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Musk shrews selectively bred for motion sickness display increased anesthesia-induced vomiting

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Abstract

Susceptibility to motion sickness is a predictor of postoperative nausea and vomiting, and studies in humans suggest that genetic factors determine sensitivity to motion sickness. The aim of the current study was to determine if a preclinical model could be selectively bred for motion-induced emesis and to assess a potential relationship to anesthesia-induced emesis. Musk shrews were tested for motion-induced emesis using a shaker plate (10 min, 1 Hz, and 4 cm of lateral displacement). Animals were rank ordered for motion-induced emesis and selectively bred to produce high and low response strains. Shrews were also tested with nicotine (5 mg/kg, sc), copper sulfate ($CuSO_4$; 120 mg/kg, ig), and isoflurane anesthesia (10 min; 3%) to determine responses to a panel of emetic stimuli. High response strain shrews demonstrated significantly more emetic responses to motion exposure compared to low response strain animals in the F1 and F2 generations. In F2 animals, there were no significant differences in total emetic responses or emetic latency between strains after nicotine or $CuSO_4$ injection. However, isoflurane exposure stimulated more emesis in F1 and F2 high versus low strain animals, which suggests a relationship between vestibular- and inhalational anesthesia-induced emesis. Overall, these results indicate genetic determinants of motion sickness in a preclinical model and a potential common mechanism for motion sickness and inhalational anesthesia-induced emesis. Future work may include genetic mapping of potential "emetic sensitivity genes" to develop novel therapies or diagnostics for patients with high risk of nausea and vomiting.

Keywords

Emesis; Vomiting; Nausea; Suncus; Genetics

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1. Introduction

As many as 35% of US adults have experienced vestibular dysfunction, and prevalence increases with age [1]. Motion sickness has significant adverse effects on cognitive and physical performance [2-5]. Although motion sickness involves several divergent brain pathways and functional components (e.g., pallor, cold sweating, and disorientation) and a link to pronounced activation of stress response systems [6-8], a cardinal feature is the activation of nausea and vomiting (NV) [9]. The incidence of NV in medical settings can reach 80%, particularly in individuals at highest risk, such as patients with a history of sensitivity to motion sickness [10, 11], and a twin study estimates that motion sickness has a heritability of 57-70% [12]. Currently used anti-motion sickness drugs (e.g., histamine and muscarinic antagonists) do not always control NV and can result in sedation, blurred vision, and dizziness [13-15]. Research to date has focused on these older drugs, often with non-specific receptor targets, in heterogeneous human cohorts and preclinical models [14, 15]. A high-throughput approach in an easily manipulated preclinical model could provide greater mechanistic insight and identify more effective therapeutic strategies for the control motion sickness.

The focus of the current study was to selectively breed an animal model of motion-induced emesis that could be applied to future molecular-genetic studies. Musk shrews were used for these experiments because, unlike mice and rats [16, 17], they are capable of vomiting and are a well-characterized species for motion-induced emesis [18-24] using standardized behavioral test conditions [20]. Furthermore, musk shrews can be tested with this standardized approach in high-throughput screening (> 40 animals per day); breed rapidly; have a short time to maturity (~35 days to adulthood); and, at 40 to 80 g, are only slightly larger than mice, which allows high density housing. Animals were tested for vestibular-induced emesis by placing test cages on a shaker plate (10 min, 1 Hz, and 4 cm of lateral displacement). Shrews were ranked from high to low emetic responses to motion and selectively bred to produce high and low response strains. Animals were also tested with nicotine (5 mg/kg, sc), copper sulfate (120 mg/kg, ig), and isoflurane anesthesia (10 min; 3%) to determine responses to emetic stimuli acting on additional neural pathways. Circulating nicotine and intragastric copper sulfate ($CuSO_4$) are believed to activate the area postrema and gut vagal afferent pathways, respectively [25-29]. In contrast, little is known about the mechanism for anesthesia-induced emesis.

2. Materials and methods

2.1. Animals

Musk shrews were descendants from breeding stock obtained from the Chinese University of Hong Kong; a Taiwanese strain of *Suncus murinus* [30]. Studies used 30 females and 30 males in the parental generation, 16 females and 20 males in the F1 generation, and 15 females and 16 males in the F2 generation (a total of 127 animals). Animals were housed in clear plastic cages (28 × 17 × 12 cm), with a filtered air supply, under a 12 h standard light cycle (lights on: 0700 h), in a temperature (~23°C) and humidity (~40%) controlled environment. Food and drinking water were freely available except during the brief test periods (~45 min). Food consisted of a mixture of 75% Purina Cat Chow Complete Formula and 25% Complete Gro-Fur mink food pellets [31]. All experiments were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. Animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care international-accredited animal care facility.

2.2. Chemicals

Nicotine ((-)-Nicotine, catalog # 36733) and $CuSO_4$ (copper (II) sulfate pentahydrate, catalog # 209198) were obtained from Sigma-Aldrich. Nicotine was made as a 2.5 mg/ml solution in sterile saline (0.15 M NaCl; subcutaneous injection = 5 mg/kg/2 ml) and copper sulfate was dissolved in filtered water (Milli-Q) at a concentration of 24 mg/ml (gavage injection = 120 mg/kg/5 ml). Isoflurane was provided via an enclosed chamber (allowed to fill for 2 min before use). Flow rates of gas were 6 L/min (from 100% O_2 compressed air canister flowing through an isoflurane vaporizer; Matrx, TEC-3). Percentage of isoflurane was set by the dial on the vaporizer. The enclosed induction chamber was 10 × 8.5 cm, height and diameter.

2.3. Emetic testing procedures

Emetic tests were conducted with a 3 to 4 week time interval between tests to allow for recover (test order: motion, nicotine, $CuSO_4$, and then isoflurane) [32, 33]. Animals were tested between 0800 and 1200 h (light phase). Testing for males and females was balanced to control for time of day effects. For motion, nicotine, and $CuSO_4$ tests, animals had 15 min of adaption in the test chambers before the emetic stimulus. For motion exposure, the test chambers (28 × 17 × 12 cm) had a clear acrylic lid placed directly on the top. These chambers were placed on a reciprocating shaker (Taitec, Double Shaker R-30, Taiyo Scientific Industrial). Horizontal motion (4 cm displacement; 2 cm left and 2 cm right; 1 Hz) was applied for 10 min based on other studies that have determined optimal parameters [20]. In nicotine or $CuSO_4$ tests, animals were subcutaneously injected with nicotine (5 mg/kg) or using a gavage needle for $CuSO_4$ (120 mg/kg), based on previous studies [21, 34, 35]. Cohorts of F1 and F2 generations were also tested for isoflurane-induced emesis. Only a subset of F1 animals were used for the isoflurane test because other members of this cohort were euthanized to collect blood for future genetic analysis. Animals were placed in a transparent induction chamber for 10 min of isoflurane exposure, and then transferred to a transparent observation chamber using our published procedure [32].

