-paired stimuli and elicit CCRs (i.e., precipitate withdrawal) when presented without the US (see Sokolowska, Siegel, & Kim, 2002).

Siegel's keynote address provided convincing evidence that drug-associated stimuli, environmental and internal, play a critical role in drug tolerance

and withdrawal. The six papers presented in this issue are concerned with a variety of effects of drug-related stimuli, including place conditioning (Bevins), selective associations produced by cocaine-associated stimuli (Weiss, Kearns, Cohn, Panlilio & Schindler), conditioned tolerance to the ataxic effects of alcohol (Brooks), the drug as a CS (Tomie, Mohamed, & Poherecky), and the conditioned reinforcing properties of drug-paired stimuli (Shelton & Beardsley, Newman & Beardsley, and Bevins).

Siegel's address and the spectrum of learning paradigms represented by these six articles confirm the central role learning and associative mechanisms play in drug-related behavior. They also illustrate that this is an active area of research that needs people with diverse backgrounds and interests including classical and operant conditioning, behavioral pharmacology and drug abuse. Clearly, people other than metaphysicians acknowledge that the "ghost" is alive and well, and worthy of study.

References

Cocteau, J. (1958). *Opium: The diary of a cure.* (Translated by M. Crosland & S. Road). New York: Grove Press.

Dafters, R., Hetherington, M., & McCartney, H. (1983). Blocking and sensory preconditioning effects in morphine analgesic tolerance: Support for a Pavlovian conditioning model of drug tolerance. *Quarterly Journal of Experimental Psychology,* **35B**, 1-11.

MacRae, J.R., & Siegel, S. (1997). The role of self-administration in morphine withdrawal in rats. *Psychobiology*, **25**, 77-82.

Sidman, M. (1960). *Tactics of scientific research.* New York: Basic Books.

Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative and Physiological Psychology,* **89**, 498-506.

Siegel, S. (1989). Pharmacological conditioning and drug effects. (1989). In A. J. Goudie & M. W. Emmett-Oglesby (Eds.), *Psychoactive drugs: Tolerance and sensitization. Contemporary neuroscience (pp. 115-180).* Totowa, NJ: Humana Press.

Siegel, S. (1991). Feedforward processes in drug tolerance and dependence. In R. G. Lister & H. J. Weingartner (Eds.), *Perspectives on cognitive neuroscience* (pp. 405-416). London, UK: Oxford University Press.

Siegel, S. (1999). Glucose enhancement of tolerance to morphine and ethanol in rats. *Psychobiology,* **27**, 372-376.

Siegel, S. (1999). Drug anticipation and drug addiction: The 1998 H. David Archibald lecture. *Addiction,* **94**, 1113-1124.

Siegel, S. (2002). The ghost in the addict: drug anticipation and drug addiction. *Transactions of the Royal Society of Canada,* **2**, 2002.

Siegel, S., Baptista, M.A.S., Kim, J. A., McDonald, R. V., Weise-Kelly, L. (2000). Pavlovian psychopharmacology: The associative basis of tolerance. *Experimental and Clinical Psychopharmacology,* **8**, 276-293.

Siegel, S., & Larson, S. J. (1996). Disruption of tolerance to the ataxic effect of ethanol by an extraneous stimulus. *Pharmacology, Biochemistry and Behavior,* **55**, 125-130.

Sokolowska, M., Siegel, S., & Kim, J. A. (2002). Intraadministration associations: Conditioned hyperalgesia elicited by morphine onset cues. *Journal of Experimental Psychology: Animal Behavior Processes,* **28**, 309-320.

Subkov, A. A., & Zilov, G. N. (1937). The role of conditioned reflex adaptation in the origin of hyperergic reactions. *Bulletin de Biologie et de Medecine Experimentale,* **4**, 294-296.

Weise-Kelly, L., & Siegel, S. (2001). Self-administration cues as signals: Drug self-administration and tolerance. *Journal of Experimental Psychology: Animal Behavior Processes*, **27**, 125-136.