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Review

Conditioned flavor avoidance and conditioned gaping: Rat models of conditioned nausea

Linda A. Parker*

Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, ON, Canada N1G 2W1

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ABSTRACT

Although rats are incapable of vomiting, they demonstrate profound avoidance of a flavor previously paired with an emetic drug. They also display conditioned gaping reactions during re-exposure to the flavor. This robust learning occurs in a single trial and with long delays (hours) between consumption of a novel flavor and the emetic treatment. However, conditioned flavor avoidance learning is not a selective measure of the emetic properties of drugs, because non-emetic treatments (even highly rewarding treatments) produce conditioned avoidance, and anti-emetic treatments are generally ineffective in suppressing conditioned avoidance produced by an emetic drug. On the other hand, conditioned gaping reactions are consistently produced by emetic drugs and are prevented by anti-emetic drugs, indicating that they may be a more selective measure of conditioned malaise in rats. Here we review the literature on the use of conditioned flavor avoidance and conditioned gaping reactions as rat measures of conditioned nausea, as well as the neuropharmacology and neuroanatomy of conditioned gaping reactions in rats.

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1. Introduction

The discovery of conditioned flavor avoidance learning in rats by Garcia et al., 1974 profoundly changed the field of animal learning research. Indeed, conditioned flavor avoidance is generally accepted as being one of the strongest forms of learning known today. A hallmark of flavor avoidance is robust learning despite long flavor-illness delays after a single pairing. Following pairings of a novel flavored solution with illness, rats not only avoid consumption of the flavored solution, but they also display conditioned gaping reactions (the wide opening of the mouth exposing the lower incisors) in rats reactions when re-exposed to that flavor. Both conditioned flavor avoidance and conditioned gaping have been

* Corresponding author. Tel.: +1 519 824 4120, extn. 56330; fax: +1 519 837 8629.
E-mail address: parkerl@uoguelph.ca

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considered by some investigators to be measures of conditioned nausea.

"Nausea" is a subjective state that humans report to be one of the most distressing side effects of chemotherapy treatment for cancer (Roscoe et al., 2000; De Boer-Dennert et al., 1997). Because nausea is poorly understood, effective treatments are very limited. Current anti-emetic therapies are highly effective in treating chemotherapy induced vomiting, but are only somewhat effective in treating chemotherapy-induced nausea. Because nausea is a subjective state, it has been difficult to develop effective pre-clinical models of nausea. Yet, animal models analogous to nausea in humans are essential to proceed efficiently and effectively in the development of new treatments. Of course no one can know if a rat experiences the same thing as a human who subjectively reports a sensation of nausea. However, below we provide evidence that the conditioned gaping model in rats may serve as such a model.

Rats detect emetic toxins, in a manner similar to that of species that vomit. For example, the nausea-inducing chemotherapeutic drug, cisplatin, causes the release of serotonin (5-HT) from enteroendocrine cells in the gastrointestinal tract, which activates 5-HT_3 receptors on vagal afferent fibers in both ferrets (Endo et al., 1995) (that vomit) and rats (Hillsley and Grundy, 1998; Horn et al., 2004). In both species, this vagal activation is blocked by 5-HT_3 receptor antagonists (Endo et al., 1995; Horn et al., 2004). As well, in the rat the area postrema detects blood-borne toxins (Bernstein et al., 1992; Eckel and Ossenkopp, 1996), as it does in vomiting species. Therefore, in the rat, the detection mechanism for vomiting is present, but the motor output is missing (Horn et al., 2004, 2013). Because the rat cannot vomit, it in fact serves as an excellent species for the investigation of the sensations that usually precede vomiting–nausea. Considerable behavioral evidence confirms that manipulations that produce vomiting in other species promotes conditioned gaping behaviors in rats and anti-emetic treatments prevent the establishment of conditioned gaping behaviors in rats (see Parker et al., 2009, for review). Rats do not gape unconditionally to an injection of a malaise-inducing drug (Limebeer et al., 2008; Horn et al., 2013); therefore, gaping does not represent a vestigial vomiting response in this non-emetic species. Instead it relies upon conditioning. Conditioned gaping can be elicited by a flavor or a context previously paired with an emetic drug; however contextually-elicited conditioned gaping requires several pairings (Limebeer et al., 2008), unlike flavor-elicited conditioned gaping. Conditioned gaping requires similar orofacial musculature as vomiting in emetic species (Travers and Norgren, 1986) and is topographically similar to the orofacial components of retching in the shrew. Fig. 1 presents the rat gape and the orofacial component of the shrew retch (prior to it vomiting). Reliable pre-clinical models of nausea are essential for the development of new treatments for this distressing condition in humans.

