Contextual Control of Flavor Neophobia

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Abstract

The role of context in the retrieval of learned information has been widely analyzed in the associative learning domain. However, evidence about the effect of context on flavor memory retrieval is more limited. We have carried out four experiments with rats testing for possible interactions between neophobia habituation and the context in which flavors are presented, by manipulating prior experience with contexts. Our results point to the relevance of context familiarity for the establishment and recovery of a safe taste memory trace. More specifically, the use of the animals' home cages as experimental context favored neophobia habituation (experiments 1A and 2), reduced dopamine levels induced by administration of the dopamine D1- like receptor antagonist SCH-23390 disrupted neophobia habituation when tested in presence of a new context (Experiment 1B), and testing in the animal's home cage increases the amount of flavor consumed, even when such flavor had a previous history of aversive conditioning (Experiment 3). We propose that exploring context without aversive consequences generates a safe memory trace of such context that becomes in the basis of increased flavor consumption.

Key words: Neophobia; Habituation; Dopamine; Flavor; Context

1. Introduction.

Any alteration in environmental conditions induces different responses that can change in intensity, duration or functionality depending on the stimulus characteristics and the novelty produced by its presentation or withdrawal. Thus, for instance, a new light or sound of medium intensity generates a set of orienting responses that allows to the animal to explore and process the stimulus more accurately. When the stimulus is presented repeatedly without consequence, the orienting responses gradually decline as the stimulus loses its novelty [1].

A particularly interesting case is that related to the responses that follow the tasting of a new flavor, because in this situation the potential value of the stimulus for the animal's survival is very high [2,3]. As described by Bermudez-Rattoni [4] animal survival depends, among other factors, on their capacity to differentiate those foods that are edible from those that have toxic components. Animals are highly adaptive in that when they come into contact with a new flavor there appears to be an unconditioned response of rejection that results in minimum consumption of the substance with that flavor, which is known as neophobia [5]. When a period of time has elapsed since the flavored item was consumed, and as the flavor memory trace is consolidated as a "safe" stimulus (that is, a stimulus without aversive consequences), consumption progressively increases, a phenomenon termed habituation of neophobia [6]. Conversely, if flavor consumption is followed by any kind of negative consequence an aversive conditioning develops [7] that is behaviorally expressed in a sharp reduction of flavor ingestion. Therefore, as a function of the consequences that follow flavor ingestion, a flavor memory trace will be established that is either

safe, favoring an increase in consumption of the flavor in future encounters, or aversive, which will result in a reduction or even the complete rejection of flavor consumption [4,8].

This proposal is compatible with the learned safety theory [9,10], but contrasts with other general interpretations of the habituation process that propose mechanisms either associative or non-associative. Thus, from a non-associative perspective, the Dual-Process Theory proposed by Groves and Thompson [11] suggests that repeated presentations of a stimulus induce two independent processes in the central nervous system that interact to produce a response. The first process takes place in the Stimulus-Response pathway and is responsible for the progressive reduction of the response. The second process acts in the state system and gives rise to an increase in response intensity due to sensitization.

An alternative theory of habituation, which has great influence in the analysis of the processes underlying habituation mechanisms, was proposed by Wagner [12,13]. From his perspective, habituation depends on the association established between the stimulus and the context in which it appears. More specifically, Wagner proposes that, after repeated presentations of the stimulus, the contextual cues will activate a representation of the stimulus in short term memory which will prevent processing of the actual event, resulting in the reduction of the response to the stimulus that characterizes the habituation process.

All the theories mentioned recognize, in a more or less explicit way, the role of context in the habituation process. However, while for Wagner [12,13]

the context is considered an essential element in the associative process that produces habituation, for the Dual-process theory of habituation [11], on the other hand, context would have merely the status of a stimulus that is also subjected to habituation after repeated presentations. For the specific case of neophobia habituation, the learned safety theory [9,10] implies that the context acquires properties as a modulator of the flavor significance by means of its capacity to recover the association between the flavor and the absence of consequences. In fact, there is some evidence showing contextual modulation of neophobia habituation. Thus, a context change, but only if the context is new, induces neophobia recovery [14,6]. However, when the change involves a familiar context, neophobia habituation remains intact [6].

From a physiological perspective, the involvement of the dopaminergic system in appetitive learning [15] and in the role of context as a learning modulator [16] makes it a possible neurochemical candidate for the development the mentioned context-dependent safe flavor memory trace based in an association between the taste and the absence of aversive consequences. More specifically, previous studies have shown modulation of dopaminergic transmission as a function of the motivational valence and novelty of the stimuli [17]. In particular, it has been observed an increase in dopamine release in the Nucleus Accumbens (NAc) shell in response to appetitive but not aversive unfamiliar stimuli. It also has been demonstrated the role of dopamine in studies of context modulation of conditioning through a circuit which involves indirect projections from the ventral Subiculum to the NAc [16].

