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Research article

Validation of the xylazine/ketamine anesthesia test as a predictor of the emetic potential of pharmacological compounds in rats

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ABSTRACT

The xylazine/ketamine anesthesia test is widely used as a predictor of the emetic potential of pharmacological compounds in rats. An emetic reflex is usually triggered by the emetic center, which is populated with many different chemoreceptors. Inhibition of the α2 adrenergic receptor (α2 receptor) is involved in the initiation of the emetic reflex, and this is the key mechanism behind the xylazine/ketamine anesthesia test. In this study, we attempt to validate this test as a predictor of the emetic potential of pharmacological compounds. Furthermore, it was investigated whether an anti-emetic potential of pharmacological compounds could be assessed within this test as well. Rats were anesthetized with a combination of low doses of ketamine and xylazine, and subsequently treated with PDE4 inhibitor rolipram, α2 receptor antagonist yohimbine, α2 receptor agonist clonidine, tricyclic antidepressant imipramine, D2-receptor antagonist haloperidol, or 5-HT3 receptor antagonist (and anti-emetic drug) ondansetron. We were able to successfully reproduce the reduction in anesthesia time after rolipram or yohimbine treatment, as found in previous studies and has been suggested to be indicative of emetic properties of these treatments is humans. Furthermore, clonidine shortened anesthesia duration whereas imipramine and haloperidol lengthened anesthesia duration. Ondansetron was unable to rescue the reduction in duration of anesthesia induced by either rolipram or yohimbine. Altogether, the xylazine/ketamine anesthesia test is a reliable measure for α2 receptor antagonism. However, it may not be appropriate to assess emesis independent of this mechanism.

1. Introduction

Nausea and emesis, i.e. vomiting, are responses of biological systems as a defense against food poisoning, disease co-morbidities, and drug side-effects [1]. Nausea is the feeling of the need to vomit, usually accompanied by autonomic symptoms such as cold sweating, salivation, gastric hypotonia and reflux of intestinal contents to the stomach. Since nausea is a feeling, it cannot be objectively studied in non-humans. Emesis comprises retching and reflexive expulsion of gastric contents through the mouth, caused by sharp and sustained muscle contraction of the chest and abdominal wall [2]. Although rodents are the most widely used laboratory animals, they are unable to express an emetic reflex, which limits the experimental evaluation of drug-induced emesis in rodents [3]. Therefore, other laboratory animals, such as ferrets, are often used to test for drug-induced emesis [4,5]. However, since rodents are most widely used for the preclinical testing of pharmacological compounds, it would be highly desirable to use these same species for the evaluation of side effects such as emesis. Thus, alternative experimental models have been developed and validated in mice and rats to assess emetic properties of experimental manipulations.

An emetic reflex is triggered by the emetic center which is located in the brainstem and functions as an integration area of emetic responses. This area is closely associated with the nucleus of the solitary tract, the dorsal motor nucleus of the vagus nerve and the area postrema (AP) [6]. The AP is located at the level of the fourth ventricle where increased permeability of the blood brain barrier is at hand and many chemoreceptors with high sensitivity to pro-emetic drugs, such as anesthetics, opioids and anticancer agents, are present [7–9]. Pharmacological compounds acting on dopamine subtype 2 (D2), mu (μ) opioid, histamine subtype 1 (H1), muscarinic cholinergic (M), 5-

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hydroxytryptamine subtype 3 (5-HT3) and neurokinin-1 (NK-1) receptors have been known to possess anti-emetic properties [8,10,11]. A well-known example of such compounds is ondansetron (5-HT3 receptor antagonist) [1].

In addition, experimental evidence suggests a possible role for α2-noradrenergic (α2) receptors in inducing emesis. Activation of α2 receptors by α2 receptor agonists such as clonidine or xylazine, has been shown to elicit dose dependent vomiting in cats and dogs [12–15]. In these species, emesis induced by clonidine or xylazine can be prevented by co-administration with the α2 receptor antagonist yohimbine [12–14]. Interestingly, yohimbine was found to induce emesis in ferrets, whereas clonidine acted anti-emetic in this species [4]. This discrepancy is believed to derive from an evolutionary difference in the physiological organization of the emetic pathways of the different species [4].

