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Potential of the rat model of conditioned gaping to detect nausea produced by rolipram, a phosphodiesterase-4 (PDE4) inhibitor

Erin M. Rock, Jessica Benzaquen, Cheryl L. Limebeer, Linda A. Parker *

Department of Psychology, University of Guelph, Guelph, Ontario, Canada N1G 2W1

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ABSTRACT

Rolipram, a phosphodiesterase-4 (PDE4) inhibitor, is of current interest as a cognitive enhancer and as a treatment for inflammatory diseases. Originally developed as an anti-depressant, rolipram's efficacy was limited due to its side effects of nausea and vomiting. The experiments reported here evaluated the potential of rolipram to produce conditioned gaping (a selective measure of nausea in rats) to a flavor in the taste reactivity test (Experiment 1) and to a context (Experiment 2). In Experiment 1, rats were intra-orally infused with 17% sucrose solution prior to being injected with rolipram (Vehicle, 0.03, 0.1 or 0.3 mg/kg). Following 3 conditioning trials, rats conditioned with 0.3 mg/kg rolipram displayed conditioned gaping reactions during the infusion of sucrose. In Experiment 2, rats received 4 conditioning trials in which they were injected with 0.3 mg/kg rolipram and placed into a distinctive chamber. At test, when returned to the chamber rats displayed conditioned gaping. These results demonstrate the ability of the conditioned gaping model to detect the nauseating properties of a rolipram-paired flavor (Experiment 1) and rolipram-paired context (Experiment 2), further validating the potential use of the conditioned gaping model as a pre-clinical screening tool to evaluate the side effect of nausea produced by newly developed drugs.

1. Introduction

Rolipram, a phosphodiesterase-4 (PDE4) inhibitor, is of current interest as a cognitive enhancer (e.g., Barad et al., 1998) and as a treatment for inflammatory disease (e.g., Houslay et al., 2005). Originally developed as an anti-depressant, rolipram increases the transmission of noradrenaline in two ways: 1) presynaptically by increasing noradrenaline release (first messenger); 2) postsynaptically by inhibiting phosphodiesterase (PDE) enzymes which deactivate cyclic adenosine monophosphate (cAMP), secondary messenger nucleotides involved in modulating the effects of hormones, neurotransmitters and drugs (Krebs and Beavo, 1979). As rolipram exerts its effects both presynaptically and postsynaptically, it offers a novel pharmacological approach in managing depression. In comparison to other anti-depressants, rolipram enables synaptic changes to occur more rapidly, resulting in a more rapid anti-depressant effect for the patient (Wachtel, 1983).

Rolipram's efficacy as an anti-depressant, however, was limited by its side effects of nausea and vomiting (Zeller et al., 1984), a common side effect of PDE4 inhibitors in humans (Bertolino et al., 1988; Hebenstreit et al., 1989), dogs (Heaslip and Evans, 1995), ferrets (Robichaud et al., 1999, 2001), and shrews (Hirose et al., 2007). The effect of rolipram on vomiting in the shrew is due in part to the occupation of the high-affinity rolipram binding site in the brain (Hirose et al., 2007).

Like rolipram, many drugs including chemotherapy treatments have the associated side effects of nausea and vomiting (Griffin et al., 1996; Ballatori et al., 2007), with patients often reporting nausea as a more troublesome symptom than vomiting (Griffin et al., 1996). Current anti-emetic drugs are more effective in alleviating vomiting than nausea (Foubert and Vaessen, 2005). As nausea is a subjective experience, the establishment of a reliable rodent model of nausea enables the investigation of the neurobiology of nausea and the assessment of the nausea-inducing properties of newly developed drugs.

Although rats are incapable of vomiting, they display characteristic gaping reactions (e.g., Grill and Norgren, 1978) when exposed to a flavored solution (see, Parker, 2003) or chamber cues (Limebeer et al., 2008) previously paired with lithium-induced nausea, although unpaired control groups do not display this gaping reaction (Zalaquett and Parker, 1989; Limebeer et al., 2008). In fact, this gaping reaction in the rat requires the same orofacial musculature as that required for vomiting in other species (Travers and Norgren, 1986). In the Taste Reactivity (TR) test (Grill and Norgren, 1978), only drugs that produce emesis in species capable of vomiting produce conditioned gaping in rats, although many non-emetic drugs produce conditioned taste avoidance (see Parker, 2003 for review). Furthermore, anti-emetic drugs interfere with the establishment of conditioned gaping reactions elicited by a nausea-paired flavor, presumably by interfering with the nausea (Limebeer and Parker, 2000; Parker et al., 2003; Parker and Limebeer, 2006). Most recently, Limebeer et al. (2008) have reported

* Corresponding author. Tel.: +1 519 824 4120x56330; fax: +1 519 837 8629.
E-mail address: parkerl@uoguelph.ca (L.A. Parker).