The general purpose of the experiments that follow is to evaluate the role played by context familiarity on the development and the recovery of the safe

memory trace of the flavor. To this end, we conducted four experiments using contexts that were new or the home cages, to evaluate a possible interaction between neophobia habituation and context novelty or familiarity (Experiment 1A), to evaluate whether dopamine levels differentially affect to the interaction between neophobia habituation and context familiarity (Experiment 1B), to check the role of novelty/familiarity by introducing in the experimental design a previously familiarized context in addition to the home and new environments (Experiment 2), and to analyze whether the intensity of a conditioned response after a taste aversion episode changes as a function of the test context degree of novelty (Experiment 3).

2. Experiments 1A and 1B

These experiments evaluated possible differences in the process of neophobia habituation as a function of the context (home cages vs. new experimental context) in which flavor is consumed (Experiment 1A) and the effect of dopamine D1- like receptor antagonist administration during saccharin habituation in the presence of the home cage vs. a new experimental context (Experiment 1B).

The available experimental evidence on contextual modulation of neophobia habituation shows that a context change, but only if the context is new, induces neophobia recovery [14,6]. A particularly interesting situation occurs when the experimental context involves the animals´ home cages [3,18]. As far as we know, there are not any evaluation of neophobia habituation or recovery of neophobia using the home cages as an experimental context, but there are some experiments analyzing latent inhibition that have reported

particular effects when using home cages as an experimental context as opposed to new or familiar contexts. Thus, it has been reported that when using a conditioned taste aversion for reproducing the latent inhibition effect, the animals' home cages seem to have properties that make it easier to establish a safe memory trace of the flavor when it is not followed by relevant consequences [19,20].

Regarding the role of different neurotransmitters in flavor processing, dopamine could be playing a relevant role in the development of the hypothetical flavor safe memory trace [21]. For instance, it has been observed an increase in dopaminergic activity when the animal is exposed to a sweet flavor in the NAc, and a decrease when the flavor had been previously associated with gastric malaise [22]. These results have lead to the proposal that dopamine is not implied in the processing of the sweet flavor *per se*, but in the positive/affective reinforcement value [23,24]. The proposal that flavor presentation without aversive consequences generates a safe memory trace could be related in some extent with the mentioned rewarding value of the flavor. In fact, the relevance of the dopaminergic system, and more specifically of the D1 receptors, on the establishment of flavor preferences has been already demonstrated [25].

Regarding the context, there are also empirical results demonstrating the role of mesolimbic dopaminergic system in place preferences learning [26]. However, and attending to the modulatory role proposed for the context in the development of the flavor safe memory trace, we propose that it could be mediated in the same way observed with classical or instrumental conditioning paradigms. More specifically, contextual modulation of latent inhibition or

extinction seems to be dependent of dopaminergic projections from the hippocampus to the NAc [27], and the activation of such circuit is linked to context novelty because when there is no context change such circuit is not activated [16]. From this perspective, the development of the saccharin safe memory trace would imply higher dopaminergic activity when the habituation context is novel than when it is familiar.

In Experiments 1A and 1B, the animals were allowed to drink a saccharin solution four consecutive days, for 5 min each day, in their home cages or in a new experimental context. In Experiment 1A we expected that the home cage would offer an additional source of safety that favored the development of the memory trace as safe, and, as a result, that consumption in home cages will be greater than in the new experimental context. In Experiment 1B we expect that the diminished dopaminergic activity in the group injected with the D1- like receptor antagonist (SCH-23390) would reduce the flavor habituation rate in the group exposed to the new context.

2.1. Method

2.1.1. Subjects

The subjects were 45 male Wistar rats (16 in Experiment 1A and 29 in Experiment 1B, n = 7/8) with weights ranging from 320 to 460 g. The animals in these and the following experiments remained undisturbed in their home cages for a minimum of three weeks before the start of the experimental treatments. Each animal was individually housed in 40 x 20 x 24 cm Plexiglas cages with wood shavings as bedding, and maintained on a regular 12:12-h light/dark cycle. The vivarium was illuminated by four 100W bulbs. All animals were placed on a water deprivation schedule (30 min/day access to water) 7 days before the start

of the experiment. In this and the next experiments the procedures were conducted in agreement with the guidelines established by the Directive 86/609/CEE of the European Community Council, and the Spanish R.D. 223/1988.