Phosphodiesterase type 4 (PDE4) inhibitors are a class of drugs which increase cAMP levels and have procognitive and antidepressant effects [16]. However, development of PDE4 inhibitors as therapeutic drugs has always been hampered by the dose dependent side effects including nausea and even emesis in humans [17,18], as was particularly evident with the classic PDE4 inhibitor rolipram [5]. The mechanism of the emetic response associated with PDE4 inhibitors is thought to be a consequence of the inhibition of PDE4 in emetic centers [4,19]. It was suggested that PDE4 inhibitors produce a pharmacological response analogous to that of α2-receptor antagonists (which elevate intracellular levels of cAMP in noradrenergic neurons). In contrast, α2 receptor activation (by agonists) decreases intracellular levels of cAMP in noradrenergic neurons, which subsequently decreases neurotransmitter secretion in the synaptic cleft. Thus, PDE4 inhibitors are thought to modulate the release of mediators including 5-HT, substance P and noradrenaline which are involved in the onset of the emetic reflex mediated at the emetic brainstem centers [4].

In order to assess the emetic potential of PDE4 inhibitors, an emesis test based on the ability to reverse α2 receptor agonist–mediated anesthesia with xylazine/ketamine in rodents was proposed [20]. The main outcome parameter in the xylazine/ketamine anesthesia test is the duration of the anesthesia. Anesthesia duration is defined as the time until completion of the righting reflex, i.e. when the rodent no longer remains on its back and turns itself spontaneously to the prone position [4,20,21]. It was observed that PDE4 inhibitors like rolipram shorten the xylazine/ketamine induced anaesthesia time [22]. This finding was similar to those observed with α2 receptor antagonists and it has therefore been argued to be the equivalent of the possible emetic potential of PDE4 inhibitors in rats [4]. This well-established ability of PDE4 inhibitors to shorten the duration of α2 receptor-mediated xylazine/ketamine anesthesia time is therefore used as a surrogate measure of emesis in rodents [23].

However, to our knowledge this emesis test has thus far only been used to evaluate the emetic properties of PDE inhibitors, NK_1 receptor agonists, and α2 receptor antagonists, all of which are supposedly mediating emesis via a similar mechanism [20,22]. Therefore, the aim of the present study was to validate this emesis test in rats by evaluating the emetic (shortened anesthesia duration) or possible anti-emetic (prolonged anesthesia duration) effects of different drugs acting on the α2 receptor in particular and on different subtypes of dopaminergic, and serotonergic receptors known to be involved in emesis. Possible anti-emetic effects were investigated by co-administrating the established anti-emetic drug ondansetron with the known emetic drugs rolipram and yohimbine in the xylazine/ketamine anesthesia test in rats. Our rationale was that ondansetron might counteract the emetic effects (i.e. shortened anesthesia duration) of rolipram and yohimbine and hence result in normalized anesthesia duration. We hypothesized that if a drug has an anti-emetic effect, it should re-stabilize the anesthesia after rolipram or yohimbine administration even if different chemoreceptors in the AP are targeted.

2. Methods

All experimental procedures were designed to minimize the potential discomfort of the animals and to reduce the number of animals used. All experimental procedures were approved by the local ethical committee for animal experiments of Maastricht University and were in agreement with the local governmental guidelines. All experimental procedures were performed according to the ARRIVE guidelines [24]. Specifically, experiments were conducted semi-random, with the animals divided in sub-groups (A, B, C), and the experimenter was blinded to the conditions. Animals were excluded from the analysis when they did not go under anesthesia. Additionally, outliers were identified by a Dixon's Q-test for outliers and subsequently excluded. If too many animals were excluded to reach sufficient power, a second day of testing was added, carefully taking into consideration that one animal will not receive the same condition twice.