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that the conditioned gaping reaction is elicited not only by a lithium-paired flavor, but also by a lithium-paired chamber. Therefore, the conditioned gaping reaction may serve as an animal model of anticipatory nausea reported by cancer patients when they return to a chemotherapy-paired environment. Conditioned gaping in rats appears to be a selective index of conditioned nausea.

Since rolipram's therapeutic efficacy is limited by its' potential to produce the side effect of nausea and vomiting in humans (Zeller et al., 1984), it would be expected to produce conditioned gaping reactions in the TR test in rats. The following experiments evaluated the potential of rolipram to produce conditioned gaping in rats (a measure of conditioned nausea) to a rolipram-paired flavor (sucrose; Experiment 1) and to a rolipram-paired context (Experiment 2).

2. Materials and methods

2.1. Experiment 1

2.1.1. Animals

The subjects were 33 male Sprague–Dawley rats (Charles River Lab, St Constant, Quebec). The animals were single-housed in shoebox cages in the colony room at an ambient temperature of 21 °C with a 12/12 light dark schedule (lights off at 8 AM) and were maintained on an ad lib schedule of food and water. All procedures adhered to the guidelines of the Canadian Council of Animal Care and were approved by the Animal Care Committee of University of Guelph.

2.1.2. Drugs

Rolipram (provided by Theravance Inc) was prepared fresh daily in sterile water and administered intraperitoneally (i.p.) at doses of 0.03, 0.1 and 0.3 mg/kg and at a volume of 2 ml/kg. The ED_{50} producing emesis in the shrew has been reported to be 0.16 mg/kg (Hirose et al., 2007).

2.1.3. Surgery

All rats were implanted with intra-oral cannulae. Twenty-four hours prior to surgery, all animals were injected with an antibiotic (Derapin: 100 mg/kg, subcutaneously; Ayerst). On the day of surgery, the rats were anaesthetized with isoflorane gas and administered Anafen (7 mg/kg, s.c.; Merial), a non-steroidal anti-inflammatory drug with analgesic properties. A thin-walled 15-gauge stainless steel needle was inserted at the base of the neck, directed s.c. around the ear and brought out behind the first molar inside the mouth. A length of Intra Medic plastic tubing with an inner diameter (I.D.) of 0.86 mm and an outer diameter (O.D.) of 1.27 mm was then run through the needle after which the needle was removed. Two square elastic discs were placed over the tubing and drawn down to the exposed skin at the back of the neck to stabilize the cannula. The cannula was secured in the oral cavity by an o-ring that was secured behind the opening of the tube by heat flanging the end of the plastic tubing prior to cannulation surgery. Immediately following surgery, rats were returned to their home cage. For three days following surgery, rats were monitored and had their cannulae flushed daily with chlorhexidine.

2.1.4. Apparatus

The TR test room was dark with two 50-Watt white lights on either side of the conditioning chamber. The conditioning chamber was made of clear Plexiglas sides (22.5×26×20 cm) with a clear lid. The chamber was placed on a table with a clear Plexiglas top. A mirror beneath the chamber on a 45° angle facilitated viewing of the ventral surface of the rat. A videocamera (Sony DCR-HC48) with firewire feed to a PC was used to record the orofacial and somatic reactions of the rat during conditioning and testing.

2.1.5. Procedure

Three days after recovering from surgery, the rats received an adaptation trial in which they were placed in the chamber with their cannulae attached to an infusion pump (Harvard Apparatus, South Natick, MA) for fluid delivery. Water was infused into their intra-oral cannulae for 5 min at the rate of 1 ml/min and rats were then returned to their home cage.

The rats received the first conditioning trial 24 h after the adaptation trial. There were a total of four trials, with 72–96 h between each trial. On each trial, rats were individually placed in the chamber and were intra-orally infused with 17% sucrose solution for 5 min at a rate of 1 ml/min while the orofacial responses were video-recorded. On trials 1–3, immediately following the sucrose infusion, the rats were injected with either Vehicle (n=9), 0.03 (n=8), 0.1 (n=9) and 0.3 (n=7) mg/kg rolipram. The fourth trial proceeded just as a conditioning trial, except that no injection was delivered afterwards.