All animal behavior was recorded with a digital video camera (Sony DCR-SR300 or HDRXR550V, wide field lenses) placed above each test chamber and connected to a computer for storage (Media Recorder; Noldus Information Technology). A trained observer was positioned outside the transparent test chambers to record the occurrence of an emetic episode (with or without a vomit), abdominal contraction, or a swaying movement using a notebook computer installed with coding software (JWatcher; http://www.jwatcher.ucla.edu/). Emetic episodes (with or without expulsion) were defined as a sequence of contractions of the abdominal region associated with forward movements of the head and separated by other episodes by a minimum of 2 s. In past studies, we have noted the occurrence of abdominal contractions (a single contraction of the abdominal region) and swaying movements (swaying the abdominal portion of the body from side to side) in association with emesis, and they were included in this report to determine potentially subtle differences between conditions.

2.4. Breeding procedures

Parental animals were ranked for emetic responses to motion exposure and divided into upper and lower 1/3 responders (n=10/group for males and females). The cutoffs were ≥ 15 (High group) and ≤ 10 (Low group) episodes for males; and ≥ 13 (High group) and ≤ 7 (Low group) for females. These High and Low group motion response parental males and females (i.e., the P-split) were selectively bred (i.e., high with high, and low with low). Because of fewer animals in F1 breeding we used a High cutoff ≥ 13 emetic episodes for both males and females. To reduce the fixation of genes that are associated with inbreeding (and likely not with the phenotype of emesis), we only bred animals that were not siblings and did not share

a parent. For breeding, one adult musk shrew female is placed in the home cage of an adult male overnight. The gestation period is a total of approximately 30 days. The average litter size was 2 pups. The pups were housed with their mother until 21 days of age. From that time, animals were housed singly and tested for emetic responses during adulthood (i.e., > 35 days of age).

2.5. Data analysis

Dependent measures included emetic episodes, episodes with vomiting, episodes without vomiting, duration (time from first to last emetic event), emetic rate (episodes/min), standard deviation of the emetic interval (SD-I), abdominal contractions, and swaying were analyzed. SD-I was calculated as the standard deviation of the intervals between emetic episodes and can be used as a measure of the variability in the rhythm of emesis during the emetic duration. In each generation, data were analyzed with ANOVA for each emetic stimulus and variable (strain by sex factorial design). Hom-Sidak tests were used to compare means after ANOVA. It is frequently difficult to apply parametric statistics to behavioral latency data, which are often skewed. In the F1 isoflurane test, females and males were combined to form High and Low groups because of the lower power in this experiment (e.g., only n = 4 High females); T-tests were used to compare groups. To address this issue we used survival plots and Cox regression analysis for comparison of latency data (time to the first emetic event). This approach permits the use of all data, including censored values (i.e., animals that did not show emesis during the test period) [36]. $P < 0.05$ was used to determine statistical significance for all tests.

3. Results

3.1. Parental and P-split generation responses to motion, nicotine, and $CuSO_4$

The initial cohorts of parental animals displayed 0 to 29 total emetic responses (10.9 ± 7.1, mean ± standard deviation) for females and 0 to 27 responses (12.4 ± 6.5, mean ± standard deviation) for males (Fig.1) to motion exposure. Animals were ranked for emetic responses to motion and divided into higher and lower 1/3 responders (n=10 per group for males and females). This selection (i.e., the P-split animals) produced significantly more total emetic episodes, episodes with a vomits, episodes without a vomit, duration, rate, and SD-I in High versus Low groups after motion exposure [$F's(1,32) \geq 7.5$, $p's \leq 0.01$, ANOVA, main effects of group; $p's < 0.05$, Hom-Sidak tests; Fig.1 and Table 1]. Motion exposure also produced a shorter emetic latency in the High compared to Low group ($p < 0.05$, Cox regression, Fig. 4). There were no significant differences in emetic responses after nicotine injection in selected groups (Fig. 2, Fig. 4, and Table 1). P-split animals displayed significantly more $CuSO_4$-induced emetic episodes in High versus Low group males [$F(1,35) = 6.5$, $p < 0.02$, ANOVA, main effect of group; $p < 0.05$, Hom-Sidak test; Fig. 3], an effect that was related to the increased number of emetic episodes without a vomit [$F(1,35) = 4.3$, $p < 0.05$, ANOVA, interaction effect; $p < 0.05$, Hom-Sidak test; Table 1]. There was no statistically significant difference in emetic latency after $CuSO_4$ injection (Fig. 4).

3.2. F1 generation responses to motion, nicotine, and $CuSO_4$

Breeding the P-split generation High females with High males, and Low females with Low males, produced n = 6 High female, n = 9 High male, n = 11 Low female, and n = 11 Low male F1 animals. The High strain offspring (i.e., the F1) showed significantly greater total emetic responses and duration to motion exposure compared to Low strain offspring [$F's(1,32 \text{ or } 29) \geq 4.2$, $p's \leq 0.05$, ANOVA, main effect of group; $p < 0.05$, Hom-Sidak test; Fig. 1 and Table 1]. This effect was also demonstrated as a reduced emetic latency after motion exposure in High versus Low strain males and females ($p < 0.05$, Cox regression, Fig. 5). There were no significant differences between High and Low F1 strains for total

emetic episodes or emetic latency after nicotine injection (Fig. 2 and Fig. 5), but nicotine produced more emetic episodes with vomiting in High versus Low males [$F(1,32) = 7.0$, $p < 0.02$, ANOVA, main effect of group; $p < 0.05$, Hom-Sidak test; Table 1]. Significant interaction effects (sex by strain) were detected for $CuSO_4$ injection in the number of emetic episodes (total and without a vomit) [F's$(1,30) \geq 4.3$, p's < 0.05, ANOVA, interaction effects; Fig. 3 and Table 1], but with no significant effects on emetic latency (Fig. 5).

3.3. F2 generation responses to motion, nicotine, and $CuSO_4$

Breeding the F1 High females with the High males (n = 4 and n = 5, respectively, i.e., those meeting the cutoff), and Low females with the Low males (n = 6 and n = 6, respectively), produced n = 11 High female, n = 10 High male, n = 11 Low female, and n = 15 Low male F2 animals. The High strain offspring (i.e., the F2) of F1 breeding showed significantly greater total emetic episodes, episodes with a vomit, episodes without a vomit, duration, and rate after motion exposure compared to Low strain offspring [F's $(1,36) \geq 7.8$, $p < 0.01$, ANOVA, main effects of group; $p < 0.05$, Hom-Sidak tests; Fig. 1 and Table 1]. Similarly, High strain males and females showed a shorter emetic latency compared to Low strain animals exposed to motion ($p < 0.05$, Cox regression; Fig. 6). Nicotine injection produced a significant increase in episodes without a vomit in High versus Low females [$F(1,43) = 4.3$, $p < 0.05$, ANOVA interaction effect; $p < 0.05$, Hom-Sidak test; Table 1], and a faster emetic rate in High compared to Low strain animals [$F(1,42) = 6.8$, $p < 0.05$, ANOVA, main effect; Table 1]. There were no significant effects of $CuSO_4$ injection on emesis in the F2 strain (Fig. 2, 3, and 6).