2.1. Animals

5 cohorts each containing 24 (4–6 months old) male Wistar rats weighing 432 ± 30 g, were individually housed in individually ventilated cages and had free access to food and water. A radio, playing softly, provided background noise to mask noises in the room. The room temperature was about 20 °C (and 60 ± 10% relative humidity). The animals were kept under a reversed 12/12-h light/dark cycle (lights on from 19:00 to 7:00 h) in order to test the animals during their naturally active period (i.e. the dark phase).

2.2. Duration of anesthesia

Experiments were conducted according to previously described procedures [4]. Briefly, a rat was anesthetized with a combination of xylazine (10 mg/kg, CEVA Santé Animale, Naaldwijk, the Netherlands) and ketamine (10 mg/kg, Ketaset®, Eurovet Animal Health, Bladel, the Netherlands) administered via intraperitoneal (i.p.) injections. Fifteen minutes later, a test compound or its vehicle was injected subcutaneously (s.c.) or i.p. and the animal was placed in dorsal recumbency. The restoration of the righting reflex, i.e. when the animal no longer remained on its back and turned itself spontaneously to the prone position, was used as an endpoint to determine the duration of anesthesia. Emesis testing was performed in batches, and the experimental conditions were semi-randomly assigned to experimental days which were separated by a wash-out period of at least 48 h to prevent drug/dose interactions. The animals that not reacted to anesthesia injections or woke up before or during vehicle or compound injection were excluded from the experiment.

2.3. Drugs

The following drugs and doses were tested: the PDE4 inhibitor rolipram (0.01; 0.03 or 0.1 mg/kg s.c. [22]); adrenergic α2-receptor antagonist yohimbine (1 mg/kg s.c. [4]); adrenergic α2-receptor agonist clonidine (0.5 or 1 mg/kg s.c. [25,26]); tricyclic antidepressant (serotonin, norepinephrine and dopamine reuptake inhibitor) imipramine (10 mg/kg i.p. [27]); serotonergic 5-HT3 receptor antagonist ondansetron (2 mg/kg i.p. [28]); and dopaminergic D2-receptor antagonist haloperidol (0.1 or 0.2 mg/kg, s.c [29–31]).

Rolipram and yohimbine were also used as an 'emesis model' and therefore tested in combination with clonidine, haloperidol, imipramine or ondansetron. All drugs were purchased from Sigma Aldrich (Zwijndrecht, The Netherlands or St. Louis, MO, USA), except haloperidol (Janssen-Cilag B.V., USA). Vehicle composition was saline (all tested drugs except rolipram) or a solution prepared from a 0.5% methylcellulose solution and tween80 (rolipram), which proportions were 98% and 2% respectively. Test compounds were freshly dissolved on every experimental day and were injected in a volume of 1 ml/kg.

Doses, vehicle composition and routes of administration were based on previous studies where these drugs showed anti-emetic or behavioral effects.

2.4. Data presentation and statistical evaluation

Since emesis testing was performed in different animal batches, on different days, results from the same drug and dose were normalized by day, pooled and subsequently analyzed. The data is expressed in percentages with the vehicle condition set to 100% (for raw values of the means (min), see Supplementary Table S1). For drugs tested in only one dose, the effects of the treatments were compared to their respective vehicle using student's *t*-tests. For drugs tested in two doses or in combined treatments, a one-way ANOVA was used followed by a multiple comparisons analysis/test (Tukey's test). Differences were considered to be statistically significant for *P* values below 0.05.

