



## Research report

## Taste-dependent sociophobia: When food and company do not mix

Matthieu J. Guitton<sup>a,b,c,\*</sup>, Yael Klin<sup>a</sup>, Yadin Dudai<sup>a</sup><sup>a</sup> Department of Neurobiology, The Weizmann Institute of Science, Rehovot 76100, Israel<sup>b</sup> Molecular Endocrinology and Oncology Research Center, Laval University Medical Center (CHUL), Quebec City, QC, Canada G1V 4G2<sup>c</sup> Faculty of Pharmacy, Laval University, Quebec City, QC, Canada G1K 7P4

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## ABSTRACT

Using a combination of the paradigm of conditioned taste aversion (CTA) and of the paradigm of social interactions, we report here that in the rat, eating while anxious may result in long-term alterations in social behavior. In the conventional CTA, the subject learns to associate a tastant (the conditioned stimulus, CS) with delayed toxicosis (an unconditioned stimulus, UCS) to yield taste aversion (the conditioned response, CR). However, the association of taste with delayed negative internal states that could generate CRs that are different from taste aversion should not be neglected. Such associations may contribute to the ontogenesis, reinforcement and symptoms of some types of taste- and food-related disorders. We have recently reported that a delayed anxiety-like state, induced by the anxiogenic drug meta-chlorophenylpiperazine (mCPP), can specifically associate with taste to produce CTA. We now show that a similar protocol results in a marked lingering impairment in social interactions in response to the conditioned taste. This is hence a learned situation in which food and company do not mix well.

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## 1. Introduction

In conditioned taste aversion (CTA), the subject learns to associate a tastant (the conditioned stimulus, CS) with delayed toxicosis (an unconditioned stimulus, UCS) to yield taste aversion (the conditioned response, CR) [8,15,27,28]. In some versions of this paradigm, the context in which the subject consumes the food may also come to serve as a cue to elicit subsequent taste aversion [26]. Not all UCSs are, however, effective in inducing CTA. For example, cutaneous pain is ineffective. Although malaise-inducing UCSs are widely used in CTA, the association of taste with delayed negative internal states that could generate CRs different from taste aversion [6,23] should not be neglected. Particularly, this is the case of anxiety and anxiety-like states [18,30]. Among several methodologies which can be used in order to induce experimentally anxiety-like state in animals, the utilization of pharmacological agents is particularly useful. Thus, injections of the serotonergic agent meta-chlorophenylpiperazine (mCPP), which acts as a 5-HT<sub>2C</sub> receptor agonist, has been shown to produce in human and in animal emotional states isomorphic to anxiety-like state [3,4,9,10]. We have recently reported that a delayed anxiety-like state induced by intraperitoneal injection of mCPP was able to specifically asso-

ciate with taste to produce long-term CTA [18]. This association has been shown to be rather specific to anxiety itself, and not to pharmacological side effects of the drug [18].

Using a combination of CTA and social interaction measurements, we report here that a similar conditioning procedure results in a marked lingering impairment in social behavior in response to the conditioned taste. This probably represents a component of the anxiety that generates a social CR in a type of protocol that commonly quantifies only gustatory CRs. This is hence a learned situation in which food and company do not mix well. Such associations may potentially contribute to the ontogenesis, reinforcement and symptoms of some types of eating and digestive disorders.

## 2. Materials and methods

## 2.1. Animals

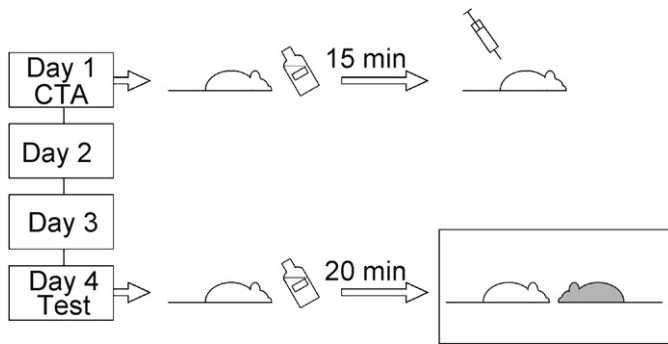
Rats (Wistar males, ~60 days old, 220–370 g) were caged individually at 22 ± 2 °C under a 12 h light/dark cycles regime. Water and food were available *ad libitum* unless otherwise indicated.