2.1.2. Apparatus and stimuli

The ‘new’ context for Experiment 1A consisted in 8 Plexiglas cages, 21 x 18 x 35.5 cm., with green plastic mesh as bedding, located in a different room to the vivarium that was illuminated by a single 54-W fluorescent white light. For Experiment 1B, the ‘new’ context consisted in 8 Plexiglas cages, 40 × 20 × 19 cm, with the floor layered with cardboard located in a different room to the vivarium illuminated by a single 75W red light. For the animals in the ‘Home’ condition all experimental sessions were conducted in the animal’s home cage described in the ‘subjects’ section. All liquid rations were provided at room temperature in 150 ml graduated plastic bottles, fitted with stainless steel spouts. Bottles were attached to the front of each cage during liquid presentations. The amount of liquid intake was measured by the difference between bottle weight before and after the liquid presentation. The flavor was a 0.04% sodium saccharin solution. Rats in Experiment 1A were drug free. For Experiment 1B Dopamine D1- like receptor antagonist SCH-23390 (0.02% mg/kg) was dissolved in warm saline and injected IP with a pretreatment time of 20 min. Saline (SAL) vehicle solutions were used for control injections (0.1 ml).

2.1.3. Procedure

After seven days of water deprivation each rat received four sessions (5 min each) of access to the corresponding saccharin solution either in the home (HOM) or in the experimental (EXP) cages on consecutive days. In addition, for Experiment 1B, each rat was IP injected with the correspondent solution (SCH or SAL) twenty minutes before each habituation trial. In this and the remaining experiments, at the end of each trial the animals received an additional 25 min period of water in their respective home cages.

2.1.4. Results

2.1.4.1. Experiment 1A.

Saccharin consumption was submitted to a 4 x 2 mixed ANOVA, with main factors Trials and Context (Home vs. New). The main effect of Trials was significant, $F(3,42)=12.36$; $p<.001$, due to the overall habituation of neophobia to flavor across trials. The Trial x Context interaction was also significant, $F(3,42)=3.33$; $p<.05$. As can be seen in Figure 1, which depicts mean saccharin consumption across trials as a function of context, the source of the Trials x Context interaction comes from higher consumption in home cages than in the new context during the first and the last trial, which was confirmed by an analysis of simple effects ($p<.05$). The main effect of Context was also significant, $F(1,14)=17.78$; $p<.01$. The effect comes from higher fluid consumption in presence of the Home (mean = 11.12 ml., SD = 0.89) as compared to the New context (mean = 9.34 ml., SD = 0.63).

Figure 1 about here

2.1.4.2. Experiment 1B.

Saccharin consumption across neophobia habituation trials was submitted to a 4 x 4 mixed ANOVA, with main factors Trials and Group (New/SAL, New/SCH, Home/SAL and Home/SCH). The analyses revealed a significant main effect of Trials, $F(3,75)=26.54$; $p<.001$, due to a progressive increase in fluid consumption across trials (the expected neophobia habituation process). The Trials x Group interaction was also significant, $F(9,75)=2.13$; $p<.05$. As can be seen in Figure 2 that depicts mean saccharin consumption across trials as a function of Groups, the interaction reflects a differential effect of the drug on neophobia habituation for the Home as compared to the New groups. Specifically, the D1 antagonist administration completely abolished the neophobia habituation process when it was tested in the experimental, but not in the home context. An analysis of simple effects ($p<.05$) comparing saccharin consumption across trials only revealed significant differences between the New-SCH and the remaining groups for trials third and fourth.

Figure 2 about here

Overall, the results of Experiments 1A and 1B were not entirely consistent, because the differential rate of the habituation process observed in the Experiment 1A as a function of context familiarity / novelty did not appeared in Experiment 1B, where the neophobia habituation course for the Hom/SAL and the New/SAL groups was similar. Perhaps, the administration of the injection before each habituation trial resulted in a sensitization process that

reduced the rate of consumption, thus masking the predicted differences [28]. In fact, as can be seen by comparing Figures 1 and 2, the general levels of consumption for all groups in Experiment 1B were lower that those in Experiment 1A. An additional variable that can contribute to the mentioned result is a possible effect of context overshadowing by the injection-related cues. In fact, previous research with taste conditioning procedures have revealed that injection cues interferes with contextual conditioning, and that such interference is more effective when the context is already familiar [29,30]. Therefore, the hypothetical additional source of safety supported by exposing the flavor in the home cages could have been overshadowed by the injection-related cues, slowing down the development of the flavor safe memory trace.

3. Experiment 2

The results of Experiment 1A showed that neophobia habituation proceeded faster when flavor exposure was conducted in the animals' home cages as compared to when it took place in the new experimental cages. This result supports the idea that the home cage context favors the establishment of a safe flavor memory trace [19,4]. However, the results do not allow us to identify whether the process responsible for the faster neophobia process is related to the mere familiarization that the animals have received during their long stay at the home cages, or if there exists an additional component that contributes to learned flavor safety.

In order to evaluate the role played by context familiarity on neophobia habituation, in the present experiment we compared the course of neophobia habituation when a flavor (saccharin) was presented in the home cages (Group

Home), in a new experimental context (Group New) or in an experimental context that had been familiarized by exposing it to the animals before the experimental sessions (Group Fam). We expected to replicate the result observed in Experiment 1A with the home cage offering an additional source of safety that would favor the development of the memory trace as safe, and, as a result, that consumption in home cages will be greater than in the new and the familiar experimental contexts.