3.4. F1 and F2 generation responses to isoflurane

High strain F1 animals (n = 4 females plus n = 6 males) tested with isoflurane displayed more total emetic episodes and abdominal contractions than Low strain F1 animals (n = 4 females plus n = 7 males) [$t(19) = 4.3$, $p < 0.04$, t-test, one-tailed, Fig. 7A and Table 2], but no difference in emetic latency (Fig. 7B). High strain F2 shrews showed more total emetic episodes, episodes with a vomit, and a longer emetic duration than Low strain animals [F's$(1,34) \geq 6.9$, p's < 0.05, ANOVA, main effects; $p < 0.05$, Hom-Sidak test; Fig. 7C and Table 2]. High strain F2 females showed a shorter emetic latency compared to Low strain females exposed to isoflurane ($p < 0.05$, Cox regression; Fig. 7D).

4. Discussion

These data show that musk shrews can be successfully bred for emetic sensitivity to motion exposure. Strain differences in motion-induced emesis did not translate into consistent differences in response to nicotine and $CuSO_4$ injections. Ultimately F2 strains showed a largely specific response to motion exposure, with a greater amount of motion-induced emesis in High versus Low group animals. Moreover, as predicted, isoflurane exposure produced more emesis in F1 and F2 High strain offspring compared to Low strain animals.

The significant difference observed in total number of emetic responses to motion exposure in the parental P-split animals was reduced in F1 generation males and females. Larger differential responses to motion exposure returned in the F2 generation. In reference to other measures of emesis (i.e., emetic latency, episodes with and without vomits, duration, and rate in Fig. 6 and Table 1), P-split and F2 animals also displayed more statistically significant categories of emetic responses compared to F1 animals. Notably there was a shorter latency to emesis (1 vs. 4 min), a longer duration (7 vs. 4 min), and a faster rate (2 vs. 1 episodes/min) in High versus Low F2 animals. Relatively few, small, and inconsistent effects were observed between High and Low strain animals injected with nicotine or $CuSO_4$.

Selective breeding for motion-induced emesis also resulted in a greater amount of emetic responses in High versus Low animals exposed to isoflurane in the F1 and F2 generations. It is unknown how inhalational anesthesia produces emesis. Inhalational anesthesia using fluranes (e.g., sevoflurane, isoflurane) produces postoperative nausea and vomiting (PONV), and a longer duration of exposure to these agents is associated with more PONV [37]. Patients are reported to show more dizziness after sevoflurane, which suggests that inhalational anesthesia could affect the vestibular system [38]. The current data support the hypothesis that isoflurane exposure acts on the vestibular system because animals selectively bred for motion-induced emesis also displayed higher levels of isoflurane-induced emesis. The effect of isoflurane on emesis appears to be more difficult to statistically assess in this model because it produces a low level of emesis (i.e., a mean of approximately 6 emetic episodes) compared to motion, nicotine, and $CuSO_4$ conditions, with average responses of greater than 10 emetic episodes.

Based on our current knowledge, this study represents the first time that musk shrews have been specifically bred for motion-induced emesis. Our prior study showed that geographically distinct strains of musk shrews have differential emetic responses to motion exposure, with Taiwan-derived animals displaying more motion-induced emesis than Guam-derived shrews [33]. Other investigators have reported selective breeding of musk shrews for veratrine-induced emesis [39], a plant alkaloid toxin believed to act on the vagus nerve [40, 41]. These veratrine-sensitive animals were also subsequently reported to display differential emetic responses to motion exposure [42, 43]; this would indicate that these high and low response animals have a general sensitivity to emetic activation – independent of the type of emetic input. In contrast, the current study suggests that our High and Low strain musk shrews have specific sensitivity to activation of the vestibular system. The current data demonstrate this difference by testing nicotine and $CuSO_4$ responses, which are indicated to act on the area postrema and vagal afferents, respectively [25-29]. An array of emetic measures were also used, including number of episodes (with and without vomiting), duration, rate, SD-I, and latency (a Cox regression approach) to further define the specific behavioral differences between High and Low strain animals.

The current results suggest that genetic factors play a significant role in emetic sensitivity to motion, and potentially isoflurane exposure. Similarly, a human twin study estimates that motion sickness has a heritability of 57-70% [12], and polymorphisms of the alpha-2-adrenergic receptor are associated with motion sickness in humans [6]. Moreover, human studies show that genetic polymorphisms in neurotransmitter receptors (serotonin type 3, mu-opioid, muscarinic type 3, and dopamine 2) are related to the severity of PONV [44-49]. Musk shrew strains with differential sensitivity to emetic stimuli could potentially serve as a laboratory model to determine the biological mechanisms for differences in the experience of emesis. Future studies could potentially focus on delineating the genetic differences of selectively sensitive musk shrews using DNA and RNA sequencing and bioinformatics.

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Highlights

> Musk shrews were selectively bred (High & Low) for sensitivity to motion-induced emesis

> Isoflurane exposure produced more emesis in High compared to Low strain animals

> Results suggest a common mechanism for motion and inhalational anesthesia-induced emesis

