

The highlight for June is by Dr. Paul J. Kulkosky from the Department of Psychology at Colorado State University-Pueblo in Pueblo, Colorado. For over three decades, Dr. Kulkosky and his colleagues have been investigating a myriad of phenomena, all of which are related to the regulation of food and drug intake. These phenomena include the schedule-induced consumption of fluids, peptidergic modulation of feeding and alcohol consumption. What has been interesting about these different areas of research is that each of them has been tied back to aversion learning and how their interaction with such learning provides insight into the normal regulation of intake. Dr. Kulkosky describes his work on schedule-induced polydipsia and how it may reveal a procedure that overrides or masks the normal control of intake by food aversions, a condition that may be important for understanding both addictions to food and drugs. His early work at the University of Washington with Steve Woods on feeding and satiety was continued when he joined Gerry Smith and Jim Gibbs' lab at Cornell. It was here that Dr. Kulkosky began exploring the role of CCK in the regulation of feeding and posed another role of taste aversions in the regulation of intake. The issue of satiety (following normal feeding) bled into nimiety (with excessive intake). Nimiety and its associated aversive consequences naturally restrained further food intake, again illustrating a possible role of food aversions in regulatory feeding. Dr. Kulkosky's work on genetic strains with differential patterns of ethanol intake reveals yet another manner by which food aversions regulate intake, in this case a genetic (and non-environmental) factor as selected strains that displayed weak aversions are the ones more likely to consume ethanol in free choice settings. The idea that taste aversions may be involved as a mechanism that regulates normal intake extends its adaptive nature beyond the position that it serves simply to prevent the consumption of a debilitating or life-threatening toxin. Aversions become more regulatory in nature. Further, the insights provided by Dr. Kulkosky show how challenges to this regulatory system (either environmental or genetic) may yield insights into addiction or non-regulatory intake.

Conditioned Taste Aversions and Nimiety

Paul J. Kulkosky

Department of Psychology

Colorado State University-Pueblo

Pueblo, CO 81001

I followed Steve Woods on a move from Columbia to University of Washington (UW) at the end of 1972, with the hope of developing a thesis on the conditioning of ingestion-related responses (1). There, I encountered an experimental culture devoted to the "Garcia Effect (2)." Tony Riley, Denis Mitchell, Kathy Chambers, Liz Lotter, Mike Vitiello, Dick Lovely and Lorne Parker were some of my fellow graduate students researching the challenging nonconformities of the conditioned taste aversion (CTA). With Dick Krinsky, we found CTA decreased saccharin drinking elicited by osmotic brain stimulation (3). Tony Riley and I initiated a series of studies on the interaction of CTA with schedule-induced polydipsia (SIP) (4, 5, 6, 7). We pursued this enquiry after Tony had moved to American University (AU) and I to NIAAA at St. Elizabeth's Hospital in Washington, D.C in 1976. The use of SIP as an animal model of alcoholism seemed explicable as an example of a paradigm that reduced the natural, potent ability of ethanol to induce CTA (8). Human addictions to food and drugs might be understood as reflections of environmental situations that counteract the function of CTA to limit intakes to adaptive levels. Consistent with this hypothesis was our elaborate observation, occupying more than an entire greenhouse at AU, that providing a naturalistic, colonial environment resulted in lowered ethanol intake in comparison to singly- or group-caged rats (9).

Satiety and the mechanisms of feeding inhibition by cholecystokinin (CCK) had also fascinated me since the days at UW. I was able to pursue this interest further after I moved in 1980 to the E. W. Bourne Laboratory of Gerry Smith and Jim Gibbs at Cornell University Medical College at White Plains, N.Y. This innovative, productive laboratory had first used the CTA design to assess their discovery of feeding inhibition by CCK in 1973 (10). Our subsequent experiments indicated that CCK and other gut neuropeptides released by food reduced those intakes by an unconditioned satiation reflex, not a CTA (11, 12). However, it was also plain that these molecules could condition a taste aversion in a choice paradigm at high doses, and the interpretation of CCK's effect was hotly debated (13). Looking into the unabridged definitions of the word "satiety," I found a neglected verbal cousin, "nimiety." This word could be used to refer exclusively to the aversive interoceptive state produced by overeating, or more generally, overindulgence in the "Act of Sport (14)." The notion of a hedonic continuum:

hunger-satiety-nimety and the involvement of peptides in its mechanism developed as an explanation of the dose-dependent satiating and CTA-inducing properties of peptides such as CCK and bombesin. Could a hedonic continuum also explain the limitation of alcohol intakes (15)?

A move to Colorado State University-Pueblo (CSU-P, then University of Southern Colorado) in 1982 gave me the opportunity to research the mechanisms of limitation of alcohol intake by blood levels of ethanol and neuropeptides. Rats had been selectively bred by Laura Draski and colleagues at University of Colorado Health Sciences Center for differences in sleep time after ethanol injection (16). At CSU-P, my students and I found that the strain with the shortest sleep times after ethanol also showed the highest intakes of ethanol, and the shortest extinction times when ethanol was used as the aversive stimulus in the CTA design (17, 18). Again the CTA paradigm provided an explanation of excessive intakes as a reflection of a selectively bred insensitivity to signals of satiety and nimety and consequently, weaker CTA formation. So, both an environmental paradigm, SIP, and a genetic paradigm, selective breeding, for inducing excessive intake could be explained as inadequacy of CTA formation. At the other end of the continuum, clinical studies with Gene Peniston at Ft. Lyon, Colorado Veterans Administration Hospital showed that elevation of a peptide stimulus of intake, endorphin, was associated with alcoholic relapse (19, 20). A hedonic continuum from hunger to nimety mediated by neuropeptides could explain the typically adaptive consumption of caloric substances. Departures from this adaptive consumption were mirrored by decreases in CTA formation. In this theory, in the absence of ingestion, neuropeptides such as endorphins rise and stimulate intake. As ingestion proceeds, peptides such as CCK rise and eventually signal satiety and inhibit ingestion. If ingestion continues beyond optimal levels, high levels of ingestion-correlated peptides signal nimety and condition taste aversion. Departures from limited, optimum consumption should be associated with decreases in CTA formation (21, 22).

Most recently, Moussa Diawara and I have employed the CTA design to assess the aversiveness of a new class of reproductive toxins found in vegetables, the psoralens (23). These molecules cause reduced birthrates and other indices of ovarian toxicity in a dose-dependent manner in rats. Administration of xanthotoxin (8-methoxypsoralen) reduced associated saccharin intake in a dose-related manner comparable to LiCl. This finding shows a conditioned aversion mechanism might regulate intake of ovarian toxins found in food. This would constitute yet another example of adaptive regulation of intakes by CTAs.

The CTA design has proven a serviceable boon to experimenters trying to unravel the mysteries of consummatory behaviors. The astounding range of its applications is clearly demonstrated by the depth of Tony and Kevin's website. We thank John Garcia and his colleagues for the insights yielded by the CTA. He elegantly cited John Locke as providing the first clear description of this phenomenon (24). None of the basic problems it has been applied to has yet

been solved to the Baconian "relief of the human estate," so much remains to be done.

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