3.1. Method

3.1.1. Subjects

24 male Wistar rats (n=8) were used in this experiment (weight range 236-370 g.) The deprivation schedule and housing conditions were the same as described for Experiments 1A and 1B.

3.1.2. Apparatus

For two thirds of the animals (those in the New and Fam Groups) each session was conducted in 21 x 18 x 35.5 cm. Plexiglas cages, with green plastic mesh as bedding, located in a different room to the vivarium illuminated by a single 54-W fluorescent white light. The remaining animals (those in the Home Group) received the experimental treatment in their home cages. The remaining apparatus and stimuli were the same as those used in Experiment 1A.

3.1.3. Procedure

During each one of the seven days in the water deprivation schedule the animals corresponding to the Fam Group were introduced in the cages located in the experimental room for 15 min each day in order to make the context familiar for the rats. The animals in the New and Home Groups remained in their home cages. From days 8 to 11 each animal received one daily trial (5 min each) of access to the saccharin solution in the correspondent context (new, familiar or home).

3.1.4. Results

Saccharin consumption was submitted to a 4 x 3 mixed ANOVA (Trials x Group: Home vs. New vs. Fam). As expected, the main effect of Trials was significant, $F(3,63)=25.07$; $p<.001$, due to the general process of neophobia habituation across trials. The Trials x Group interaction was non-significant, $F(6,63)=1.23$; $p>.30$. As can be seen in Figure 3 (panel A), which depicts mean saccharin consumption across trials as a function of context condition, the lack of interaction reflects the fact that the neophobia habituation process across trials was similar for all groups. However, *a priori* analyses based in our hypothesis (t test for related samples, one-tailed, $p<.05$) revealed that saccharin consumption was higher for the Home Group as compared to the New group for trials 1, 2 and 4, and compared to the Fam Group for trial 1. Finally, consumption in the Fam Group was significantly higher than in the New Group for trials 2 and 4.

Figure 3 about here

Finally, the main effect of Groups was significant, $F(1,21)=5.14$; $p<.05$. As can be seen in Figure 3 (panel B), which depicts mean saccharin consumption collapsed across trials as a function of groups, consumption was higher in the Home as compared to the New and the Fam groups, $t(14)=2.81$; $p<.01$, and $t(14)=2.02$; $p<.05$, respectively. The differences in consumption between the New and Familiar groups were close to the standard levels of significance, $t(14)=1.65$; $p>.07$.

The results from Experiment 2 showed that neophobia habituation is facilitated when the flavor is consumed in the animals' home cage as compared to a new experimental context, confirming the results observed in Experiment 1A. Additionally, the animals in the Fam Group showed a trend of increased consumption when compared to the New group. These data gives support to the hypothesis that suggests that context, as represented by the home cage, most likely facilitates the establishment of a safe memory trace of the flavor due to extensive familiarization without aversive consequences [19,4].

4. Experiment 3

The results of the previous experiments seem to indicate that exposing a flavor in a home cage context facilitates the learning of such flavor as "safe", and that such an effect is based on previous familiarization with the context without consequences by mere pre-exposure. We could thus anticipate that a flavor previously associated with an aversive consequence would be perceived as less aversive if presented at the home cage than if presented in a new context.

To evaluate this possibility we conducted an additional experiment pairing saccharin consumption with LiCl to induce a conditioned taste aversion to the flavor. Subsequently, we evaluated the intensity of the conditioned response to the flavor in the presence of the same context of conditioning (Group A/A), in a new experimental context (Group A/Bnew), in a different but previously familiarized context (Group A/Bfam), and in the home cages (Group A/Home).

Previous research on context-specificity of simple taste aversion learning has resulted in mixed results, with some experiments showing a reduction of conditioned response after a context-switch [31], and others intact conditioning [32]. A possible solution to such discrepancy propose that the effect of a context change between conditioning and test stages in simple conditioned taste aversion seems to be dependent on context novelty vs. familiarity at time of testing, with a reduction in the expression of the conditioned response only when conditioning is conducted in a new context [33]. From this perspective, we would expect no effect of context change in our experiment since all the animals were familiarized with the conditioning context prior to the association between the flavor and the US. However, in spite of previous familiarization with context of conditioning, we predict a reduction in the expression of flavor aversion in the A/Home Group, due to the proposed capacity of the home cages to recover a memory of the flavor as safe.

4.1. Method

4.1.1. Subjects

32 male Wistar rats (n=8) were used in this experiment (weight range 278-367 g.) The housing and maintenance conditions were the same as described for previous experiments.