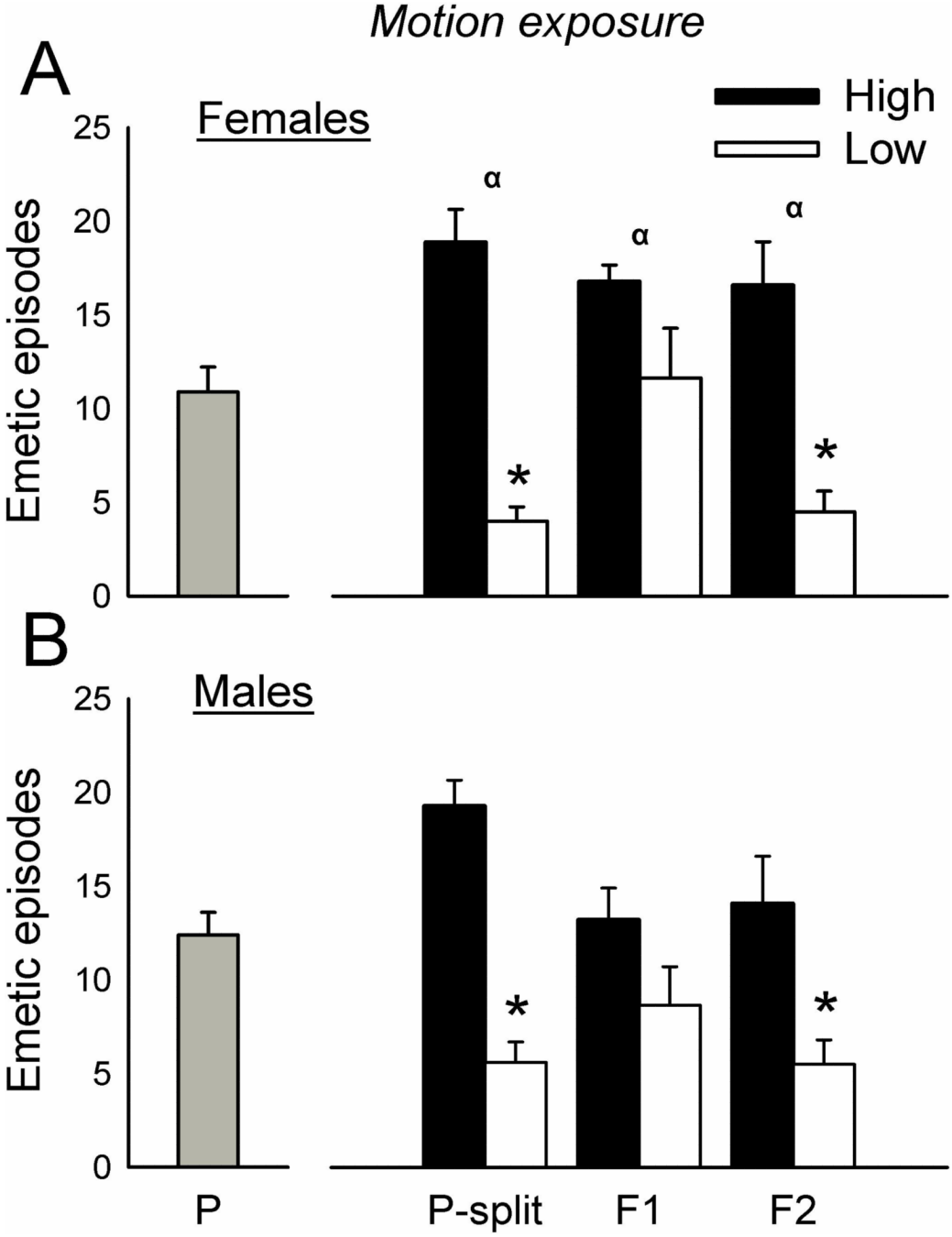

Fig. 1.

Total emetic episodes (with and without a vomit) to motion exposure (10 min, 1 Hz, 4 cm lateral displacement) in the parental (P), upper and lower responders from P (P-split), and two generations of offspring (F1 and F2). The P generation was divided into upper (High) and lower (Low) 1/3 responders for motion-induced emesis (P-split) and then bred. **A)** Females. **B)** Males. * = $p < 0.05$, Hom-Sidak test, High versus Low. $^{\alpha}$ = $p < 0.05$, ANOVA, main effect of strain. Values are mean ± SEM.

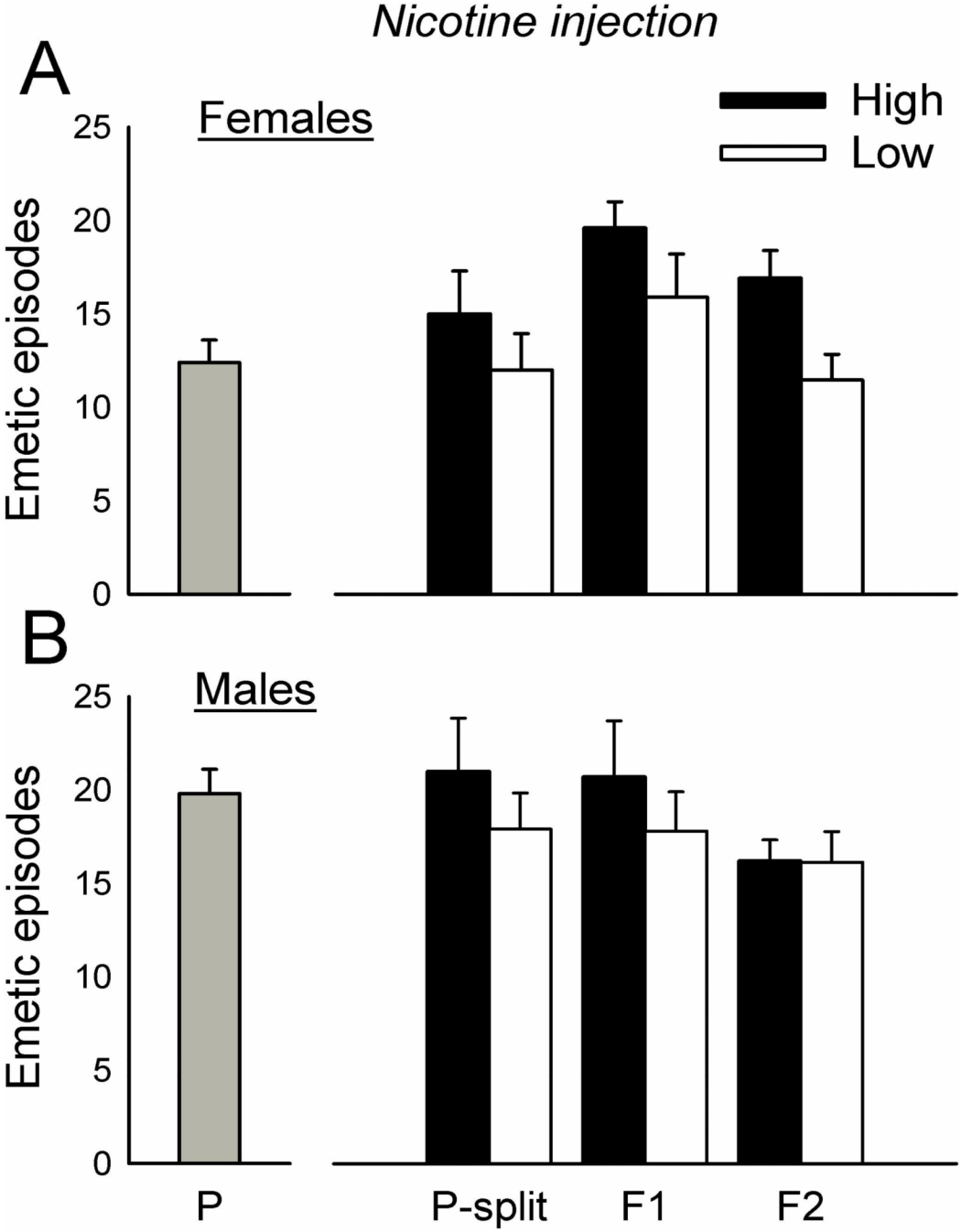

Fig. 2.

Total emetic episodes (with and without a vomit) to nicotine (5 mg/kg, sc) in the parental (P), upper and lower responders from P (P-split), and two generations of offspring (F1 and F2). The P generation was divided into upper (High) and lower (Low) 1/3 responders for motion-induced emesis (P-split) and then bred. **A)** Females. **B)** Males. Values are mean ± SEM.