The videos were later scored by an observer blind to the experimental conditions using “The Observer” (Noldus, Inc, NL) software for the behaviors of: gaping (large openings of the mouth and jaw, with lower incisors exposed), chin rubs (bringing the chin in direct contact with the chamber floor and projecting the body forward), paw treads (forward and backward movement of the forepaws in synchronous alternation), passive drips (passive drips of sucrose from the mouth), and the number of seconds displaying tongue protrusions and mouth movements. The summation of gaping, chin rubbing and paw treading created a total disgust score. The summation of seconds of tongue protrusions and mouth movements created a hedonic reaction score.

2.2. Experiment 2

2.2.1. Animals

The subjects were 16 male Sprague–Dawley rats (Charles River Lab, St Constant, Quebec). The animals were group-housed in shoebox cages in the colony room at an ambient temperature of 21 °C with a 12/12 light dark schedule (lights off at 8 AM) and were maintained on an ad lib schedule of food and water. All procedures adhered to the guidelines of the Canadian Council of Animal Care and were approved by the Animal Care Committee of University of Guelph.

2.2.2. Drugs

Rolipram (provided by Theravance Inc) was prepared fresh daily in sterile water and administered i.p. at a dose of 0.3 mg/kg and at a volume of 2 ml/kg.

2.2.3. Apparatus

The distinctive context utilized for conditioning varied the dimensions of location, chamber and olfactory cues from the home cage environment. The room was dark with two 50-Watt red lights on either side of the conditioning chamber. The conditioning chamber was made of opaque Plexiglas sides (22.5×26×20 cm) with an opaque lid. The chamber was placed on a table with a clear Plexiglas top. A mirror beneath the chamber on a 45° angle facilitated viewing of the ventral surface of the rat. Four plastic containers were permanently attached to holes on each side of the chamber in which a cotton dental roll saturated with vanilla flavor extract (Clubhouse; 35% alcohol) was placed to create the olfactory cue in the chamber. The cotton dental roll was inaccessible to the rat, with a newly saturated cotton roll used for each rat placed in the context.

2.2.4. Procedure

The rats received 4 conditioning trials separated by 72–96 h. On each trial, rats were injected with VEH (n=8) or 0.3 mg/kg rolipram (n=8) immediately before placement into the context for 30 min. Seventy-two hours following the last conditioning trial, the rats received a 15 min test trial in a drug-free state, while the orofacial responses were video-recorded. The videos were later scored using “The Observer” (Noldus, Inc, NL) software by an observer blind to the experimental conditions for the behaviors of: gaping (large openings

of the mouth and jaw, with lower incisors exposed) and numbers of seconds spent rearing (both front paws off the floor of the chamber) and actively locomoting (forward movement of both front paws on the floor of the chamber).

3. Results

3.1. Experiment 1

Fig. 1 presents the behaviors elicited during the 5 min intra-oral infusion of 17% sucrose solution paired with the various doses of rolipram across trials. The upper left hand section demonstrates that the mean (±sem) frequency of gaping reactions increased in a dose-dependent manner across trials. The 4 (conditioning drug)×4 (trial) mixed factors analysis of variance (ANOVA) revealed significant main effects of conditioning drug, $F(3, 29)=5.8$; $p<0.01$, trial, $F(3, 87)=23.4$; $p<0.01$ and a conditioning drug by trial interaction, F (9, 87)=3.6; $p<0.001$. Subsequent ANOVAs for each trial revealed a significant conditioning drug group effect only on trial 4, F (3, 29)=4.6; $p<0.01$. Bonferroni post-hoc comparison tests revealed that a dose of 0.3 mg/kg rolipram established greater conditioned gaping following 3 conditioning trials than did VEH or 0.03 mg/kg ($ps<0.01$), with no other significant effects.

Total disgust reactions (summation of gaping, chin rubbing and paw treading) displayed during the infusion on each trial is depicted in the upper right hand section. Analysis of the total disgust reactions revealed a similar pattern as gaping alone, with the only discrepancy being that during trial 4, conditioning drug group 0.3 displayed more disgust reactions than 0.1 mg/kg rolipram as well as the other groups. By neither measure did conditioning drug group 0.1 mg/kg or 0.05 mg/kg rolipram establish conditioned disgust to the sucrose solution.