4.1.2. Apparatus

Three different sets of 8 boxes each were used in this experiment. The first set was composed of the animals' home cages. The two remaining sets of boxes were located in an experimental room illuminated by a single a single 54-W fluorescent white light and were counterbalanced between groups. Context A was composed of 21 x 18 x 35.5 cm Plexiglas cages with floors composed of parallel, 0.4 mm diameter steel bars spaced 1.4 cm from center to center. The ceiling was an aluminum grating. A 100 dB, 5000 Hz PC-generated white noise was continuously present during all experimental manipulations conducted in Context A. Context B consisted of 8 circular boxes measuring 30 cm high x 30 cm in diameter and made of black plastic. The floor of these boxes was identical to those of the context A boxes. There were no sounds in context B. As described in previous experiments the sodium saccharin solution (0.04%) was provided at room temperature in 150-ml graduated plastic bottles, fitted with stainless steel spouts. The bottles were attached to the front of each cage during liquid presentations. The amount of liquid intake was measured by the difference between bottle weight before and after liquid presentation. The unconditioned stimulus was a 0.5% of body weight intraperitoneal (i.p.) injection of 0.2-M LiCl.

4.1.3. Procedure

After 7 days on a 23.5-h water deprivation schedule that was maintained throughout the experiment, the animals were exposed to the conditioning

context for four consecutive days (15 min each day). After this manipulation, the animals in A/A, A/Bnew and A/Home were returned to their home cages, and the rats in A/Bfam Group were introduced for an additional 15 min period in Context B in order to familiarize the animals with the test context. The conditioning trial was conducted in Context A on day 5, and consisted for all animals in allowing 5 min access to the saccharin solution, followed immediately by an i.p. injection of LiCl. Conditioning was tested on days 6 and 7 by giving to the subjects 5 min of access to the saccharin solution each day. The test was conducted in the same context as conditioning (Group A/A), in a different and new experimental context (Group A/Bnew), in a different but familiarized context (Group A/Bfam), and in the home cages (Group A/Home). Saccharin consumption was recorded on conditioning and test days.

4.1.4. Results

A one-way ANOVA conducted on mean consumption in the conditioning trial with the main factor Groups revealed that there were no differences in consumption before conditioning, $F(2,28)=1.71$, $p>.18$.

A 2 x 4 mixed ANOVA (Trials x Groups) performed on mean consumption in the test trials revealed a significant main effect of Trials, $F(1,28)=149.85$, $p<.001$, due to the extinction of the conditioned taste aversion the second test day. The Trials x Group interaction was also significant, $F(3,28)=6.92$, $p<.01$. The interaction is depicted in Figure 4 (panel A) which shows mean consumption across trials as a function of groups. An analysis of simple effects ($p<.05$) revealed no significant differences between groups during the first trial. Differences emerged in the second trial between A/Home vs. A/A, and A/Home vs. AB/new groups, due to an increase in consumption for the

A/Home group, and between A/Bfam vs. A/Bnew groups due to higher consumption in the familiar as compared to the new group. The increase in consumption observed in the A/Home and the A/Bfam groups could be reflecting the beneficial effect on flavor processing of conducting test for conditioned taste aversion in presence a familiar context.

Figure 4 about here

Finally, the main effect of Groups was also significant, $F(2,28)=3.99$, $p<.05$. As can be seen in Figure 4 (panel B), which depicts mean consumption collapsed across test trials as a function of groups, saccharin consumption was higher for the A/Home group when compared to the A/Bnew group. This impression was confirmed by post-hoc comparisons (Tukey tests, $p<.05$) that only revealed significant differences between A/Home and A/Bnew groups.

These results demonstrated that the animal's home cage modulate the expression of a conditioned response previously acquired in presence of a different context. We can interpret the increase in consumption observed in the A/Home Group at testing as direct support to the hypothesis that home cage is a context that facilitates the perceived safety of a flavor that is consumed in its presence.

5. Discussion

The experimental results revealed that habituation of neophobia proceeds faster when the flavor is repeatedly presented without consequences

in the presence of the animals' home cages as compared to the presence of a new experimental context (Experiments 1A and 2), and that neophobia habituation rate evaluated in a new context but not in a familiar context is modulated by dopaminergic activity (Experiment 1B). Finally, the expression of conditioned taste aversion was affected by a context change between conditioning and testing when testing was conducted in a familiar context, showing a reduced conditioned response that was more intense in the home cages (Experiment 3).

The results of Experiment 1A were not enough to confirm that the development of the association between the taste and the absence of aversive consequences is modulated by context familiarity, because a simple explanation of the differences observed in terms of competing responses induced by the new context can explain the results [6]. However, the increased rate of neophobia habituation observed in presence of the home cages as compared to a previously familiarized flavor in Experiment 2 gives support to our proposal of context modulation of the flavor safe memory trace.

