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Review

Conditioned taste aversion and drugs of abuse: History and interpretation

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ABSTRACT

Conditioned taste aversion (CTA) learning describes a phenomenon wherein an animal learns to avoid consumption of a particular taste or food following its pairing with an aversive stimulus. Although initially demonstrated with radiation and classical emetics, CTAs have also been shown with drugs of abuse. The ability of rewarding drugs to support CTA learning was described as paradoxical by many investigators, and a number of attempts have been made to resolve this paradox. The present review offers a historical perspective on the CTA literature with a particular focus on CTAs induced by self-administered drugs. Specifically, this review describes and summarizes several interpretations of CTA learning that offer possible mechanisms by which drugs of abuse support CTAs, including sickness, drug novelty, reward comparison and conditioned fear. It is concluded that the reported "paradox" is no paradox at all in that drugs of abuse are complex pharmacological compounds that produce multiple stimulus effects, not all of which are positive reinforcing. Finally, a possible role of drug aversion in drug self-administration is discussed.

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1. Introduction

Conditioned taste aversion (CTA) learning describes a phenomenon wherein an animal learns to avoid consumption of a particular taste or food following its pairing with an aversive stimulus. CTA was conceptually introduced in the 1950s and 1960s when John Garcia and his colleagues published a series of papers demonstrating the nature of CTA as a learning phenomenon (see Freeman and Riley, 2009 for a review of the history of CTA). In their initial experimental demonstration of CTA, Garcia et al. (1955) gave rats a pairing of a novel saccharin taste and exposure to gamma radiation, following which they were given a choice between saccharin and water in the absence of radiation. The authors reported that irradiated animals decreased their saccharin preference compared to their initial preference and to sham-irradiated controls (see Fig. 1; Garcia et al., 1955).

In subsequent years, several aspects of CTA were elucidated that made it a very special (and *specialized*, see below) form of learning. For example, the initial report by Garcia et al. (1955) demonstrated the robust nature of CTA learning in that the decrease in saccharin preference persisted for at least 30 days of continuous saccharin/water exposure following the taste-radiation pairing (see Fig. 1). Additionally, acquisition of CTA required few pairings (and often only one; Garcia et al., 1955; Swank and Bernstein, 1994). For instance, in the 1955 report a single pairing of saccharin and radiation was enough for the rats to acquire a CTA and significantly suppress their saccharin preference. Moreover, CTA learning occurred with long inter-stimulus delays. In one paper, Garcia and

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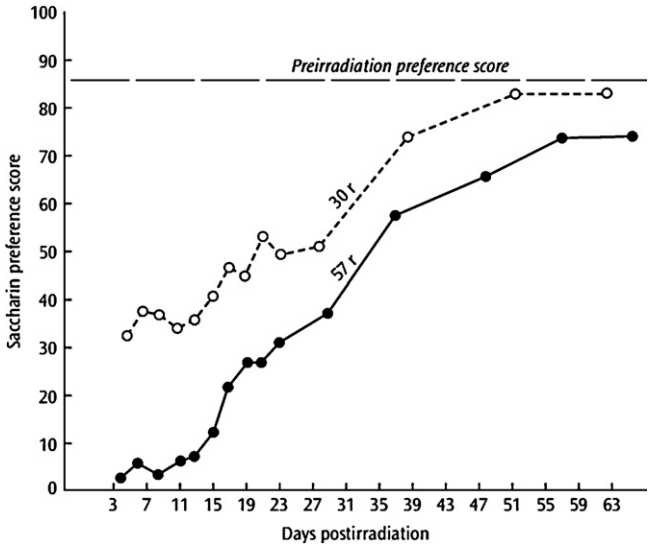

Fig. 1. Conditioned taste aversion: first experimental demonstration. Median saccharin preferences scores [(saccharin solution intake/total fluid intake) × 100] during extinction for groups initially given access to saccharin solution and concurrently exposed to gamma radiation (at 30 or 57 r). Redrawn from Garcia et al. (1955).

his colleagues showed that aversions to saccharin were conditioned even if injections of apomorphine (aversive stimulus) were delayed for as long as 75 min following saccharin presentation (Garcia et al., 1966; see also McLaurin and Scarborough, 1963; Revusky, 1968). Finally, taste aversion learning was shown to be selective to gustatory stimuli. In one demonstration of this, rats selectively associated saccharin with irradiation-induced nausea but not with foot shock; conversely, rats selectively associated an audiovisual cue with the foot shock but not radiation (Garcia and Koelling, 1966). These demonstrations put CTA at odds with traditional learning theory that held that learning occurred with multiple conditioning trials, required short inter-stimulus intervals and was independent of the nature of CS and US (i.e., most CSs and USs serve equally well in conditioning) (Freeman and Riley, 2009).

