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The role of histamine in estradiol-induced conditioned consumption reductions

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Abstract

Conditioned consumption reductions (CCRs) develop toward novel taste stimuli as a consequence of associating those tastes with certain physiological changes. Few studies have focused on the neurochemical basis of this learned behavior. The purpose of these experiments was to reexamine the role of histamine in CCRs elicited by estradiol. Previous studies have suggested that histamine mediates CCRs induced by radiation, centrifugal rotation, and estradiol. However, because the animals were trained in a drug state, but tested in a nondrug state, it is possible that state-dependent learning confounded the results of these studies. The following series of experiments was performed to test this possibility for estradiol-induced CCRs. Implementing our own methodologies in Experiment 1, we demonstrated that an estradiol-induced CCR was blocked by treatment with the histamine 1 receptor blocker, chlorpheniramine maleate, before sucrose consumption during acquisition. In Experiment 2, identical states were maintained during acquisition and extinction by administering chlorpheniramine prior to sucrose exposure during both phases. The results indicated that chlorpheniramine blocked the estradiol-induced CCR. However, circumventing state-dependency in Experiment 3 by administering chlorpheniramine following exposure to sucrose during acquisition augmented the estradiol CCR. Taken together, the results of these experiments suggest that the ability of chlorpheniramine to abolish estradiol-induced CCRs is not due to state-dependency or to the antihistaminergic properties of chlorpheniramine. It is proposed that the results of all of the experiments can be accounted for by the aversive properties of chlorpheniramine.

Keywords: Conditioned taste aversions; Conditioned consumption reductions; Preexposure effects; State-dependent learning; Estradiol; Histamine; Chlorpheniramine maleate

1. General introduction

When consumption of a novel tasting substance is followed by administration of a chemical agent that produces physiological changes indicative of malaise, animals will reduce their consumption of the substance during subsequent encounters. This learned response typically has been referred to as a conditioned taste aversion. There has been an assumption that those agents capable of inducing conditioned taste aversions produce some type of illness, and thus all reductions in consumption that occur after pairing an agent with a novel taste are based on aversive conditioning. However, this assumption has been challenged. A number of years ago, it was suggested that conditioned reductions in intake can result from states that differ from illness [1]. For instance, pairing a food with a satiety-producing agent will elicit a learned reduction in the consumption of that particular food [2]. More recently, it has been suggested that conditioned taste aversions induced by some agents are qualitatively different than those induced by the classic illness agent lithium chloride (LiCl) [3,4]. Because of these concerns and the fact that estradiol is a long-term satiety hormone, we have decided to adopt the terminology conditioned consumption reduction (CCR), because it is behaviorally descriptive and is not laden with inferences as to mechanism [5–7].

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There are a considerable number of chemical agents that are capable of inducing CCRs [8]. One agent that has been studied extensively as an unconditioned stimulus in CCR experiments is the hormone estradiol. The ability of estradiol to produce a conditioned decrement in food intake has been demonstrated across different species, routes of administration, and conjugated forms for both females and males [9–23]. The successful treatments have included subcutaneous injections of estradiol, estradiol benzoate, and estradiol cypionate, subcutaneous implantation of a melted estradiol pellet, an estradiol-filled Silastic capsule, and an osmotic minipump filled with estradiol benzoate, oral administration of 17α-ethinyl estradiol, and intravascular administration of a brain-enhanced estradiol chemical delivery system. The species have included Sprague–Dawley, Wistar and Long–Evans rats, Crl: CD-1(ICR)BR and Rockland–Swiss mice, and humans. Although it unequivocally has been found that high supraphysiological doses of estradiol produce strong CCRs, low physiological doses appear to be ineffective in both females and males. For instance, in one study, it was demonstrated that a supraphysiological dose of 250 μg/kg of 17-β estradiol produced strong CCRs to a saccharin solution, while physiological doses, such as 0.4 and 2 μg/kg, did not [10].