3. Results

3.1. The effect of rolipram, yohimbine, and clonidine on anesthesia duration

Administration of PDE4 inhibitor rolipram 15 min after induction of xylazine/ketamine anesthesia resulted in a dose-dependent reduction of the duration of anesthesia ($F_{(3,40)} = 14.33$; $P < 0.001$) (Fig. 1A). Administration of the α2 receptor antagonist yohimbine ($t_{(26)} = 5.60$; $P < 0.001$) and α2 receptor agonist clonidine ($F_{(2,18)} = 19.27$; $P < 0.001$) also shortened the duration of anesthesia (Fig. 1B and C, respectively). The duration of anesthesia was shortened even further by a combination of rolipram and clonidine ($F_{(2,21)} = 13.99$; $P < 0.001$) (Fig. 1D), whereas a combination of clonidine and yohimbine did not alter the duration of anesthesia compared to yohimbine alone ($F_{(2,18)} = 25.83$; $P < 0.001$) (Fig. 1E). Since clonidine is also considered an α2 receptor agonist, a combination of clonidine and ketamine was administered to mimic the effects of xylazine (also an α2 receptor agonist) and ketamine. Interestingly, animals treated with clonidine and ketamine could not be anesthetized (see Table 1), showing that clonidine is less selective for the α2 receptor than xylazine, a phenomenon that has been described in the literature before [32].

Table 1
Effects of ketamine, xylazine, and clonidine on anesthesia time in rats.

Compounds/Drugs	Mean duration of anesthesia (min) + SEM	N
Ketamine (10 mg/kg, i.p.)	0 (0)	8
Clonidine (1 mg/kg, s.c.)	0 (0)	8
Ketamine (10 mg/kg, i.p.) & clonidine (1 mg/kg, s.c.)	0 (0)	8
Ketamine (10 mg/kg, i.p.) & xylazine (10 mg/kg, i.p.)	53.37 (3.68)	15

Effects of ketamine, xylazine, and clonidine on anesthesia time in rats. Animals treated with ketamine (10 mg/kg i.p.), clonidine (1 mg/kg s.c.), or a combination of ketamine and clonidine could not be anesthetized. Only a combination of ketamine and xylazine (10 mg/kg i.p.) succesfully induced anesthesia in rats.