The lower left hand section of Fig. 1 presents the mean (±sem) frequency of passive drips displayed during the intra-oral infusion of 17% sucrose by the various groups across trials. There was a dose-dependent increase in passive drips across trials. The 4×4 mixed factors ANOVA revealed significant main effects of conditioning drug, F (3, 29)=3.2; $p<0.05$, trial, F (3, 87)=22.0; $p<0.01$ and a significant conditioning drug by trial interaction, F (9, 87)=3.5; $p<0.01$. Subsequent single factor ANOVAs for each trial revealed a significant conditioning drug group effect on trial 3, F (3, 29)=4.3; $p<0.025$, and trial 4, F (3, 29)=3.9; $p<0.025$. Bonferroni post-hoc comparison tests revealed that on trials 3 and 4, group 0.3 mg/kg rolipram displayed significantly more passive drips than group VEH ($ps<0.01$), with no other significant effects.

The lower right hand section of Fig. 1 presents the mean (±sem) seconds of hedonic reactions (summation of tongue protrusions and mouth movements) displayed during the intra-oral infusion of the 17% sucrose solution (the data for tongue protrusions alone was also analyzed, but revealed an identical pattern of findings as that for the summed hedonic reactions). As is apparent in Fig. 1 (lower right), the two higher doses of rolipram (0.3 and 0.1 mg/kg) produced suppressed hedonic reactions. The 4×4 mixed factors ANOVA revealed a significant main effect of conditioning drug, F (3, 29)=5.0; $p<0.01$ and a conditioning drug by trial interaction, F (9, 87)=2.9; $p<0.01$. Subsequent single factor ANOVAs for each trial revealed a significant conditioning drug group effect on trial 3, F (3, 29)=3.3; $p<0.05$, and trial 4, F (3, 29)=6.6; $p<0.01$. Bonferroni post-hoc comparison tests revealed that on trial 4 (but not trial 3), both