Although a substantial amount of work has been done on the identification of neural areas involved in CCRs, fewer studies have focused on the neurochemical basis of this learned behavior. One neurochemical that has received some attention is histamine. Studies investigating the cellular basis of CCRs have targeted peritoneal mast cell degranulation as a potential mediator of the learning paradigm [24]. Mast cells, which contain biological agents such as serotonin and dopamine, also are known to be large depositories for histamine [25]. Evidence supporting the mast cell hypothesis is provided by three different findings. First, ionizing radiation, which has been used in many CCR studies as an unconditioned stimulus [26–28], activates degranulation of peritoneal mast cells [29]. Second, this radiation-induced degranulation is abolished by the intraperitoneal administration of pyrilamine, a histamine 1 receptor (H_1R) antagonist [30]. Third, administration of another H_1R antagonist, chlorpheniramine maleate (C), before pairing a saccharin solution with gamma radiation, prevents the formation of a CCR normally produced by that dose of irradiation [27]. Further support for an involvement of histamine in CCRs has been found for other procedures that can induce learned reductions in consumption when paired with a novel taste substance. Injecting C prior to pairing a saccharin solution with centrifugal rotation abolishes the subsequent formation of a CCR, while administration of the histamine 2 receptor (H_2R) antagonist, cimetidine, has no effect [31].

An association between estradiol and histamine also has been demonstrated. 17-β estradiol increases the secretion of histamine that has been triggered by compound 48/80, a mast cell degranulator [32]. This elevated release of histamine is blocked by the application of the estrogen receptor antagonist, tamoxifen [32]. Predicated on these findings, it was purported that CCRs produced by estradiol also are mediated by histamine. To test this hypothesis, an experiment similar in design to the aforementioned CCR radiation study was conducted. As was true for a radiation-induced CCR, administration of C before pairing sucrose with estradiol blocked the acquisition of a subsequent CCR [21,22]. These results have been discussed by several investigators and have led some to suggest that the effects of estradiol are mediated peripherally and are not due to direct action on the brain [2,5,8,14,33].

The results of these studies suggest that histamine plays a role in CCRs induced by at least some conditioning agents. However, there is an important factor that confounds the interpretation of the results of these studies. The animals were conditioned to the novel tastant in a drug state but were tested for saccharin preference in a nondrug state. Therefore, their failure to acquire a CCR may have been due to state-dependent learning [26,34]. In such a case, the antihistamine might not have been responsible for preventing the acquisition of the radiation-, rotation-, or estradiol-induced CCRs. Instead, the failure to provide identical states during the training and testing days may have interfered with the retrieval of the previously learned avoidance response on conditioning day. In fact, it has been shown that injecting C before access to a novel taste during both acquisition and extinction does not abolish a radiation-induced CCR [26]. This implies that the failure to acquire an estradiol-induced CCR after administration of C is based on state-dependent learning. However, there is a factor that confounds the interpretation of the state-dependent results as well. Chlorpheniramine has a depressive effect on drinking [26,31,34]. This raises the question of whether C was acting as an unconditioned intake suppressor and leaves the state-dependent issue unresolved.

The following three experiments were designed to determine whether C blocks an estradiol-induced CCR, and if it does, whether this effect is based on state-dependent learning. Experiment 1 was conducted to verify that administration of C before access to sucrose during acquisition abolishes an estradiol-induced CCR. Experiment 2 was designed to determine the outcome of maintaining identical states during acquisition and extinction testing by giving C before access to sucrose during both phases of testing. Finally, in Experiment 3, C was administered after sucrose exposure on acquisition day to circumvent the problem of state-dependency and the unconditioned suppression of consumption by C. If C blocks an estradiol-induced CCR due to its antihistaminergic properties and not due to state-dependency, then administering the drug should abolish the CCR whether it is given before or after sucrose consumption. On the other hand, the state-dependency hypothesis would predict that maintaining either identical