Sex-related differences in descending norepinephrine and serotonin controls of spinal withdrawal reflex during intramuscular saline induced muscle nociception in rats

Jing Lei a,b, Lin Jin c, Ye Zhao d, Mei-Yu Sui a,e, Li Huang a,e, Yong-Xiang Tan a,e, Yan-Ke Chen a, Hao-Jun You a,e,*

a Center for Biomedical Research on Pain (CBRP), College of Medicine, Xi’an Jiaotong University, Xi’an 710061, PR China
b Center for Sensory-Motor Interaction (SMI), Laboratory for Experimental Pain Research, Aalborg University, Fredrik Bajers Vej 7 D-3, DK-9220 Aalborg, Denmark
c College of Life Science, Northwest University, Xi’an 710069, PR China
d Department of Physiology, College of Medicine, Xi’an Jiaotong University, Xi’an 710061, PR China
e Center for Biomedical Research on Pain (CBRP), College of Medicine, Xi’an Jiaotong University, Xi’an, Shaanxi 710061, PR China. Fax: +86 29 82657041.

E-mail address: yhj@mail.xjtu.edu.cn (H.-J. You).

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A B S T R A C T
Sex-associated differences in the perception and modulation of pain have widely been reported in humans as well as animals. The aim of the present study performed in conscious rats of both sexes was to systematically investigate the role of sex in endogenous descending controls of nociceptive paw withdrawal reflex during experimental muscle pain elicited by intramuscular (i.m.) injection with different doses (0.1–0.4 ml of 0.9–5.8%) of saline. Ipsilateral i.m. injection of 0.2–0.4 ml, but not 0.1 ml, isotonic (0.9%) saline elicited long lasting (about 7 d), secondary and contralateral mechanical hyperalgesia in female rats, whereas male rats exhibited a bilateral, short-term (less than 1 d) mechanical hyperalgesia only during the exposure to 0.4 ml IT saline injection (P<0.05). A bolus of 0.4 ml, but not 0.1–0.2 ml, IT saline significantly induced a one-week, secondary and contralateral heat hypoalgesia in both male and female rats (P<0.05). In contrast to the IT saline injection, 0.1 ml hypertonic (5.8%, HT) saline started to evoke bilateral mechanical hyperalgesia in male and female rats. During the HT saline induced muscle nociception, mechanical hyperalgesia in female rats was greater in magnitude and longer in duration than that of in male rats (P<0.05). Heat hypoalgesia was bilaterally found in male rats receiving either 0.2 ml or 0.4 ml HT IT saline injection, whereas female rats showed heat hypoalgesia, subjected only to the 0.4 ml HT saline injection (P<0.05 and P<0.001). Intrathecal (i.th.) administration of either 6-hydroxydopamine hydrobromide (6-OHDA) or 5,7-dihydroxytryptamine (5,7-DHT) significantly attenuated the HT saline induced heat hypoalgesia, not mechanical hyperalgesia, in male rats. By contrast, in female rats i.th. 6-OHDA markedly blocked heat hypoalgesia, and mechanical hyperalgesia was prevented by 5,7-DHT treatment. It is suggested that i.m. injection of saline dose-dependently elicits ipsilateral secondary and contralateral mechanical hyperalgesia and heat hypoalgesia, which are differently modulated by descending noradrenaline (NA) and serotonin (5-HT) pathways in rats of both sexes. Importantly, the present findings here are not only consistent with our previous study indicating a supraspinal nociception discriminator with different triggering thresholds to govern peripheral A-δ and C-fiber mediated responses (You et al., 2010), but further strengthen this hypothesis that compared with male rats, supraspinal nociception discriminator in female rats exhibits a lower facilitatory threshold and a higher inhibitory threshold. This may bring our attention to better understand why females are commonly reported to be more sensitive and less tolerant to noxious stimulation.

In conclusion, sex-related differences are important in descending modulations of pain and anesthesia. Less noxious stimuli could activate descending inhibition in males but not females, whereas less noxious afferents may elicit descending facilitation in female, but not male rats. Central noradrenergic and serotonergic pathways are differently involved in the action of descending modulations of nociception in rats of both sexes.