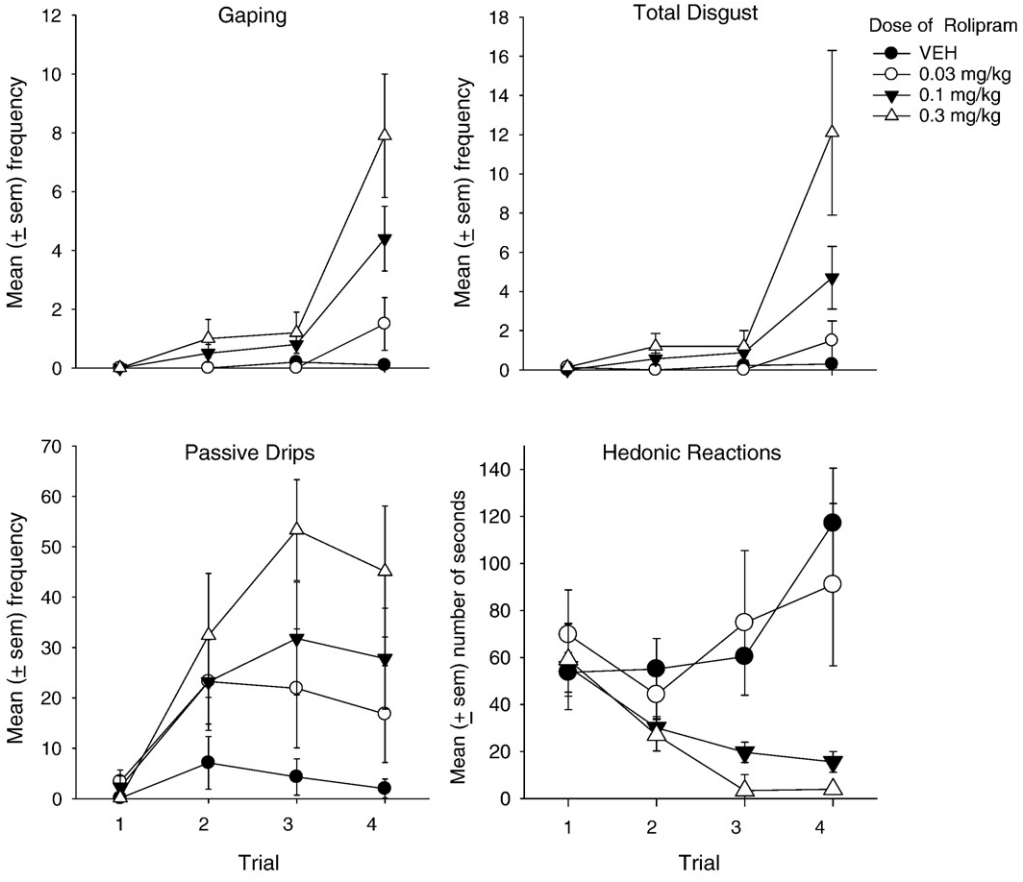

Fig. 1. Mean (±sem) frequency or duration of each of the Taste Reactivity behaviors elicited by the 5 min intra-oral infusion of 17% sucrose solution paired with VEH, 0.03, 0.1, 0.3 mg/kg rolipram across trials.

groups 0.1 mg/kg rolipram and 0.3 mg/kg rolipram displayed suppressed hedonic reactions relative to group VEH (*ps*<0.01).

3.2. Experiment 2

Rolipram (0.3 mg/kg) produced conditioned gaping as well as a conditioned increase in activity when rats were returned to the context. The upper section of Fig. 2 presents the mean (±sem) frequency of conditioned gaping displayed during the 15 min test trial by rats conditioned with either VEH or 0.3 mg/kg rolipram. A 2 (conditioning drug)×3 (time interval) mixed factor ANOVA revealed significant main effects of conditioning drug, $F(1, 14)=6.2$, $p<0.05$, time interval, $F(2, 28)=4.2$, $p<0.05$, and a conditioning drug by time interval interaction, $F(2, 28)=4.2$, $p<0.05$. Only during the first 5-min interval did rats conditioned with rolipram (0.3 mg/kg) display significantly more gaping than VEH conditioned rats, $t(14)=2.2$, $p<0.05$.

The rolipram conditioned rats also displayed a conditioned increase in active locomotion and rearing during the test trial. The middle section of Fig. 2 presents the mean (±sem) time (sec) that rats were engaged in active locomotion and the lower section of Fig. 2 presents the mean (±sem) sec that the rats were engaged in rearing during the test trial. The 2 (conditioning drug)×3 (time interval) mixed factor ANOVA for active locomotion revealed significant main effects of conditioning drug, $F(1, 14)=6.3$, $p=.025$ and time interval, $F(2, 28)=16.5$, $p<0.001$; the rolipram conditioned rats were significantly more active and all rats tended to be more active in the first 5-min interval. The 2×3 ANOVA for the rearing data revealed only a significant main effect of conditioning drug; the rolipram conditioned rats displayed more rearing during the test trial than the VEH conditioned rats.