## 2.2. CTA training

CTA was induced as previously described [18,27]. Briefly, rats were trained over 3 days to obtain their daily water ration from two pipettes, each containing 10 ml. The time of pipette exposure was of 30 min the first day and 10 min on the 2 subsequent days. On Day 4, the rats were presented with glycine (ICN Biomedicals, Aurora, OH, 1%, w/v) instead of water. Fifteen minutes later, they received the UCS, which was i.p. injection of a solution of either mCPP (Sigma, St. Louis, MO, 0.5 mg/kg) or LiCl (Merck, Darmstadt, 0.15 M, 2% body weight). The rats were then allowed 10 min access to 20 ml water on Days 5 and 6. Animals were tested either in a Taste-Choice

\* Corresponding author at: Molecular Endocrinology and Oncology Research Center, Laval University Medical Center (CHUL), Quebec City, QC, Canada G1V 4G2. Tel.: +1 418 654 2296; fax: +1 418 654 2761.

E-mail address: [matthieu.guitton@pha.ulaval.ca](mailto:matthieu.guitton@pha.ulaval.ca) (M.J. Guitton).



**Fig. 1.** Experimental protocol. During CTA training (Day 1), animals were exposed to the unknown taste. Fifteen minutes later, animals received an i.p. injection of saline, mCPP, or LiCl. Test took place 3 days after the CTA training (Day 4), animals received anew the conditioned taste. Twenty minutes later, animals were presented with an age-matched, unfamiliar, naïve conspecific, in an experimental arena. Social interactions were then quantified during 20 min.

(TC) situation or in *No Taste-Choice (NTC)* situation on Day 7, as specified under Section 3. In the TC test, the rats were allowed free access for 10 min to an array of 6 pipettes, 3 × 5 ml glycine and 3 × 5 ml water. The aversion index (AI) was defined as [(water consumed)/(water + tastant consumed) × 100] [27]. In non-conditioned rats, glycine is preferred over water (AI < 50). In the NTC test, the rats were presented for 10 min with 2 pipettes containing 10 ml glycine each. In the experiments in which social interaction was measured, all the rats were presented on Day 7 for 10 min with 2 pipettes containing 10 ml glycine each.

### 2.3. Social interaction test

Three days after CTA conditioning the rats were presented for 10 min with the non-reinforced taste CS. Twenty minutes later each rat was submitted to a social interaction test, performed in a transparent plastic arena (21 cm × 37 cm × 26 cm). Pairs of age-matched male rats, unfamiliar with each other, were placed in the unfamiliar test arena for an observation period of 20 min (Fig. 1). Their social behavior [29] was scored simultaneously by two independent observers. The interaction time was defined as the time spent in active social interactions (*sniffing, following, grooming the partner, wrestling, crawling over or under*). In addition, the number of behavioral events was quantified for each rat in the following categories: number of social events (*sniffing, following, grooming the partner, crawling over or under*), number of aggressive events (*wrestling or biting*), number of conspecific-following behavior, and number of conspecific-escapes. After each trial, the rats were returned to their home cages and the arena was washed with 70% ethanol followed by water, and thoroughly dried to remove odor cues.

### 2.4. Experimental groups

Two sets of rats were used. The first set ( $n = 16$ ) was used to quantify mCPP-induced CTA under different test conditions. These rats were conditioned using glycine as CS and mCPP as the UCS, as detailed above. Three days after the CTA training, half of the rats were presented with the CS in the TC test, and the other half in the NTC test.