Fig. 1. The orofacial characteristics of the rat gape are very similar to those of the shrew retch. Unlike the rat, the shrew vomits in response to emetic stimulation. Although rats do not gape unconditionally, they do display conditioned gaping to flavors or contexts previously paired with an emetic drug. As well, anti-emetic drugs selectively suppress conditioned gaping reactions, without modifying conditioned flavor avoidance. Therefore conditioned gaping serves as a predictive model of emesis in rats.

2. Conditioned flavor avoidance: the nature of the unconditioned stimulus

The early conditioned flavor avoidance literature investigated the nature of associations between flavors and stimuli with known emetic properties, such as radiation, apomorphine or lithium chloride (LiCl) (Garcia et al., 1974). The robust associations formed led to the understanding that flavor avoidance is a unique learning process by which an organism rapidly associates a flavor conditioned stimulus (CS) with the emetic or nausea-inducing effects of an unconditioned stimulus (US). Conditioned flavor avoidance learning was shown to be a highly sensitive means of detecting the malaise-inducing properties of a drug and could be induced at doses lower than those necessary to reduce food and water consumption (for review see Riley and Tuck, 1985). This sensitivity was eloquently linked to neurobiological discoveries of central gustatory-visceral pathway convergence (Garcia, 1989).

As conditioned flavor avoidance learning became well characterized with known emetic agents, researchers began to evaluate the potential of agents other than those typically used to produce emesis to produce flavor avoidance learning. These investigations revealed that the ability of a drug to produce emesis in an animal capable of vomiting was not a necessary prerequisite for that drug to produce a conditioned flavor avoidance in rats (e.g., Nachman and Hartley, 1975; Ionesco and Buresova, 1977; for an excellent review see Grant, 1987). Paradoxically, even very low doses of drugs of abuse produce flavor avoidance, suggesting that nausea is not a prerequisite for this type of learning (Berger, 1972; Cappell and LeBlanc, 1973). The most convincing evidence of the paradoxical effects of rewarding drugs to produce flavor avoidance was reported in the late 1970s. Wise et al. (1976) presented rats with saccharin solution prior to sessions of operant intravenous self-administration of amphetamine. In subsequent tests, the rats avoided drinking the saccharin, but maintained responding for amphetamine. As well Reicher and Holman (1977) injected rats with amphetamine prior to placement in a distinctive chamber with access to a flavored solution. When later tested drug-free, the rats preferred the chamber, but avoided the flavored solution. Finally, White et al. (1977) trained rats to run down an alley to obtain food reward. Once they consumed the food in the goal box, the rats were injected with morphine, LiCl or saline. When subsequently tested, the rats treated with morphine increased their running speed, but the rats treated with LiCl decreased their running speed; however both groups suppressed their consumption of food while in the box. Each of these important papers illustrated that drugs of abuse produce paradoxical rewarding/aversive effects in rats.

The "paradox" of flavor avoidance learning produced by rewarding drugs led to hundreds of studies that have attempted to explain how a given drug injection could simultaneously produce both positive and negative consequences (see Hunt and Amit, 1987). One possibility was that all doses of drugs that produce flavor avoidance also have an aversive side effect (e.g., see Davis and Riley, 2010 for review). The selective association between a flavor and the aversive effects of the drug produces flavor avoidance (Reicher and Holman, 1977). However, the nature of the aversive effects of the drugs that produce avoidance of a flavored solution has not been well characterized. Another possibility for the paradoxical flavor avoidance produced by rewarding drugs was that any change in hedonic state (positive or negative) produces avoidance of a novel flavor with which it is

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