The highlight for November is by Dr. Nicole Schramm-Sapyta from the Department of Pharmacology and Cancer Biology at the Duke University Medical Center in Durham, NC. In 2004, Dr. Schramm-Sapyta and her colleagues at Vanderbilt assessed the rewarding effects of cocaine in adolescent and adult rats and noted no distinct differences in the acquisition of cocaine-induced place preferences between the two groups. Given her focus on the balance of the rewarding and aversive effects of drugs in impacting vulnerability to abuse, she began examining any differential aversive effects of cocaine between adults and adolescents to determine if such differences might account for the differential abuse patterns in these age groups. It is this work that is described in her highlight. As she reports (see Schramm-Sapyta et al. Pharmacology, Biochemistry and Behavior 2006 8:344-352), there are clear differences in the acquisition of cocaine-induced aversions with adolescent rats displaying weaker aversions at intermediate and low doses of cocaine. This differential acquisition of drug-induced aversions is also seen with LiCl, THC and alcohol, supporting the position of a general insensitivity in adolescent rats to the aversive effects of a host of compounds. The fact that aversions are influenced by a variety of factors, including age, is well documented. The importance of Dr. Schramm-Sapyta’s work lies in the fact that such differences extend beyond classical toxins to drugs of abuse. The significance also lies in her analysis of the relevance of these differences to drug use and abuse. Traditional analyses of the vulnerability to addiction have focused on a drug’s rewarding effects and how such effects are modulated by age, sex, history, etc. Including a role for the drug’s aversive effects in drug addiction (as a protectant factor) and an assessment of how such effects are influenced by variables such as age is an important point in our understanding of drug use and abuse.

Conditioned Taste Aversion Learning in Adolescent and Adult Rats
Nicole Schramm-Sapyta, PhD

I must first admit that, unlike many of the esteemed colleagues highlighted in these pages, I was not initially interested in conditioned taste aversion for its own sake, or even as a model learning paradigm. My primary research interest is in drug addiction, and CTA has proven to be an incredibly useful tool in that pursuit.

During my tenure as a postdoctoral fellow in Danny Winder’s laboratory at Vanderbilt University, then as a research associate in Cynthia Kuhn’s laboratory at Duke University, I have been struck by the observation that drugs of abuse have simultaneously rewarding and aversive effects. THC makes some people relax, but others have severe paranoia. Alcohol may be fun while one is drinking it, but the hangover the next morning can be miserable. Some of these effects are dependent upon the dose and the individual taker. However, cocaine can be both aversive and rewarding at the same doses (and in the same animal). Ettenberg and Geist demonstrated in the early 1990s (Ettenberg and Geist 1991) that rats approach a compartment associated with cocaine, but gradually increase the time to arrive there, an effect alleviated by anxiolytic drugs. Other reports reveal complicated effects of this dichotomy. For alcohol, some people who experience aversive effects, particularly hangovers, avoid drinking in the future (Prat et al. 2008). People who
experience anxiogenic effects of THC tend to avoid it in the future (Thomas 1996). In contrast, those who develop more severe hangovers from alcohol and who drink to alleviate their symptoms tend to become alcoholics (Earleywine 1993). We were particularly intrigued by the dual effects of cocaine. Recent work has shown that cocaine’s aversive effects are minimally related to its peripheral actions (Freeman et al., 2005) with the full extent of its aversive effects probably dependent upon its anxiogenic properties (Ettenberg and Geist 1991). Primarily, we were interested in the balance between cocaine’s rewarding and aversive effects and how that balance relates to the development of drug addiction.

I am also interested in understanding what differentiates a casual drug user from an addict, and one factor that seems to drive that distinction is the age-of-onset of drug use. People who start drug use at a younger age are more likely to become addicted, but the literature is currently unclear whether this relationship is causal or merely correlational. Many in the field, including me (Schramm-Sapyta et al. 2004), had hypothesized that younger users would find drugs of abuse more rewarding than adults. This hypothesis has been tested many times, using the conditioned place preference task, with largely unsatisfying results. There is no clear consensus in the literature that drugs of abuse are more rewarding to younger animals than to adults (one exception is nicotine, which is clearly more rewarding to younger animals). This finding led Dr. Kuhn and me to look at the other side of the coin: Are these drugs less aversive to younger animals?

Overwhelmingly, the answer is yes! Our work with cocaine (Schramm-Sapyta et al. 2006), THC (Schramm-Sapyta et al. 2007) and ethanol (manuscript in preparation) shows that younger rats exhibit reduced taste aversion to these substances compared to adults. Others have published similar reports with nicotine (Shram et al. 2006; Wilmouth and Spear 2004) and amphetamine (Infurna and Spear 1979). Interestingly, we also observed similar results with lithium chloride. This observation suggested to us that younger rodents (and by extrapolation, younger humans) might be generally less susceptible to aversive experiences than adults.

Reviewers questioned whether our observations were the result of a failure in the young animals to learn the drug-taste association or a reduction in the aversive effects themselves. Several lines of evidence suggest that the reduction lies in the aversive effects, not the ability to learn. Primarily, many unconditioned aversive effects of drugs of abuse are reduced in younger rodents. For example, nicotine is anxiolytic in adolescent male rats, but anxiogenic in adults (Elliott et al. 2004). Adolescent rats are less sensitive to ethanol’s social inhibitory effects (Varlinskaya and Spear 2004b), hangover-induced anxiety (Doremus et al. 2003; Varlinskaya and Spear 2004a) and sedative effects (Little et al. 1996; Swartzwelder et al. 1998). The anxiogenic and sedative effects of THC are also reduced in adolescents (Schramm-Sapyta et al. 2007). Second, young rodents learn as well or better than adults in most other learning paradigms, particularly in learning tests involving activity (as opposed to freezing) (Spear 2000; Spear and Brake 1983).

Reduced aversive effects could have profound implications for human adolescent drug takers, but the link between aversion and vulnerability to addiction has not yet been
conclusively demonstrated. Younger drug takers may be more likely to take drugs at higher and more frequent doses, which could promote development of addiction. On the other hand, many teenagers experiment with drugs of abuse at high levels and then outgrow it, naturally reducing or ceasing use as they mature. Our future experiments, therefore, are focused on three main questions:

1. How do the aversive effects of drugs of abuse relate to voluntary drug intake?
2. How do age-related differences in aversion relate to age differences in intake?
3. To what extent do the neurophysiological mechanisms of taste aversion relate to the mechanisms of addiction? Are they protective or facilitative?

These are our current works in progress: “Stay tuned!”

References


Earleywine M (1993) Hangover moderates the association between personality and drinking problems. Addict Behav 18: 291-7


Freeman KB, Konaklieva MI, Riley AL (2005) Assessment of the contributions of Na+ channel inhibition and general peripheral action in cocaine-induced conditioned taste aversion. Pharmacol Biochem Behav 80: 281-8


Schramm-Sapyta NL, Morris RW, Kuhn CM (2006) Adolescent rats are protected from
the conditioned aversive properties of cocaine and lithium chloride. Pharmacol Biochem Behav 84: 344-52