The second set included 8 groups of 16 rats each. In each group, half of the animals were “naïve” and half “experimental”, as detailed below. In the naïve group, the remaining 8 rats were also naïve. In the LiCl group, the experimental animals received a classical LiCl-induced CTA training. In the mCPP group, the experimental animals received in training mCPP i.p. instead of LiCl i.p. as the UCS. In the backward conditioning group, the experimental animals were submitted to a backward conditioning procedure, in which the mCPP UCS preceded the exposure to the glycine CS by 3 h. In the noCS group, the experimental animals received mCPP i.p. in training but the glycine CS was replaced by water. In the 4 h group, the experimental animals were trained as in the mCPP group, but tested for social interaction 4 h rather than 20 min after the exposure to the CS in the test (time at which effects of the drug have been shown to be strongly decreased [14]). In the different taste group, the rats were conditioned with as in the mCPP group but tested for social interactions after exposure to saccharine in the CTA taste. In the mCPP(s) group, the rats were trained as in the mCPP group but with saccharine as the CS, and tested for their social interactions after receiving saccharine in the test.

### 2.5. Statistical analysis

Results are expressed as mean ± S.E.M. Non-parametric statistical analysis was applied to treat the behavioral data. Significance was assessed Mann-Whitney non-parametric *U* test.

## 3. Results

### 3.1. Effect of mCPP-induced CTA training on liquid consumption

The serotonergic agonist mCPP (0.5 mg/kg i.p.) administered 15 min after the offset of drinking of an unfamiliar taste (glycine 1%), induced long-term CTA (AI =  $63 \pm 3.05$  vs. AI =  $28.97 \pm 4.1$  for mCPP-treated and control animals, respectively,  $p < 0.01$ ). This mCPP-induced CTA, quantified in a TC situation (see under Section 2), is however weaker than that induced by the conventional UCS, LiCl i.p. (on LiCl-induced CTA (AI =  $96.7 \pm 0.7$ ). Furthermore, the mCPP-induced taste aversion can be masked in the NTC situation, in which no alternative thirst quencher is available (Table 1).

### 3.2. Effect of CTA training on post-retrieval social interactions

The total time spent in active social behavior over the 20 min of the test was  $624 \pm 30$  s in the naïve group (Fig. 2A). The time spent in active social behavior was not significantly different in any of the other groups, with the notable exception of the mCPP and mCPP(s) groups. In these two groups, the total time spent in active behavioral interaction between the two animals, was significantly lower than in any of the other groups ( $438 \pm 42$  and  $465 \pm 23$  s, for mCPP and mCPP(s), respectively,  $p < 0.001$ ). In all the groups, except the mCPP and mCPP(s) groups, the total number of social events (*sniffing, following, grooming the partner, wrestling, and crawling over or under*) was highly conserved across groups and similar for the experimental and naïve animals in any given group ( $71.9 \pm 6.4$  and  $73.4 \pm 7.5$  for animals from the naïve group, Fig. 2B). However, a totally different situation was observed in the mCPP and mCPP(s) groups. Experimental animals from the mCPP and mCPP(s) groups displayed markedly less social events than any of the experimental animals of the other groups, and less social events than the co-tested naïve animals ( $26.3 \pm 3.4$  for experimental animals from the mCPP groups and  $34.5 \pm 3.0$  for experimental animals from the mCPP(s) group,  $p < 0.001$ , compared to co-tested naïve animals, Fig. 2B). Further, when compared to naïve animals from other groups, naïve animals from the mCPP and mCPP(s) groups performed significantly less social acts ( $58.5 \pm 4.2$  for naïve animals from the mCPP groups and  $57.9 \pm 5.4$  for naïve animals from the mCPP(s) group, respectively, compared to the naïve animals from other groups,  $p < 0.01$ ). This makes sense, because if the experimental animal displays aberrant social behavior, this is likely to affect the social behavior of the naïve partner as well.