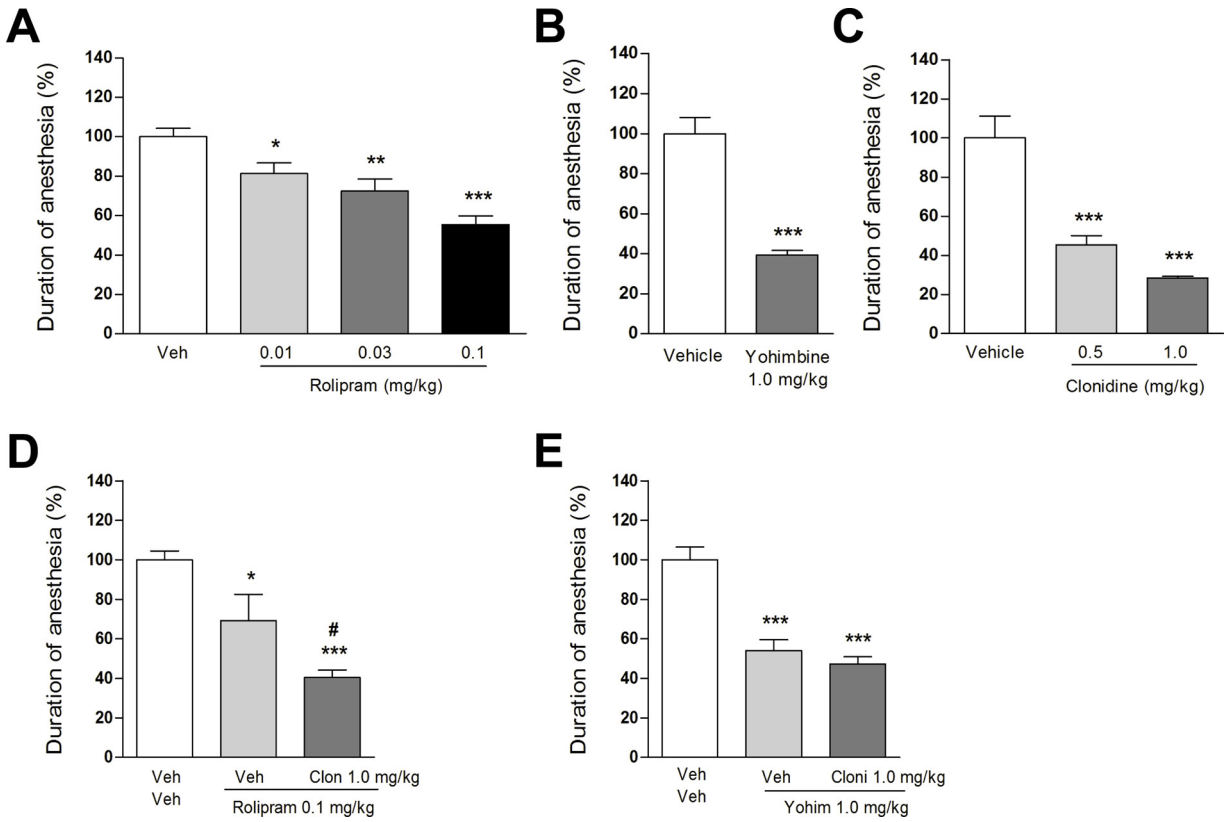

Fig. 1. Effect of the PDE4 inhibitor rolipram, α2 receptor antagonist yohimbine, and α2 receptor agonist clonidine on the duration of anesthesia induced by the combination of xylazine (10 mg/kg, i.p.) and ketamine (10 mg/kg, i.p) in rats. (A) Rolipram dose-dependently reduced the duration of anesthesia. Similar effects were found for (B) yohimbine, and (C) clonidine. A combination of (D) rolipram and clonidine further decreased the duration of anesthesia, and (E) yohimbine and clonidine did not change the duration of anesthesia compared to yohimbine alone. The duration of anesthesia was assessed by the return of righting reflex. The data is normalized and expressed as mean + SEM (student's *t*-test or post hoc Tukey's tests following a significant one-way ANOVA, when compared to vehicle treatment: *P < 0.05; **P < 0.01; ***P < 0.001; when compared to vehicle + rolipram treatment: #P < 0.05).