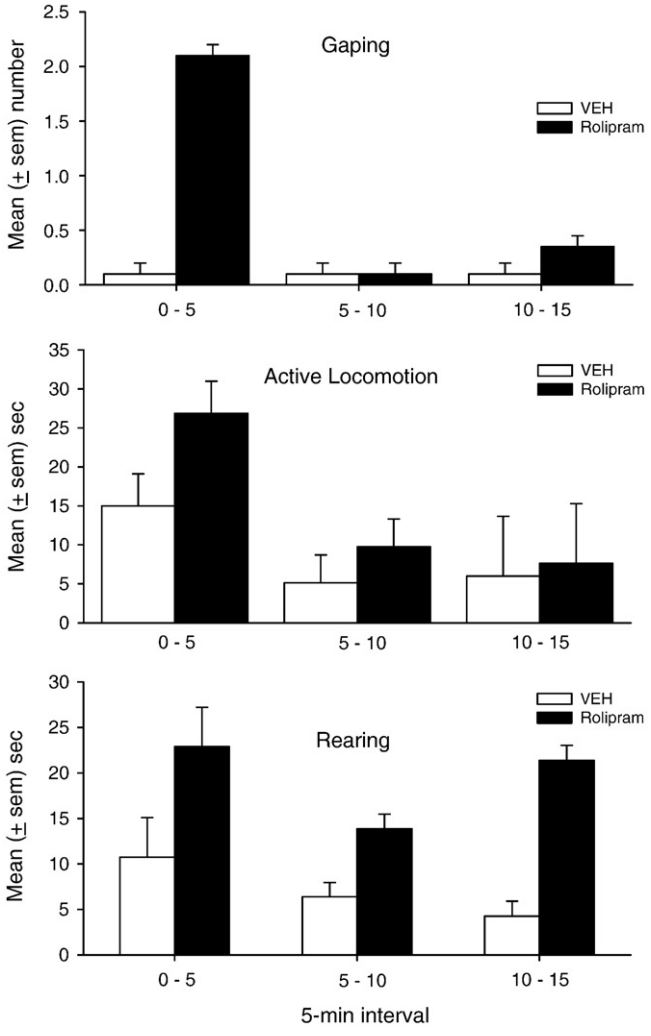

Fig. 2. Mean (±sem) frequency of gaping, duration (sec) of active locomotion and duration of rearing expressed in 5 min intervals for the rolipram and VEH groups during the 15 min test trial of Experiment 2.

4. Discussion

When re-exposed to a rolipram-paired flavor or a rolipram-paired context, rats conditioned with 0.3 mg/kg rolipram displayed conditioned gaping in the absence of the conditioning drug. Since conditioned gaping reactions are selectively produced by emetic agents (e.g., Parker, 2003), these findings suggest that 0.3 mg/kg rolipram produced nausea in rats. In Experiment 1, rats exposed to sucrose previously paired with 0.3 mg/kg rolipram displayed conditioned gaping and conditioned disgust reactions in the TR test following 3 conditioning trials. After only 2 conditioning trials, rolipram (0.3 mg/kg) produced passive dripping reactions and after 3 gaping conditioning trials, rolipram (0.1 and 0.3 mg/kg) suppressed hedonic reactions, suggesting that these reactions may be more sensitive markers of the aversive properties of rolipram. However, even non-emetic compounds such as rewarding drugs also produce suppressed hedonic reactions and passive drips (e.g., Parker, 1995), indicating that these behaviors are not selective measures of nausea, as is the conditioned gaping reaction.

Rats not only gaped when re-exposed to a rolipram-paired flavor, but they also gaped when re-exposed to a rolipram-paired chamber in Experiment 2. This paradigm is believed to model that of anticipatory nausea displayed by chemotherapy patients when returning to the treatment environment (Limebeer et al., 2006, 2008). In addition, to displaying conditioned gaping in the rolipram-paired chamber, the rats also displayed conditionally increased activity, whether assessed by active locomotion or rearing. This effect is consistent with the potential of rolipram to increase the transmission of noradrenaline (e.g., Krebs and Beavo, 1979).

Rolipram not only produces nausea and vomiting in humans (Zeller et al., 1984), but also in dogs (Heaslip and Evans, 1995), ferrets (Robichaud et al., 1999, 2001), and shrews (Hirose et al., 2007). In rats, immunohistochemical detection of Fos-like immunoreactivity (FLI) demonstrated that rolipram elevated FLI in brain regions potentially relevant to both the anti-depressant and the emetic effects of PDE4 inhibition (Bureau et al., 2006). Consistent with the anti-depressant effects, rolipram elevated FLI in the locus coeruleus, habenula, paraventricular nucleus of the thalamus, amygdala and nucleus accumbens, structures implicated in arousal, memory and affective processes. Consistent with the emetic effects, rolipram also elevated FLI in caudal brainstem nuclei including the area postrema and nucleus of the solitary tract; these effects on the brainstem nuclei were reversed by pre-treatment with an anti-emetic Neurokinin (NK_1) antagonist (Bureau et al., 2006).

PDE4 inhibitors, such as rolipram, are currently of interest because of their potential to enhance learning in rodent models (e.g., Barad et al., 1998) and because of their potential to treat diseases such as asthma and chronic obstructive pulmonary disease, depression, Parkinson's disease and Alzheimer's disease (Houslay et al., 2005). Rolipram was originally developed as an anti-depressant (Zeller et al., 1984) and it was evaluated in Phase II trials for Parkinson's disease (Parkes et al., 1984), however, it was never approved because of the side effects of nausea and vomiting (Zeller et al., 1984). Newer generations of PDE4 inhibitors are currently being developed with the goal of clinical efficacy in the absence of nausea and vomiting (Houslay et al., 2005). Such drug development would benefit by the addition of the TR test methodology to the pre-clinical screening of such compounds. A dose–response comparison of the efficacy of the drug to produce its target response with the efficacy of the drug to produce nausea (as assessed by conditioned gaping in the TR test) would provide an early detection of the potential side effects of newly developed pharmaceuticals.

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