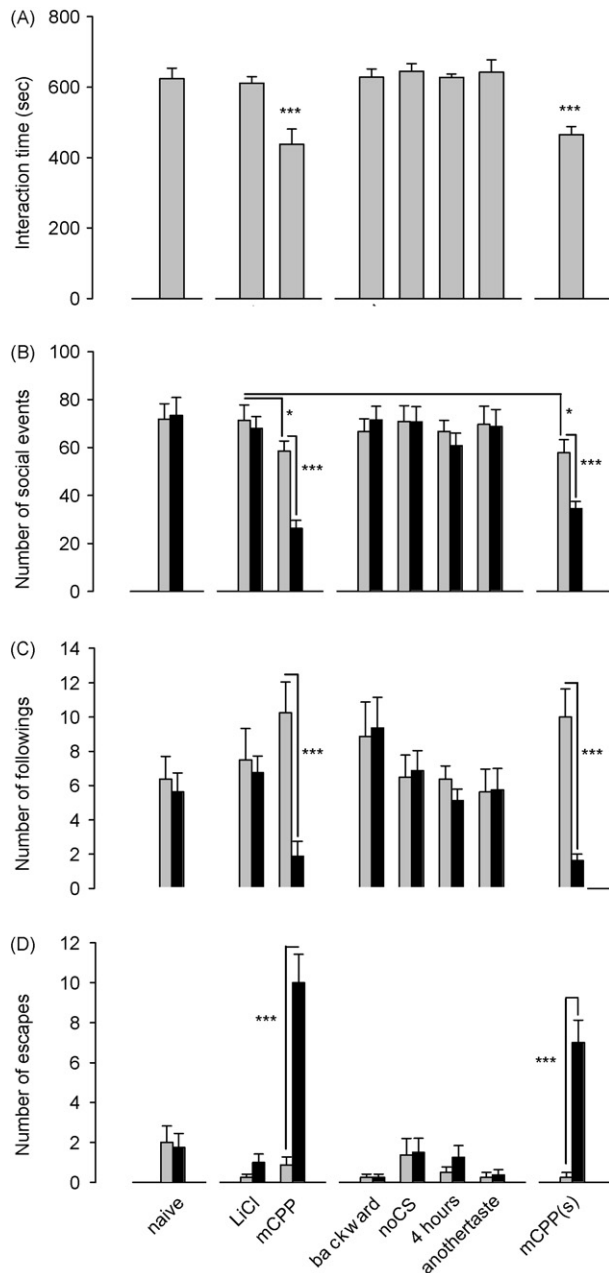
In all groups except the mCPP and mCPP(s) groups, the number of followings was relatively stable and not statistically different between experimental and naïve animals (Fig. 2C). However, in the mCPP and mCPP(s) groups, the number of followings of naïve animals was remarkably high compared to any other group of animals,

**Table 1**

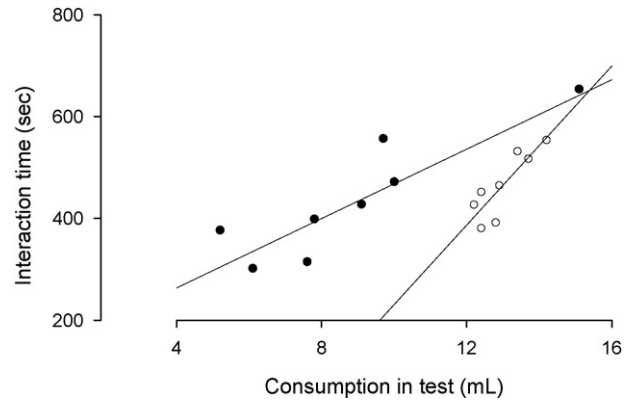
Consumption of glycine solution after CTA training

	Control	LiCl	mCPP
No Taste-Choice	9.9 ± 0.5	0.7 ± 0.1	9.2 ± 0.6
Taste-Choice	G = 10.3 ± 0.8 W = 4.3 ± 0.7	G = 0.2 ± 0.03 W = 6.3 ± 0.8	G = 4.3 ± 0.4 W = 7.5 ± 0.6

Consumption of glycine solution after CTA training in which glycine was used as the CS, under two test conditions: *No Taste-Choice (NTC)*, in which the rats were provided with the CS solution only, and *Taste-Choice (TC)*, in which the rats were presented with the CS and water simultaneously. Data are in ml;  $n = 8-20$  each. Separate groups were used for each condition. LiCl, CTA training using LiCl i.p. as the UCS; mCPP, CTA training using mCPP i.p. as the UCS; G, glycine; W, water. The LiCl groups displayed strong aversion of the CS under both the NTC and the TC conditions, whereas the mCPP groups displayed significant aversion only under the TC conditions. G = glycine consumption; W = water consumption.