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Introduction

More recently, basic and clinical studies have confirmed the presence of sex-associated differences in the perception of pain and its modulation. Compared with men, women tend to exhibit greater
sensitivity, lower pain threshold and tolerance levels to experimental painful stimuli (Berkley, 1997; Fillingim and Maixner, 1995; Weisse et al., 2005). Furthermore, women suffer more frequently from chronic pain conditions such as fibromyalgia and temporomandibular joint dysfunction (Rollman and Lautenbacher, 2001; Unruh, 1996; Wiesenfeld-Hallin, 2005). In addition to human studies, animal experiments revealed sex-related differences in pain or nociception at behavioral systemic level as well as electrophysiological cellular level, i.e. spinal wide-dynamic range neurons activities to noxious stimuli (Tall and Crisp, 2004; You et al., 2006). Using positron emission tomography (PET) and fMRI, gender differences in the central neural processing of pain have been initially revealed (Henderson et al., 2008; Paulson et al., 1998). Thus, different central neurophysiological activities in subjects of both sexes responding to noxious stimuli may importantly contribute to sex-related differences in the perception and modulation of pain. It is also accepted that other endogenous and exogenous factors such as genetic factors (Mogil et al., 2003), sex hormones (Fillingim and Arendt-Nielsen, 2005; You et al., 2010), the rigid von Frey filament provides a sensitive, objective and quantitative mechanical nociceptive test (Vivancos et al., 2004). As elsewhere (You et al., 2010), a volume of 0.1 ml, 0.2 ml and 0.4 ml 5.8% hypertonic (HT) saline was intramuscularly injected into the left gastrocnemius (GS) muscle in male and female rats to establish muscle nociception, respectively. The injection site was located at the middle part of the ipsilateral GS muscle, and the depth of the needle insert into the GS muscle was about 0.5 cm. The injection procedure was performed manually and lasted more than 30 s. As control, a volume of 0.1 ml, 0.2 ml and 0.4 ml 0.9% isotonic (IT) saline was used, respectively.

Materials and methods

Animals

Age-matched male and female Sprague–Dawley rats weighing 250–300 g (10 weeks age) were provided by the Animal Center of College of Medicine, Xi’an Jiaotong University, and housed pairwise with the same sex in plastic boxes under a 12:12-h light dark cycle (lights on at 08:00 AM) at 22–26 °C with food and water available ad libitum. The experiments were approved by the Animal Care and Use Committee of the university. IASP’s guidelines for pain research in conscious animals were strictly followed (Zimmermann, 1983), and all efforts were made to minimize the suffering and reduce the number of animals used. The animals were acclimatized to the laboratory and habituated to the test boxes for at least 1 h each day for 5 d prior to testing. The rats were used only once and sacrificed at the end of the experiment by intraperitoneal injection of an overdose of sodium pentobarbital (200 mg/kg).

Surgery for intrathecal catheterization

Under sodium pentobarbital anesthesia (50 mg/kg b.w.), the intrathecal (i.th.) catheterization was performed using PE-10 polyethylene tubing (OD: 0.5 mm, ID: 0.25 mm). The catheter was passed through a lit cut with a surgical scissor in the spinal arachnoid of T6-7 region, and advanced subarachnoidly to the region of the spinal lumbar enlargement. The length of the intrathecal section of the catheters was around 6 cm, and the total volume of each catheter was less than 4 μl. The outer end of the tubing was firmly fixed to the paravertebral muscles to prevent the inset tubing from moving. The wound was washed with sterile saline, treated with antibiotics, and the muscles and skin were sutured by layers. The whole operation was performed in strictly sterile conditions. After the catheterization, the animals were put back to the box for recovery. The total recovery period after the intrathecal catheterization was 3 d, and animal showing significant signs of motor dysfunction were strictly excluded from the experiments.

Intramuscular injection of saline and other drugs administration

As elsewhere (You et al., 2010), a volume of 0.1 ml, 0.2 ml and 0.4 ml 5.8% hypertonic (HT) saline was intramuscularly injected into the left gastrocnemius (GS) muscle in male and female rats to establish muscle nociception, respectively. The injection site was located at the middle part of the ipsilateral GS muscle, and the depth of the needle insert into the GS muscle was about 0.5 cm. The injection procedure was performed manually and lasted more than 30 s. As control, a volume of 0.1 ml, 0.2 ml and 0.4 ml 0.9% isotonic (IT) saline was used, respectively.

Lth. administration of either 10 μg dose of 6-hydroxydopamine hydrobromide (6-OHDA; Sigma-Aldrich Chemie GmbH, Germany) or 20 μg 5,7-dihydroxytryptamine (5,7-DHT, Sigma-Aldrich Chemie GmbH, Germany) was performed via the intrathecal catheter 4 d prior to the i.m. injection of HT saline. Both neurotoxins were administrated in a volume of 10 μl, and 0.9% NaCl with 0.2 mg/ml ascorbic acid served as vehicle. After the administration of either neurotoxins or vehicle, the catheters were flushed with 5 μl of 0.9% NaCl. All lth. administration process was performed manually within 30 s.