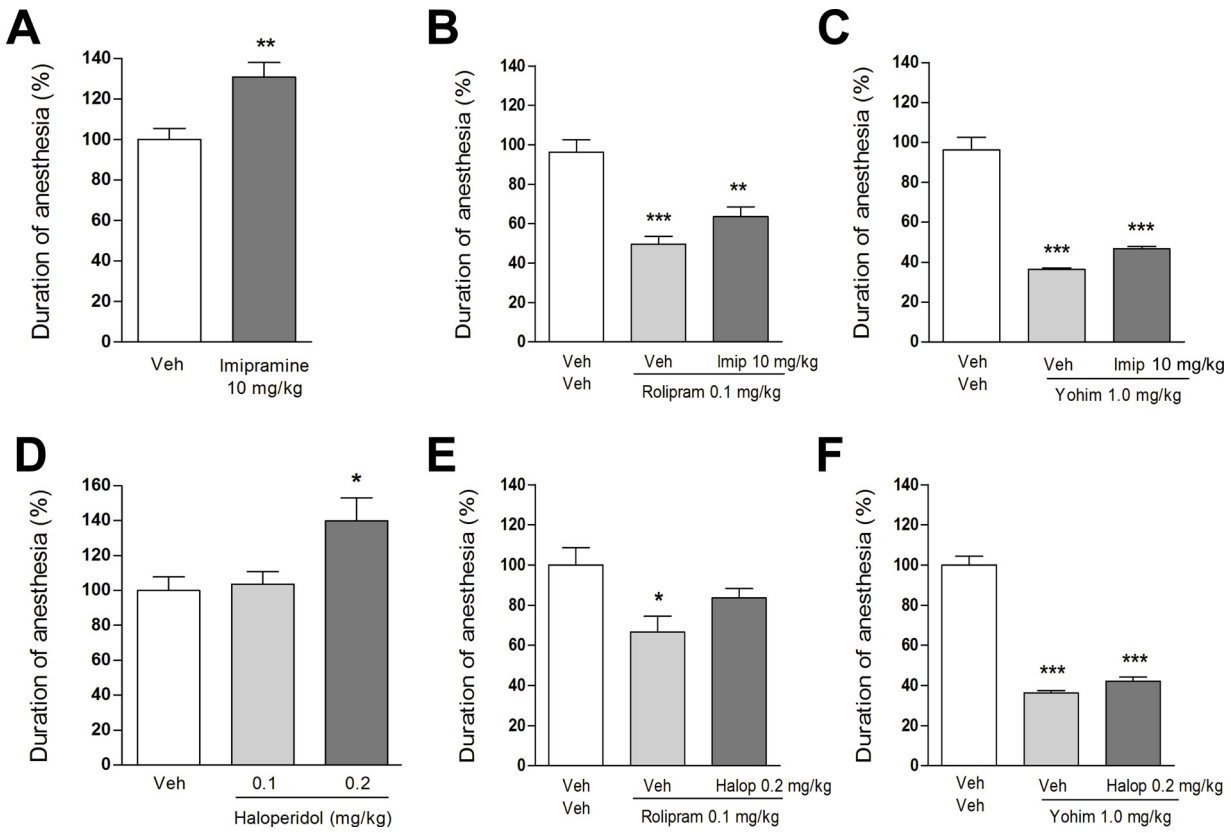

Fig. 2. Effect of the tricyclic antidepressant (serotonin, norepinephrine and dopamine reuptake inhibitor) imipramine, and dopaminergic D2-receptor antagonist haloperidol on the duration of anesthesia induced by the combination of xylazine (10 mg/kg, i.p.) and ketamine (10 mg/kg, i.p) in rats. (A) Imipramine increased the duration of anesthesia, and a combination of (B) imipramine and rolipram, and (C) imipramine and yohimbine did not alter the duration of anesthesia compared to rolipram or yohimbine alone. Administration of (D) haloperidol also increased the duration of anesthesia, and a combination of rolipram and haloperidol normalized the duration of anesthesia compared to administration of rolipram alone. A combination of (E) haloperidol and yohimbine did not change the duration of anesthesia compared to yohimbine alone. The duration of anesthesia was assessed by the return of righting reflex. The data is normalized and expressed as mean + SEM. A significant difference from the vehicle group (Veh) is depicted with asterisks (student's *t*-test or post hoc Tukey's tests following a significant one-way ANOVA, *P < 0.05; **P < 0.01; ***P < 0.001).

3.2. The effect of imipramine and haloperidol on anesthesia duration

Administration of the tricyclic antidepressant imipramine increased the duration of anesthesia ($t_{(16)} = 3.16$; $P < 0.01$) (Fig. 2A). However, a combination of imipramine and rolipram ($F_{(2,28)} = 15.74$; $P < 0.001$), and a combination of imipramine and yohimbine ($F_{(2,26)} = 29.08$; $P < 0.001$) did not alter the duration of anesthesia compared to respectively rolipram or yohimbine alone (Fig. 2B, C). Similar to imipramine administration, haloperidol increased the duration of anesthesia ($F_{(2,39)} = 4.82$; $P < 0.05$) (Fig. 2D). Interestingly, a combination of haloperidol and rolipram normalized the duration of anesthesia back to vehicle level ($F_{(2,16)} = 5.17$; $P < 0.05$) (Fig. 2E). A combination of haloperidol and yohimbine did not alter the duration of anesthesia compared to yohimbine alone ($F_{(2,20)} = 15.88$; $P < 0.001$) (Fig. 2F).

3.3. The effect of ondansetron on anesthesia duration

Administration of the 5-HT3 antagonist and anti-emetic drug ondansetron did not alter the duration of anesthesia ($t_{(10)} = 0.19$; $P = 0.859$) (Fig. 3A). Interestingly, ondansetron was unable to normalize the duration of anesthesia when co-adminstered with rolipram ($F_{(2,25)} = 8.93$; $P < 0.001$) or yohimbine ($F_{(2,18)} = 40.85$; $P < 0.001$) (Fig. 3B, C) suggesting an alternative mechanism of action for ondansetron which is unrelated to the α2 receptor mechanism.