**Fig. 2.** Effect of CTA training on post-retrieval social interaction. Three days after CTA conditioning the rats were presented for 10 min with the non-reinforced taste CS. Twenty minutes later each rat was submitted to a social interaction test with an age-matched, unfamiliar, naïve conspecific. All naïve groups were independent. Behavior was scored for 20 min, as detailed under Section 2. *Naïve*, both members of the interacting pair were naïve; *LiCl*, CTA training on glycine with LiCl as the US; *mCPP*, CTA training on glycine with mCPP as the US; *Backward*, backward conditioning with mCPP as the US; *noCS*, water instead of glycine as the US; *4 h*, as in the mCPP group but tested for social interaction 4 h rather than 20 min after the offset of the CS presentation in the test; *another taste*, as in the mCPP group but tested with saccharine rather than glycine; *mCPP(s)*, as in mCPP but using saccharine as the CS in training and testing. (A) Time spent in active social behavior during 20 min after the offset of the CS presentation in the test. Social interactions included sniffing, following, grooming the partner, wrestling, and crawling over or under. (B) The total number of social events. (C) The number of followings. (D) The number of escapes. In B–D, black represents experimental animals and gray naïve conspecific animals;  $n = 16$  per group (8 experimental, 8 naïve conspecific). \*  $p < 0.01$ , \*\*\*  $p < 0.001$  (Mann–Whitney non-parametric  $U$  test).



**Fig. 3.** The correlation between consumption of the taste CS in the test and the social interaction time. Empty circles correspond to mCPP-conditioned animals conditioned and tested with glycine, and filled circles correspond to mCPP-conditioned animals conditioned and tested over saccharine. The linear regression is given by  $y = 35.22x + 127.2$  (rsqr = 0.795) and  $y = 78.06x - 549.7$  (rsqr = 0.732), for glycine and saccharine, respectively.

and was significantly higher than the number of followings of the corresponding experimental animals, which were extremely low compared to any other of the group ( $10.3 \pm 1.8$  and  $1.9 \pm 0.9$  for the naïve and experimental animals respectively in the *mCPP* group,  $p < 0.001$ ; and  $10 \pm 1.7$  and  $1.62 \pm 0.37$  for the naïve and experimental animals respectively in the *mCPP(s)* group,  $p < 0.001$ ). In contrast, the number of escapes (Fig. 2D) remained very low for experimental and naïve animals, independent of the group, again, the only exceptions being the rats from the *mCPP* and *mCPP(s)* groups. In the latter groups, experimental animals displayed a significantly higher number of escapes when compared to the co-tested naïve animals, or to any of the other groups ( $0.87 \pm 0.4$  and  $10 \pm 1.4$  for the naïve and experimental animals respectively in the *mCPP* group,  $p < 0.001$ ; and  $0.25 \pm 0.25$  and  $7 \pm 1.1$  for the naïve and experimental animals, respectively in the *mCPP(s)* group,  $p < 0.001$ ). Note that the patterns of escapes appeared to be the mirror image of the number of followings.

### 3.3. Individual relationship between consumption and social behavior

A linear relationship was found between the consumption of the conditioned tastant during the second presentation (single taste exposure, 3 days after the CTA training) and the time of social interactions spent by the animal (which is taken here as an indicator of its social behavior). The linear regression corresponds to the following equations:  $y = 35.22x + 127.2$  (rsqr = 0.795) for glycine and  $y = 78.06x - 549.7$  (rsqr = 0.732), for saccharine (see Fig. 3). The different slope of the different taste may reflect difference in the non-conditioned hedonic valence of each of the tastes [1,22].