In the same line, the results from Experiment 1B showed that the reduction of dopamine levels by D1 receptors blockade differentially affected to the saccharin habituation process as a function of context familiarity. More specifically, when the habituation process was evaluated in the animals' home cage there were no differences across habituation trials between the groups injected with the saline solution and the DA antagonist. However, when the context was new, the habituation rate was slower for those animals that received the DA antagonist. These results are in line with those revealing that context specificity of Latent Inhibition (the reduced conditioned response

observed when the to-be-CS is preexposed without consequences before conditioning) is linked to the increase in dopamine release from the VTA indirectly activated by the subiculum-NAc connection. The inactivation of this circuit through lesions of the subiculum impaired the context modulator role, but only when it was new [16]. Therefore, considering the role of the dopaminergic system in those phenomena related to contextual specificity [16,34] our results indicate the contextual information plays a relevant role in the acquisition of safety learning.

The results from Experiment 3 indicate that context familiarity is a key factor for the flavor memory trace retrieval. Again, context novelty or familiarity was a relevant factor in determining the effect of presenting the flavor in a context different to that in which taste aversion conditioning had been established. Thus, when the context was different and new, taste aversion was expressed with the maximum intensity, but when the context was different and familiar the conditioned response remained unchanged as compared to the group that maintained the same context across stages (Group A/A). These results are parallel to those analyzing neophobia habituation [6], and the habituation of the orienting responses to a light [35]. However, the increase in consumption observed for the animals tested in their home cages in Experiment 3 introduced a new element to our understanding of contextual control. In the same line of evidence, presentation of saccharin in context Home resulted in a reduction in the expression of the taste aversion learning established in a previous stage.

As we mentioned above, the effect of context familiarity on the course of neophobia habituation can be readily explained from non-associative

perspectives of habituation considering, for instance, that the presence of the new context either activates the state system inducing a sensitization process [11] or increase the number of competing responses elicited, which would compete with the drinking response [6]. However these theories can not explain the faster neophobia habituation observed when the context change involved the animals' home cage (Experiment 2), and neither a sensitization process nor a competing response perspective can explain the reduced taste aversion learning observed when conditioning is conducted at the home cages (Experiment 3).

An alternative explanation for our results came from a theory considering the development of a flavor safe memory trace by mere exposure to the flavor [4]. Thus, when considering the role played by the animals´ home cages in latent inhibition experiments, De la Casa et al. [19] proposed an explanation analogous to the learned safety theory by Rozin and Kalat [9,10] to explain the progressive reduction of conditioned taste aversion observed when the delay between the flavor (the CS) and the gastric malaise (the US) increases. More specifically, the learned safety theory suggests that any new flavor is considered potentially dangerous, but once the animal has consumed the flavor and there are no aversive consequences it is stored as a safe flavor. The longer the time without aversive consequences after flavor consumption, the stronger the learned safety of such flavor. Bermudez-Rattoni and his group [4,21] suggested a theory based on similar grounds as the learned safety perspective. Thus, Bermudez-Rattoni [4] considers that tasting a new food will result in a taste memory trace that incorporates either a safety component when there are no harmful consequences after its consumption, or an aversive component

when the ingestion is followed by any kind of malaise. The idea of a safe memory trace is also compatible with the suggestion that a prior history of no aversive consequences in the familiar context could facilitate the acquisition of a hypothetical flavor-no consequence association [36,37], which would result in a stronger safe memory trace of the flavor [4] inducing a faster habituation process.

In order to explain the results of our experiment we propose to apply the above-mentioned ideas to the differential effects observed in neophobia habituation (Experiment 1A and 2), and conditioned taste aversion (Experiment 3) as a function of context novelty vs. familiarity. The starting point is that when an animal faces a new context, a set of responses appears that is intended to explore the new environment [38][1]. One result of such exploration is that the context will be coded either safe or potentially dangerous depending on the consequences that appear in its presence. When time exploring the context without experiencing aversive consequences is extended, the safety value of the context will increase, thus generating a safe context memory trace functionally similar to the safe flavor memory trace [4]. The maximum expression of context safety would be expressed in the animals´ home cage, because the long exposure without aversive consequences (or even with the appetitive consequences derived from the constant temperature, the presence of food and water, the absence of predators, etc.) reaches maximum expression. As a consequence, a new stimulus presented in a highly familiar context such as the home cage will be considered as safer than when it is presented in a new or in a short-time familiarized context. The safe context would promote higher fluid consumption by means of some kind of energization

process similar to that proposed by Konorski [39] to explain how a conditioned context can control the response to a conditioned stimulus. Flavor consumption in the home cage will thus result in a reduction of neophobia as observed in our Experiments 1A and 2. Similarly, testing in home cages for a flavor aversion acquired in an experimental context will reduce the expression of conditioning, as observed in Experiment 3.

The present data therefore contributes to our understanding of the role of context in flavor consumption, but leaves unanswered questions regarding the relative contribution of associative and/or non-associative factors to explain the differences observed between new, familiar and home cage contexts. Some possible ways to verify the hypothetical safe memory trace of the context could include, for instance, examining the possible effects of the testing modulation of aversive conditioning as a function of context familiarity using other stimuli different to flavors, or attempting to differentiate different physiological bases for safe vs. aversive context memory trace. In this sense, one possibility could be to study whether inactivation of hippocampal structures related to context processing affects differentially to codification and recovery of the safe memory trace in function on the familiarity/novelty of the contexts.