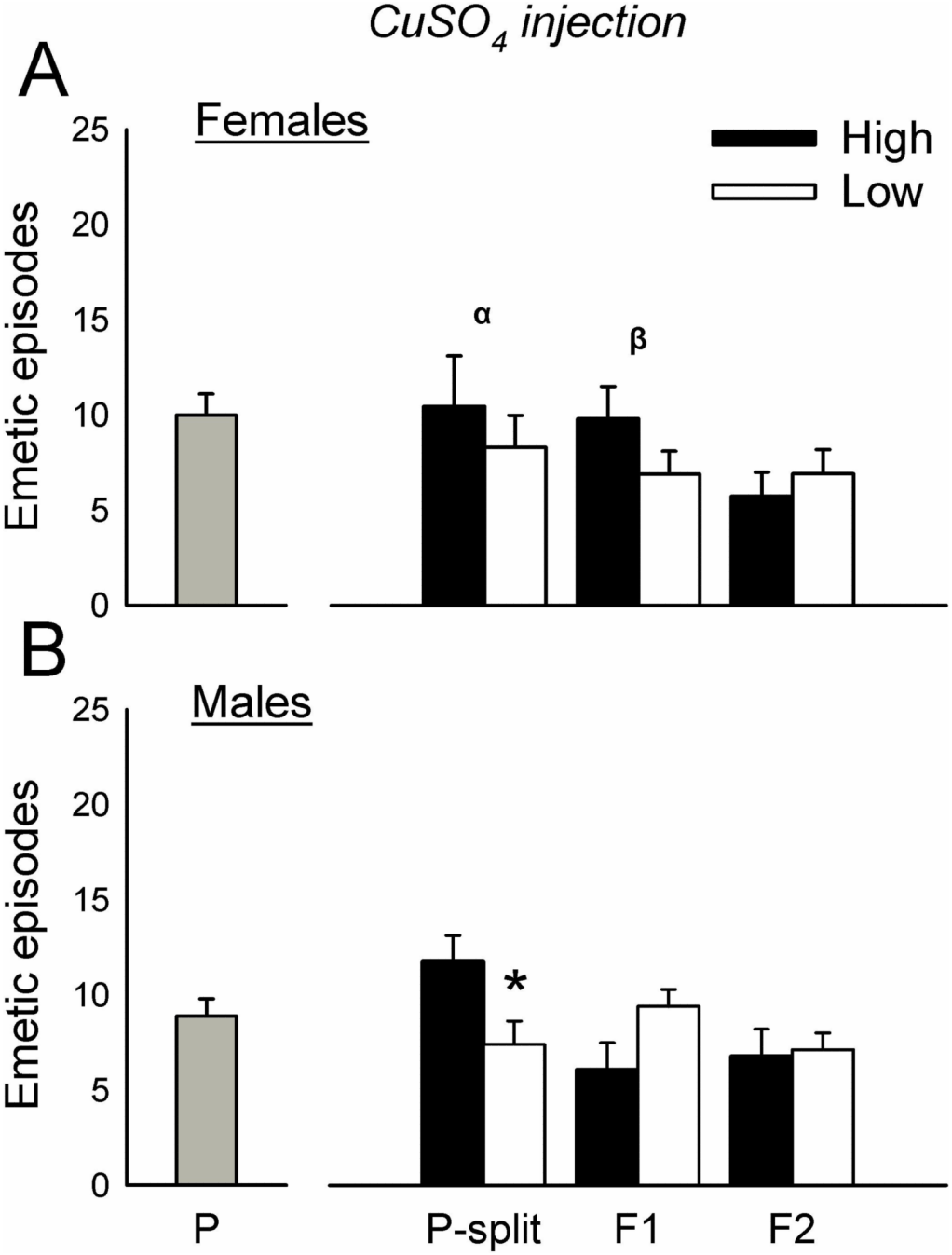

Fig. 3.

Total emetic episodes (with and without a vomit) to $CuSO_4$ (120 mg/kg, ig) in the parental (P), upper and lower responders from P (P-split), and two generations of offspring (F1 and F2). The P generation was divided into upper (High) and lower (Low) 1/3 responders for motion-induced emesis (P-split) and then bred. **A)** Females. **B)** Males. * = $p < 0.05$, Hom-Sidak test, High versus Low. $^{\alpha}$ = $p < 0.05$, ANOVA, main effect of strain. $^{\beta}$ = $p < 0.05$, ANOVA, interaction effect. Values are mean ± SEM.

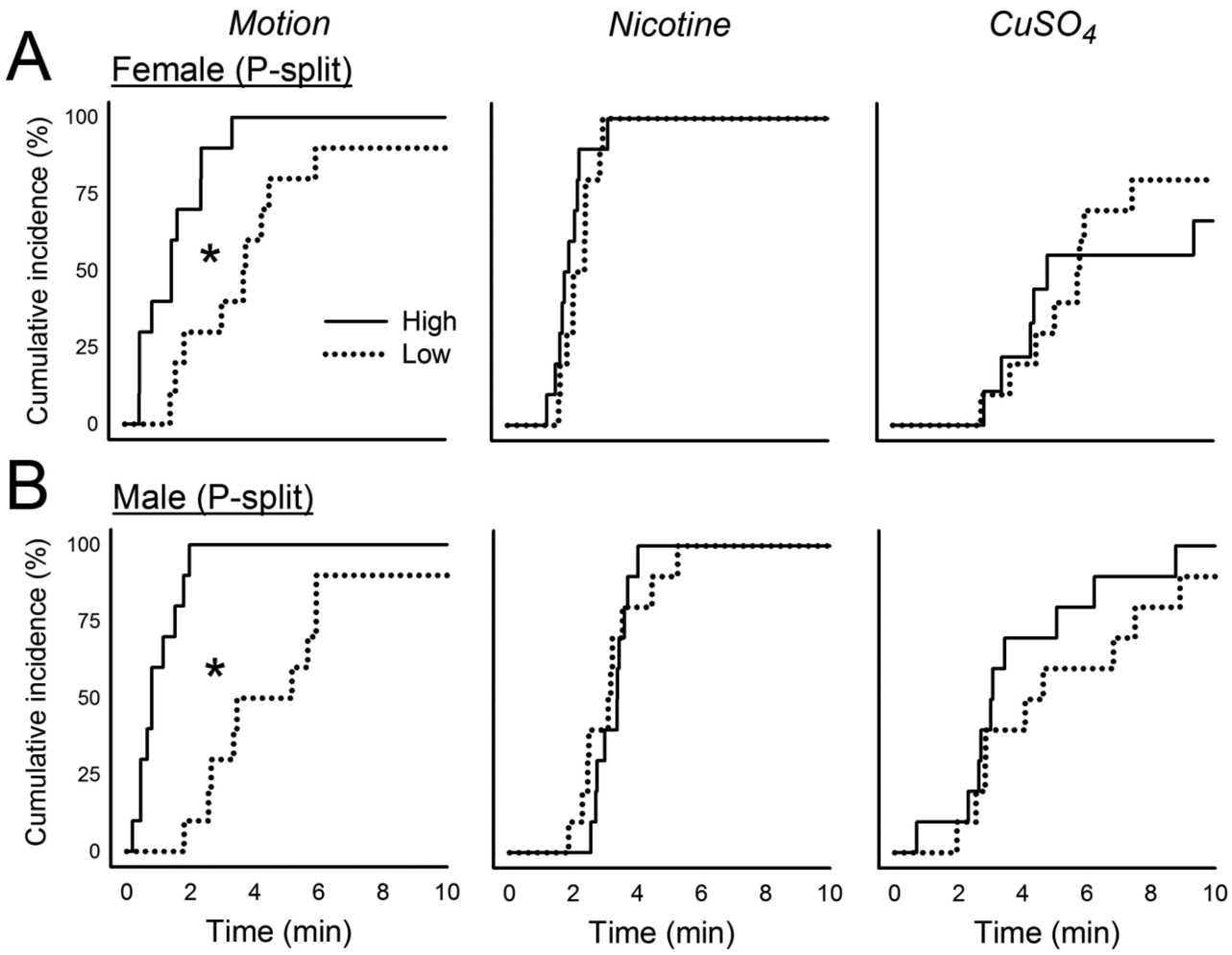

Fig. 4.