4. Discussion

The aim of the studies outlined here was to validate the xylazine/ketamine anesthesia test in rats by evaluating the emetic (shortened anesthesia duration) or possible anti-emetic (prolonged anesthesia duration) effects of different drugs acting on the α2 receptor in particular and on different subtypes of dopaminergic, and serotonergic receptors known to be involved in emesis. As expected, both rolipram and yohimbine significantly reduced the duration of xylazine/ketamine anesthesia. This is in concordance with previous research in rats and ferrets [4,20,22]. Yohimbine is an α2 receptor antagonist, and administration of yohimbine during xylazine/ketamine induced anesthesia would counteract the effects of α2 receptor agonist xylazine, thereby waking the animals up. Similarly, PDE4 inhibitors such as rolipram are believed to produce a pharmacological response similar to α2 receptor antagonists [4].

Interestingly, the α2 receptor agonist clonidine also reduced the duration of anesthesia, where it would be expected that it would enhance the effects of xylazine and thereby lengthen the duration of anesthesia. Furthermore, when administering ketamine and clonidine instead of ketamine and xylazine, animals could not be anesthetized. Previous research has shown that although xylazine and clonidine are both α2 receptor agonists, their mechanisms of action are by no means the same [32]. Clonidine is not a particularly selective α2 receptor agonist, as it also acts on the imidazoline subtype 1 (I_1) receptor [33]. Activation of I_1-receptors in the nucleus paragigantocellularis may result in a downstream activation of noradrenergic neurons in the locus

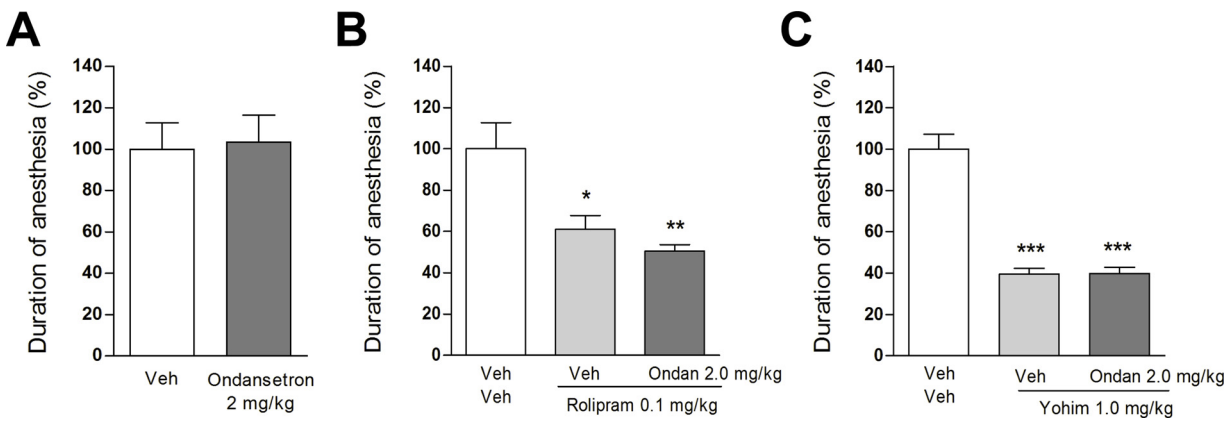

Fig. 3. Effect of the anti-emetic 5-HT3 antagonist ondansetron on the duration of anesthesia induced by the combination of xylazine (10 mg/kg, i.p.) and ketamine (10 mg/kg, i.p) in rats. (A) Ondansetron did not alter the duration of anesthesia, and a combination of (B) ondansetron and rolipram, and (C) ondansetron and yohimbine did not alter the duration of anesthesia compared to rolipram or yohimbine alone. The duration of anesthesia was assessed by the return of righting reflex. Data is normalized and expressed as mean + SEM. A significant difference from the vehicle group (Veh) is depicted with asterisks (student's *t*-test or post hoc Tukey's tests following a significant one-way ANOVA, *P < 0.05; **P < 0.01; ***P < 0.001).