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Footnotes.

[1] The behavioral activation induced by the context would be, at least in part, mediated by an increase of dopaminergic activity. In fact, as revealed by lesion studies, the dopaminergic projections from parahippocampal areas (e.g., from the ventral subiculum to the NAc) are essential for contextual information processing [27]. However, this increase would be restricted to those situations in which the context is novel [16]

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Figure captions:

Figure 1. Mean amount of saccharin solution consumed as a function of experimental context (New vs. Home cages) on each of the four exposure days. Error bars represent SEMs. Stars denote statistically significant effects.

Figure 2. Mean amounts of saccharin solution consumed as a function of the experimental context (New vs. Home cages) and Drug (SAL: Saline vs. SCH: D1- like receptor antagonist SCH-23390) on each of the four exposure days. Error bars represent SEMs. Stars denote statistically significant effects.

Figure 3. Mean amounts of saccharin solution consumed by animals tested in the Home cages, in the Familiar (Fam) or in the New cages on each of the four exposure days (Panel A) and collapsed across trials (Panel B). Error bars represent SEMs. Stars denote statistically significant effects.

Figure 4. Mean amounts of saccharin solution consumed after an episode of taste aversion by animals tested in the Home cages, in the Familiar (Fam) or in the New cages on each of the two test days (Panel A) and collapsed across trials (Panel B). Error bars represent SEMs. Stars denote statistically significant effects.

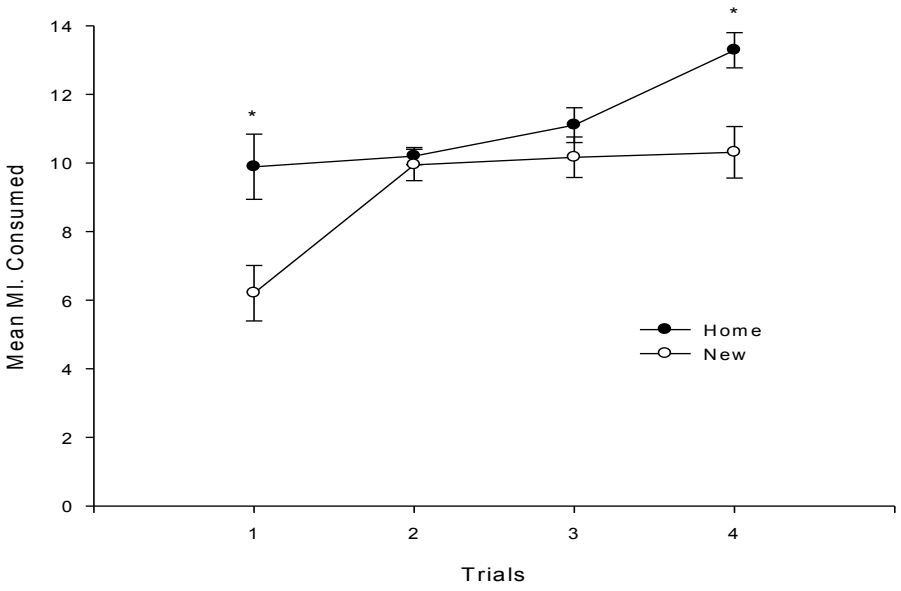
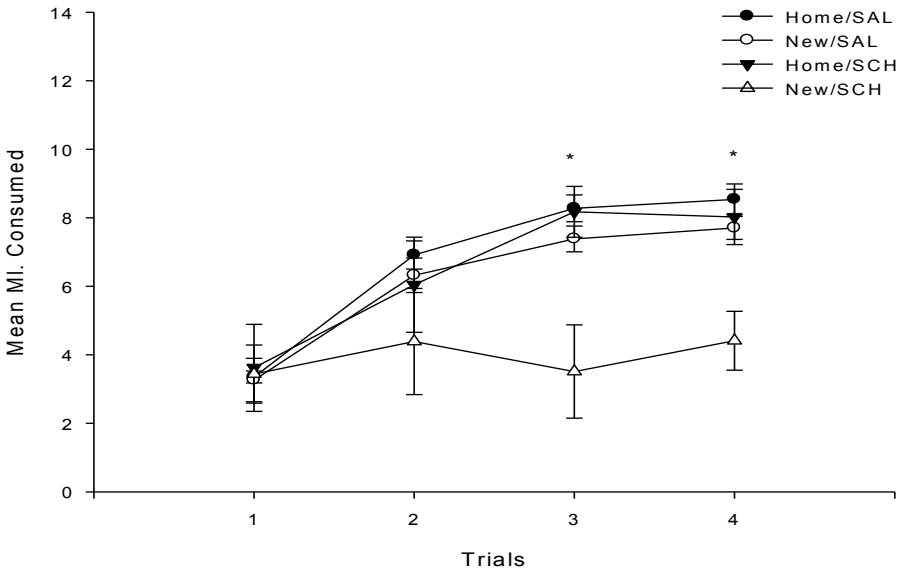


Figure 1.