Cumulative latency to the first emetic episode after motion exposure (10 min, 1 Hz), nicotine injection (5 mg/kg, sc), or $CuSO_4$ injection (120 mg/kg, ig) in animals divided into upper (High) and lower (Low) 1/3 responders for motion-induced emesis (P-split). **A)** Females. **B)** Males. * $p < 0.05$, Cox regression, High versus Low.

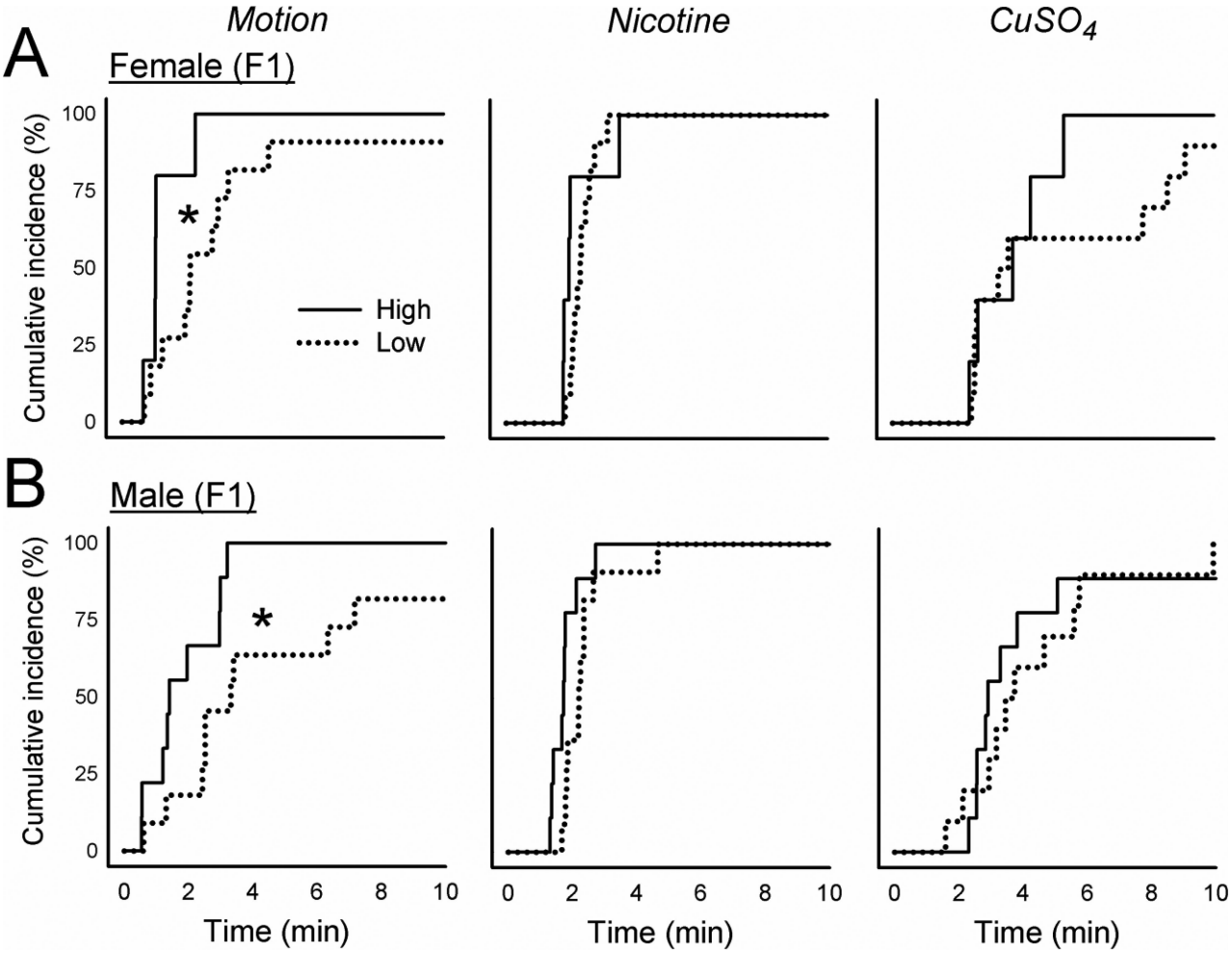

Fig. 5.

Cumulative latency to the first emetic episode after motion exposure (10 min, 1 Hz), nicotine injection (5 mg/kg, sc), or $CuSO_4$ injection (120 mg/kg, ig) in the F1 generation of strains selectively bred for motion-induced emesis. **A)** Females. **B)** Males. * $p < 0.05$, Cox regression, High versus Low.