The explanation of these inconsistencies with the learning theory of the day came in the form of the interpretation of CTA as a specialized form of learning. As argued in the three early reviews of the field (Garcia and Ervin, 1968; Revusky and Garcia, 1970; Rozin and Kalat, 1971; see Freeman and Riley, 2009 for a review of these papers), the exceptional nature of taste aversion learning (i.e., one-trial learning, long-delay learning and selective associations) made sense in the light of the ecological context of the animal. Allowing for the normal time course of digestive function (i.e., some delay between ingestion of food and the effects of its consumption), the ability to learn over long delays prevents the repeated consumption of potentially poisonous foods. This "preparedness" also extended to the selective nature of CTA that facilitated associations between biologically relevant stimuli (i.e., taste and sickness) but retarded associations between biologically irrelevant stimuli (i.e., audiovisual cue and sickness). Moreover, the advantage of one-trial learning allowed the animal to quickly recognize and avoid potentially harmful substances.

2. The role of sickness in conditioned taste aversion

As described, the initial demonstrations of CTA used radiation and other illness-inducing agents, such as lithium chloride (LiCl), apomorphine and cyclophosphamide, all of which share the ability to produce gastrointestinal distress. It is not surprising then that early studies suggested nausea, gastrointestinal illness and malaise (terms used interchangeably) or general "toxicosis"[1] as the mechanism by which different treatments (both pharmacological and non-pharmacological) induced CTA (Garcia and Ervin, 1968; Garcia et al., 1955; Garcia and Koelling, 1966). According to this general view, the gastrointestinal distress produced by these agents served as a US with which a taste stimulus (CS) was paired resulting in a conditioned aversion to the taste and its avoidance upon subsequent exposure. This view fit well with the interpretation of CTA as a specialized form of learning, evolved through natural selection to allow organisms to avoid potentially dangerous (i.e., toxic) foods.

Support for this general position came from a number of studies that demonstrated that lesions of the area postrema, a brain region responsible for monitoring blood-borne toxins, attenuated taste aversions produced by emetics and radiation (Berger et al., 1973; Curtis et al., 1994; Ossenkopp and Giugno, 1985, 1989; Rabin et al., 1983, 1984a,b; Ritter et al., 1980). Additional evidence came from the demonstration that antiemetic drugs attenuated CTA learning (Coil et al., 1978; Provenza et al., 1994; Racotta et al., 1997; Symonds and Hall, 2000; although see Goudie et al., 1982; Rabin and Hunt, 1983 for opposing results).

A problem with this interpretation arose, however, when some known toxins were reported ineffective in inducing taste aversions (see Riley and Tuck, 1985 for a list of well-known toxins ineffective in producing CTA). For example, sodium cyanide (a rodenticide) failed to produce taste aversion at near lethal doses in rats (Nachman and Hartley, 1975). Failure to illicit CTA by cyanide poisoning was also reported by Ionescu and Buresova (1977; although see O'Connor and Matthews, 1997 for cyanide-induced CTA in possums). Similar results were reported for other toxins such as strychnine (Nachman and Hartley, 1975), malonate and gallamine (Ionescu and Buresova, 1977), as well as aluminum chloride, warfarin and others (Riley and Tuck, 1985).

Additionally, Barker et al. (1977) showed that the degree of visible sickness did not correlate well with the strength of taste aversions that were produced by irradiation, LiCl or cyclophosphamide. Further, a number of antiemetic drugs, which are used to reduce gastrointestinal distress, have been demonstrated to be capable of inducing CTAs. Such ability, for example, has been reported for scopolamine (Berger, 1972). Other illness-*reducing* agents, such as tetrahydrocannabinol (THC), have been reported to induce taste aversions as well (Amit et al., 1977; Corcoran et al., 1974; Switzman et al., 1981). Moreover, pretreatment with either scopolamine or the antiemetic prochlorperazine did not attenuate aversions induced by LiCl, amphetamine or morphine (Goudie et al., 1982).

As becomes evident from these observations, the ability of a treatment to serve as an effective US within the CTA preparation is not clearly dependent on its ability to produce sickness or toxicosis. As described above, non-toxic agents have been reported to induce taste aversions; moreover, some well-known toxins have been reported to fail to produce taste aversions. This led several authors to conclude that sickness or general toxicity is not a necessary condition to produce a CTA (Barker et al., 1977; Berger, 1972; Gamzu, 1977; Hunt and Amit, 1987), although it may be sufficient for some compounds.

[1] It is important to note that toxicity was often not defined, and the term was used to mean a number of different things. Some researchers, for example, limited the use of the term "toxicity" to discussion of the effects produced by classical toxins such as LiCl and cyclophosphamide. For others, toxicity was defined in terms of the drugs' effects on feeding and drinking behavior (i.e., reduction in both feeding and drinking). More frequently, however, the term was used to mean some form of sickness or gastrointestinal distress (see, for example, Boland, 1973; Dantzer, 1980; Gemberling et al., 1980; Lindberg et al., 1982 and others).