Home/SAL
New/SAL
Home/SCH
New/SCH
Mean Ml. Consumed
Trials
0
2
4
6
8
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12
14
1
2
3
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*
*

Figure 2.

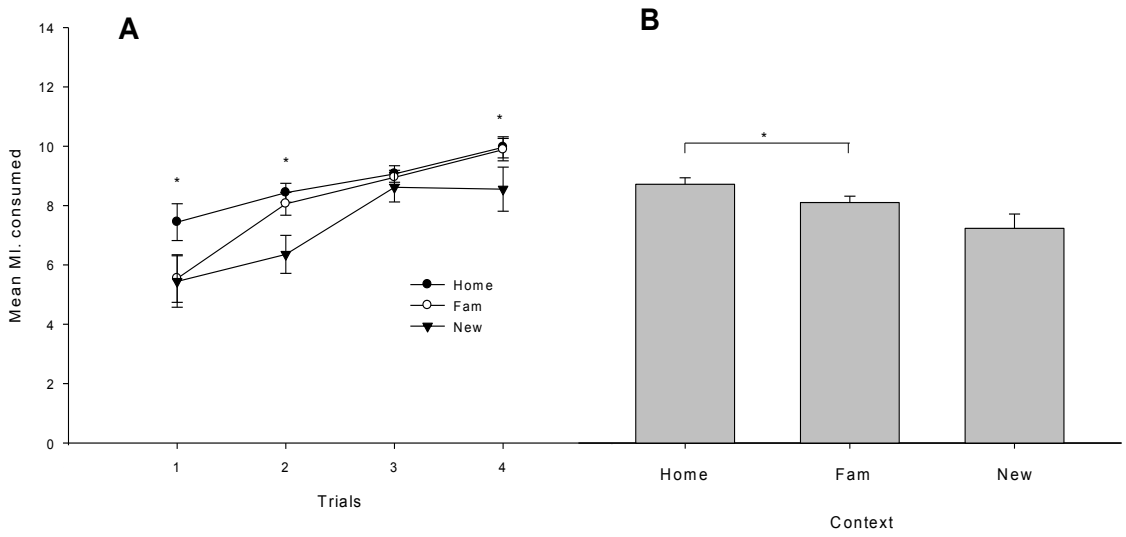
A
B
Mean Ml. consumed
14
12
10
8
6
4
2
0
1
2
3
4
Trials
Home
Fam
New
*
Home
Fam
New
Context

Figure 3.

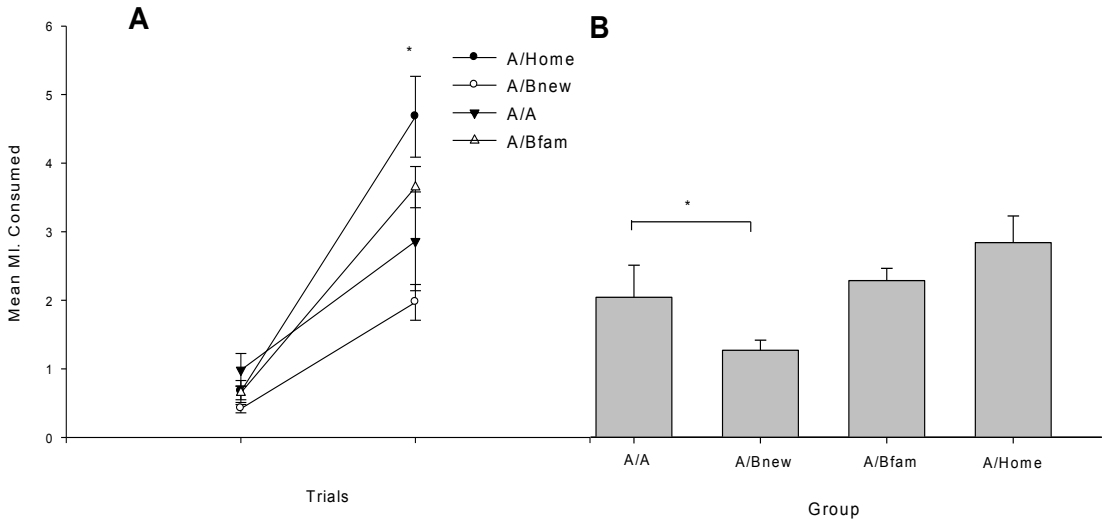
A
B
Mean Ml. Consumed
6
5
4
3
2
1
0
*
A/Home
A/Bnew
A/A
A/Bfam
Trials
*
A/A
A/Bnew
A/Bfam
A/Home
Group

Figure 4.