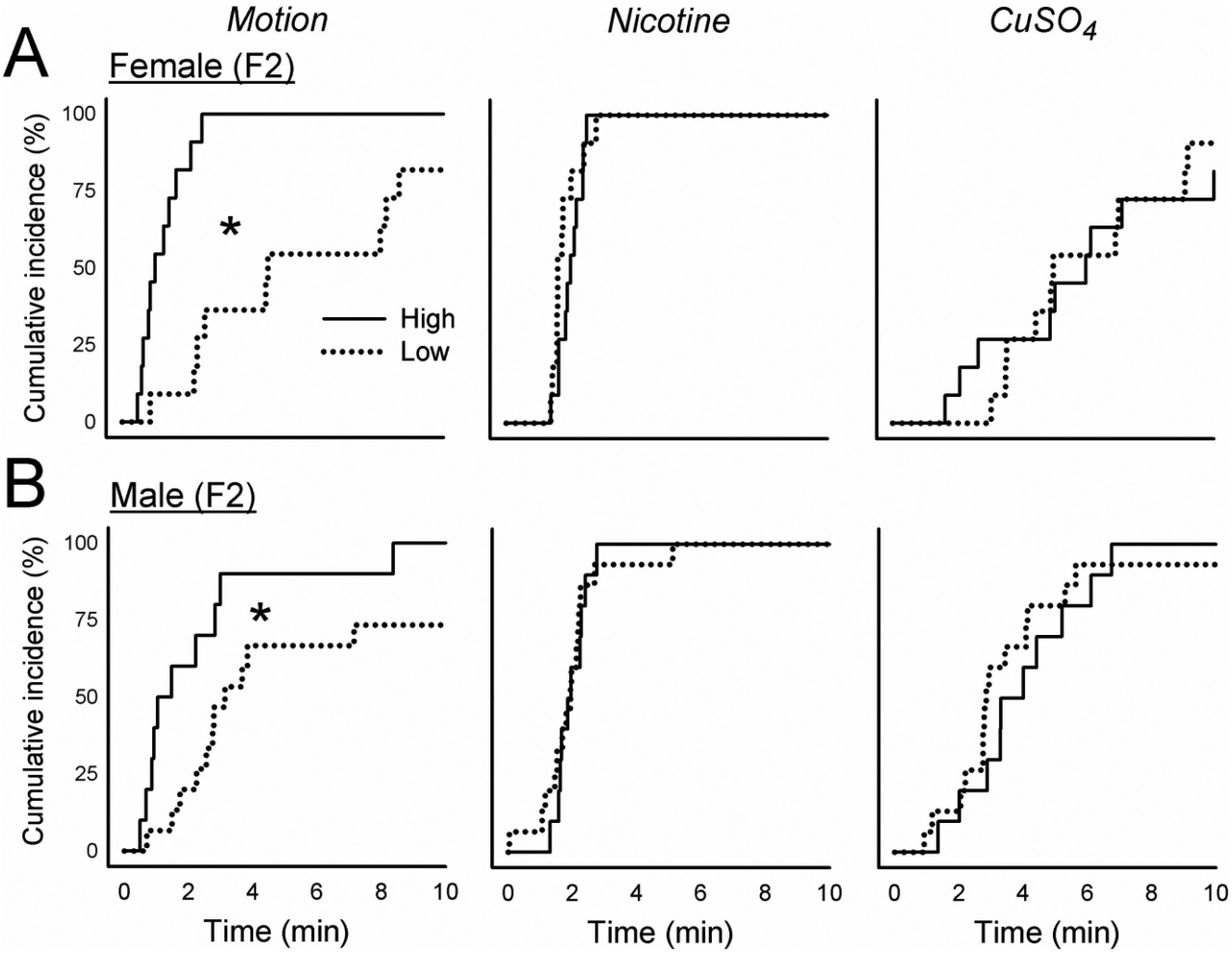

Fig. 6.

Cumulative latency to the first emetic episode after motion exposure (10 min, 1 Hz), nicotine injection (5 mg/kg, sc), or $CuSO_4$ injection (120 mg/kg, ig) in the F2 generation of strains selectively bred for motion-induced emesis. **A)** Females. **B)** Males. * $p < 0.05$, Cox regression, High versus Low.

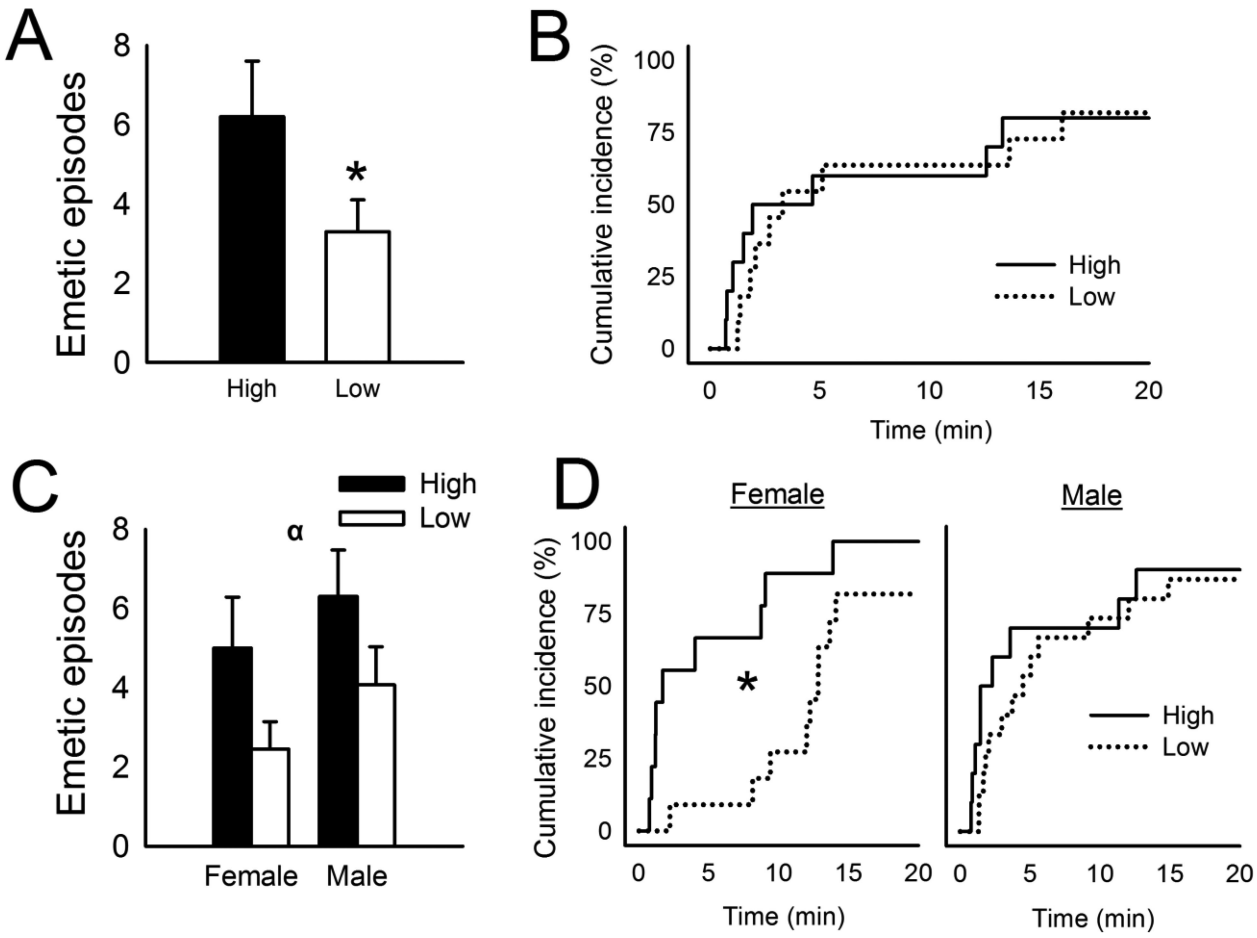

Fig. 7.

Isoflurane-induced emesis in the F1 and F2 generation of musk shrews selectively bred for motion-induced emesis (High and Low response strains). **A)** Total number of emetic episodes to isoflurane exposure (10 min; 3%) in the F1 generation. * = $p < 0.05$, t-test. Values are mean ± SEM. **B)** Cumulative latency to the first emetic episode to isoflurane exposure in the F1 generation. **C)** Total number of emetic episodes to isoflurane exposure (10 min; 3%) in the F2 generation females and males. $^{\alpha}$ = $p < 0.05$, ANOVA, main effect of strain. Values are mean ± SEM. **D)** Cumulative latency to the first emetic episode to isoflurane exposure in the F2 generation females and males. * $p < 0.05$, Cox regression, High versus Low.