## 4. Discussion

### 4.1. The multiple outcomes of mCPP-induced CTA

In the present experiments, we used the well-established anxiogenic 5-HT<sub>2C</sub> receptor agonist mCPP as a pharmacological tool to induce anxiety-like state in the rat [3,4,9,10]. We conditioned rats by providing them with an unfamiliar taste, glycine, followed 15 min later by i.p. injection of mCPP. As described previously [18], this leads to a significant yet moderate CTA, as quantified by taste aversion in a multiple pipettes, taste-choice situation. Rats may have shown avoidance to the drinking spout instead of aversion to the

tastant. In this case, such an avoidance would have been translated by a reduction in approach behavior to spout. This was, however, clearly not the case, as demonstrated by the results presented in Table 1. Surprisingly, in addition to the relatively mild potency of mCPP i.p. in inducing *bona fide* taste aversion, this UCS has a remarkable outcome on another important behavioral facet, which is social behavior. Rats are social animals and display a rich repertoire of social behaviors. In this view, testing social interactions in rats offers a possibility to test high-level behavior, in addition to the simple aversive behavior classically observed with CTA paradigm. This result raises the known general consideration, which is that in classical conditioning, the experimenter usually selects a single CR and focuses on it, potentially leading to the neglect of other important CRs [24]. A related question is whether the effect on social interaction stems from a CR clearly distinct from that induced by the taste-US association. This is not likely to be the case. Hence, training-induced change in locomotor activity can be ruled out by the fact that mCPP-treatment does not lead to modification of motor activity. Indeed, when tested in an open field paradigm, rats receiving mCPP at the same concentration than in this study (0.5 mg/kg), did not display significant differences in the total number of crossings [18]. Similarly, general effect on consumption can be ruled out by the results observed in the group referenced as “another taste”. It is noteworthy that amphetamine-induced CTA has also been suggested to be able to have an affective CR, in the form of a conditioned fear-arousal [25]. In the present experiments, the question of whether anxiety was or not the CR is important. The fact that mCPP-induced CTA can be abolished by a co-treatment with ethanol at concentrations known to be anxiolytic, but without affecting other neurotransmission pathways is a good cue in this sense [18].

Induction of anxiety-like state by acute administration of mCPP in the rat is manifested, among others, in a decrease in social interaction [20,21]. Our data show that the exposure to the taste CS mimics some of the aspects of this anxiety-like state-induced sociophobia in the conditioned rats. In particular, the alterations of the social behavior observed in our case can be defined as a combination of a decrease of the social interactions per se, and an increase of the occurrence of behavior of social withdrawal. In this context of sociophobia during the interaction situations, the modifications observed for the following and escape responses are of major importance. Indeed, they suggest that the decrease of the social interactions is not only a passive phenomenon, but rather an active one, with an active participation of the treated animal evidenced by its withdrawals from its partner. This retrieval-induced state lingers long after a single exposure to the non-reinforced CS. By predicting the US, the taste cue hence appears to trigger a persistent emotional and social response. These data are congruent with the notion that retrieval is itself experience, the memory of which extends much beyond the retrieval session [2].

#### 4.2. Potential relevance to food disorders

The association of a gustatory stimulus with social withdrawal might represent conditioned augmentation of a natural predisposition of ecological significance, as one could imagine the potential advantage of social withdrawal in securing recently acquired food or avoiding risks of post-ingestion lethargy. The taste CS might hence have a latent pre-existing relation to the anxiogenic US, which tolerates a long interstimulus interval (ISI) and culminates in a functionally useful social CR [12]. Phylogenetic considerations notwithstanding, it is apt to consider the potential relevance of this taste-anxiety-sociophobia association to eating disorders [13,19,22]. Interestingly is that anorexia and

bulimia nervosa present a significant comorbidity with social phobia [19]. Furthermore, the strong co-occurrence of anxiety and food disorders may reinforce the idea of a privileged relationship between emotions and perception in the processes at the ontogenesis of food disorders [17]. Often, the onset of anxiety states precedes the onset of anorexia or bulimia nervosa [7,11,16]. If taste-anxiety associations tolerate long ISIs, the opportunity for the generation and reinforcement of eating disorders in susceptible individuals could increase; and if encounter with the conditioned taste replicates a lingering emotional and social pathology, reinforcement of the CS-CR association could ensue. This echoes the proposed effect of mood congruency on depression [5], which might further exacerbate the pathology. Thus, the taste-anxiety-sociophobia paradigm presented here might provide an animal model to further advance our understanding of some aspects of the ontogeny and physiology of some eating and anxiety disorders.

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