coeruleus, thereby increasing noradrenergic signaling. α2 receptors are known to inhibit this noradrenergic signaling. Furthermore, clonidine is a known hypotensive agent [34], and a reduction in blood pressure has been shown to increase the firing-rate of noradrenergic neurons in the locus coeruleus, via the activation of baroreceptors [35]. Taken together, clonidine both stimulates noradrenergic signaling via activation of I_1-receptors and a reduction in blood pressure, while simultaneously inhibiting noradrenergic signaling via activation of α2 receptors. This may explain why clonidine combined with ketamine does not induce anesthesia, or why clonidine does not lengthen the duration of xylazine/ketamine anesthesia. This also explains why administration of clonidine does not rescue the shortened duration of anesthesia induced by yohimbine. However, clonidine is a known sedative [36,37], and even though clonidine can enhance the firing-rate of noradrenergic neurons in the locus coeruleus after blocking α2 receptors [38], it still inhibits noradrenergic firing in the locus coeruleus under normal conditions in vivo [39,40]. Furthermore, previous research has shown that two other I_1-receptor/α2 receptor agonists, rilmenidine and moxonidine, both decrease noradrenergic firing in the locus coeruleus, despite having a 30x higher affinity for I_1-receptors compared to α2 receptors [41]. Additionally, the affinity of clonidine for I_1-receptors and α2 receptors is highly similar [42]. In fact, transdermal clonidine patches are being considered as a treatment for hyperemesis gravidarum, a pregnancy complication associated with severe nausea and vomiting (for a meta-analysis, see [43]). Altogether, it remains highly suprising that clonidine shortens the duration of anesthesia to such extreme extent.

Both imipramine and haloperidol increased the duration of xylazine/ketamine anesthesia. It is well known that drowsiness is a common side effect of both these drugs [44,45]. This might explain the lengthening of the duration of anesthesia in this test. However, imipramine is also known to have emetic side-effects in humans [45]. Yet, duration of anesthesia was still lengthened, which suggests that either the emetic potential of imipramine could not be measured with xylazine/ketamine anesthesia, or the drowziness was too large a confounder. This suggests that the xylazine/ketamine anesthesia test is not always a good predictor of emetic potential, especially when the drug has no α2 receptor antagonistic actions or has an arousal-related side-effect that could bias the experimental outcome. The potential of side-effects as a confounding factor is further emphasized by the normalization of the duration of anesthesia when rolipram is combined with haloperidol. Here, the drowziness induced by haloperidol could theoretically be sufficient to prevent the shortening of anesthesia duration. However, it cannot be excluded that haloperidol possesses anti-emetic properties resulting in a shortened anesthesia time.

As expected, the 5-HT3 antagonist and anti-emetic drug ondansetron did not affect the duration of xylazine/ketamine anesthesia. Interestingly, ondansetron could not rescue the shortened duration of anesthesia induced by rolipram or yohimbine, despite its anti-emetic actions. Previous research has shown that although only mildly, ondansetron was able to reverse emetic effects of rolipram in ferrets [5]. This further suggests that the xylazine/ketamine anesthesia test is mostly a test to measure whether a pharmacological compound possesses α2 receptor actions, and it does not directly measure emetic potential of any type of pharmacological compound per se. However, α2 receptor antagonism itself still remains a good predictor of emetic potential. Nevertheless, it should be taken into consideration that emesis is not only caused by α2 receptor antagonism.

Altogether we were able to reproduce the shortened duration of anesthesia caused by rolipram and yohimbine, and this is most likely the result of α2 receptor antagonism. However, the emetic potential of imipramine could not be measured with this xylazine/ketamine anesthesia test, and it also seems to be sensitive to confounders such as other arousal related side-effects caused by the compounds. The xylazine/ketamine anesthesia test is a reliable test for assessing whether compounds possess (either direct or indirect) α2 receptor antagonistic properties, and α2 receptor antagonism remains a good predictor of emetic potential. However, this test seems prone to arousal-related side-effects of different pharmacological compounds and as such may not always be reliable to predict emesis caused by mechanisms independent of α2 receptor antagonism.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neulet.2019.01.026.

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