Table 1

Emetic responses to Motion, Nicotine, and $CuSO_4$

		Motion					Nicotine					$CuSO_4$			
		Female		Male			Female		Male			Female		Male	
		High	Low	High	Low		High	Low	High	Low		High	Low	High	Low
Episodes with vomit															
P-Split	*a*	**5.2** (±1.3)*	**1.0** (±0.5)	**3.8** (±0.7)*	**1.4** (±0.5)		**1.9** (±0.6) (	**0.8** (±0.5)	**1.2** (±0.4)	**1.7** (±0.6)		**4.4** (±1.3)	**2.1** (±0.7)	**3.5** (±0.8)	**3.5** (±0.3)
F1		**4.4** (±0.7)	**3.5** (±0.8)	**4.7** (±0.9)	**2.7** (±0.8)	*a*	**1.8** (±0.5)	**1.2** (±0.4)	**2.8** (±0.7)*	**0.8** (±0.3)		**3.0** (±1.3)	**3.2** (±0.8)	**2.2** (±0.5)	**4.2** (±0.5)
F2	*a*	**3.9** (±0.7)*	**1.0** (±0.3)	**4.6** (±0.7)*	**1.1** (±0.3)		**1.0** (±0.4)	**1.1** (±0.3)	**1.4** (±0.4)	**1.0** (±0.3)		**2.3** (±0.6)	**2.1** (±0.4)	**2.8** (±0.9)	**2.7** (±0.4)
Episodes w/out vomit															
P-Split	*a*	**13.8** (±1.5)*	**3.0** (±0.6)	**14.0** (±1.7)*	**4.2** (±1.0)		**12.5** (±1.9)	**9.8** (±1.4)	**19.2** (±2.5)	**14.9** (±1.6)	*a*, *β*	**6.0** (±1.6)	**5.5** (±1.3)	**10.9** (±2.2)*	**3.7** (±1.1)
F1		**12.4** (±1.1)	**8.1** (±1.9)	**8.6** (±1.5)	**5.9** (±1.5)		**17.8** (±1.7)	**14.7** (±2.1)	**17.9** (±3.1)	**17.0** (±2.2)	*β*	**6.8** (±0.9)	**3.7** (±0.9)	**3.9** (±1.2)	**5.2** (±0.9)
F2	*a*	**12.7** (±2.2)*	**3.5** (±1.0)	**9.5** (±2.5)*	**4.5** (±1.1)	*β*	**15.9** (±1.5)*	**10.4** (±1.2)	**14.8** (±1.0)	**15.1** (±1.5)		**3.5** (±0.9)	**4.8** (±1.3)	**4.0** (±0.9)	**4.5** (±1.0)
Duration (time from 1st to last episode; min)															
P-Split	*a*	**7.7** (±0.3)*	**4.3** (±0.6)	**7.6** (±0.4)*	**4.6** (±0.4)		**3.7** (±0.8)	**3.7** (±1.0)	**7.6** (±1.8)	**7.8** (±1.5)		**12.0** (±3.8)	**11.1** (±2.9)	**8.9** (±2.2)	**6.4** (±2.7)
F1	*a*	**7.8** (±0.5)	**6.9** (±0.6)	**7.5** (±0.5)*	**5.5** (±0.6)		**6.9** (±1.0)	**5.1** (±0.7)	**8.4** (±1.4)	**8.3** (±1.6)		**11.2** (±1.4)	**11.7** (±1.9)	**8.3** (±3.2)	**11.5** (±3.0)
F2	*a*	**7.3** (±0.5)*	**4.0** (±0.7)	**7.2** (±0.6)	**5.8** (±1.2)		**4.6** (±0.6)	**4.2** (±0.5)	**6.1** (±1.2)	**9.1** (±1.5)		**6.4** (±1.3)	**10.8** (±2.2)	**7.9** (±1.5)	**6.7** (±1.3)
Rate (episodes/min)															
P-Split	*a*	**2.4** (±0.2)*	**1.0** (±0.2)	**2.2** (±0.2)*	**1.3** (±0.2)		**4.3** (±0.5)	**3.2** (±0.4)	**3.3** (±0.5)	**2.5** (±0.4)		**1.6** (±1.5)	**1.5** (±0.6)	**2.8** (±0.9)	**2.6** (±0.8)
F1		**2.1** (±0.2)	**1.6** (±0.3)	**1.6** (±0.2)	**1.7** (±0.3)		**3.1** (±0.5)	**3.0** (±0.3)	**2.7** (±0.4)	**2.7** (±0.4)		**0.8** (±0.2)	**0.7** (±0.1)	**1.9** (±0.6)	**1.4** (±0.4)
F2	*a*	**2.1** (±0.2)*	**1.4** (±0.3)	**1.9** (±0.2)	**1.3** (±0.2)	*a*	**3.6** (±0.2)	**2.6** (±0.3)	**3.5** (±0.6)	**2.5** (±0.4)		**1.9** (±1.1)	**0.6** (±0.1)	**1.0** (±0.4)	**1.6** (±0.3)
SD-I (min)															
P-Split	*a*	**0.5** (±0.1)*	**1.1** (±0.2)	**0.6** (±0.1)	**0.9** (±0.2)		**0.3** (±0.1)	**0.4** (±0.2)	**0.7** (±0.2)	**0.8** (±0.2)		**1.8** (±0.4)	**2.6** (±0.7)	**1.6** (±0.4)	**1.8** (±0.9)

	Motion				Nicotine				$CuSO_4$			
	Female		Male		Female		Male		Female		Male	
	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low
F1	**0.6** (±0.1)	**0.9** (±0.2)	**0.8** (±0.1)	**0.8** (±0.2)	**0.5** (±0.1)	**0.3** (±0.1)	**0.8** (±0.2)	**1.0** (±0.3)	**2.5** (±0.5)	**3.7** (±0.7)	**3.3** (±2.1)	**2.7** (±0.7)
F2	**0.6** (±0.1)	**0.8** (±0.3)	**0.6** (±0.1)	**0.9** (±0.2)	**0.2** (±0.0)	**0.5** (±0.1)	**0.7** (±0.3)	**1.0** (±0.2)	**2.2** (±0.5)	**2.9** (±0.4)	**2.2** (±0.4)	**2.2** (±0.6)

* = $p < 0.05$, Hom-Sidak test, High vs. Low;

α = $p < 0.05$, ANOVA, main effect of strain

β = $p < 0.05$, ANOVA, interaction effect

Table 2

Emetic responses to isoflurane

	F1			F2			
				Female		Male	
	High	Low		High	Low	High	Low
Episodes with vomit	**1.9** (±0.8)	**0.5** (±0.3)	α	**1.8** (±0.7)	**0.8** (±0.3)	**2.4** (±0.5)*	**0.6** (±0.2)
Episodes w/out vomit	**4.3** (±0.9)	**2.7** (±0.7)		**3.2** (±0.9)	**1.6** (±0.5)	**3.9** (±1.0)	**3.5** (±0.9)
Duration (min)	**10.4** (±1.8)	**9.7** (±3.4)	α	**11.1** (±1.2)	**3.7** (±1.2)	**12.3** (±1.5)	**10.3** (±1.0)
Rate (episodes/min)	**0.9** (±0.3)	**0.7** (±0.3)	β	**0.4** (±0.1)*	**1.1** (±0.3)	**0.6** (±0.1)	**0.5** (±0.1)
SD-I (min)	**2.8** (±0.6)	**2.6** (±0.9)		**3.9** (±1.0)	**1.3** (±0.5)	**3.8** (±1.3)	**3.7** (±0.4)
AbCon	**10.3** (±2.6)*	**3.1** (±0.7)		**6.8** (±1.7)	**6.8** (±0.8)	**8.8** (±0.8)	**8.5** (±1.9)

*F1: = $p < 0.05$, t-test, one-tailed, High vs. Low

*F2: = $p < 0.05$, Hom-Sidak test, High vs. Low

α = $p < 0.05$, ANOVA, main effect of strain

β = $p < 0.05$, ANOVA, interaction effect