Experimental design

Withdrawal thresholds to mechanical and heat stimulation were measured for both ipsilateral and contralateral hind paws (heel part) 30 min prior to and 5–30 min, 1–4 h, and 1–7 d post the intramuscular injection of 5.8% HT saline. Both male and female rats were randomly divided into different groups; 8–10 rats in each group were randomly arranged for the investigation with different purposes. The detailed experimental design is illustrated in Fig. 1.

Assessment of mechanical withdrawal threshold

Animals were placed in individual Plexiglas chambers with mesh floors and transparent covers (20 × 20 × 25 cm). Responses to mechanical stimulation of hind paw were tested using von Frey filament equipment coupled with a hand-held force transducer (Electrovonfrey, model no: 2290; ITC Inc. Woodland Hills, CA). This electronic meter provides a sensitive, objective and quantitative mechanical nociceptive test (Vivancos et al., 2004). As elsewhere (You and Arendt-Nielsen, 2005; You et al., 2003, 2010), the rigid von Frey filament was applied vertically to the plantar surface of the heel part of the hind paw according to the mapping of the withdrawal field of the GS muscle. The force that elicited a withdrawal of hind paw was recorded following three stimulus presentations at a 2-min interval and the mean values of the three readings were used for data analysis. The filament that elicited a withdrawal response in 50% of trials was...
taken to be the mechanical threshold (\( g \)). A reduced or increased threshold for the withdrawal response compared with the threshold before the HT saline injection was defined as hyperalgesia or hypoalgesia, respectively.

Assessment of paw withdrawal latency to noxious radiant heat stimuli

The rats were tested individually in a Plexiglas cubicle placed onto a constant temperature controlled transparent glass plate used to avoid temperature sink from the tested hind paws. A radiant heat was generated by the IITC plantar test analgesia meter (model no: 390G; IITC Inc. Woodland Hills, CA, USA). The heat stimulus was a high-intensity beam (setting = 30–40% intensity of full power) aimed at the heel part of the hind paw. The withdrawal latency was defined as the time from the onset of noxious heat stimulation to withdrawal of the tested hind paw. The intensity of the beam was adjusted so that the latency of the paw withdrawal reflex was around 10–11 s in untreated animals. A painful, but tolerable, sensation could be elicited using this 10–11-s heat stimulation on the operator’s hand. To avoid excessive tissue injury, manual cut-off of the heat stimulus was performed if no paw withdrawal reflex could be evoked during 20 s of heat stimulation.

Assessment of motor function

Briefly, animals were placed onto a Rota-Rod treadmill (Model 755; IITC, Woodland Hills, CA) rotating at a gradually increasing speed from 5 to 30 rpm for 30 s and maintained for another 120 s at 30 rpm. Rats with motor dysfunction after the chronic i.th. catheterization and the neurotoxic lesion with either 6-OHDA or 5,7-DHT were excluded to the remaining experiments.

Biochemical analyses by high-performance liquid chromatography (HPLC)

As described elsewhere (Tjølsen, 1991; You et al., 2010), using HPLC associated with electrochemical approach (adjusted to 0.7 V versus the Ag/AgCl electrodes) endogenous levels of noradrenaline (NA) and serotonin (5-HT) in the lumbar spinal cord were detected 1, 4 and 7 d after the administration of the two different neurotoxic drugs, respectively. Results were all calculated in nmol/g fresh spinal cord tissue.

Statistic analysis

All results were expressed as means ± SEM. The data were analyzed using SigmaStat™ (Systat Software Inc., California, USA) and compared by means of one-way/two-way repeated measures ANOVA with a post-hoc Bonferroni \( t \)-test for analysis of the differences in the observation time among different groups. \( P < 0.05 \) was considered statistically significant.

Results

Changes of withdrawal reflex elicited by mechanical and heat stimuli during i.m. injection of different doses of saline induced muscle nociception

Bilateral paw withdrawal reflexes to mechanical and heat stimuli were assessed 30 min prior to and 5–30 min, 1–4 h and 1–7 d post the i.m. injection of either 0.9% IT saline or 5.8% HT saline into the left (L.) gastrocnemius (G.) muscle (m.). Solid dark areas on the heel part of the bilateral hind paws represent the stimulation site of mechanical and heat stimuli. Intrathecal (i.th.) application of 6-OHDA and 5,7-DHT was performed 3 d after the i.th. catheter operation and 4 d prior to the i.m. injection of 0.4 ml 5.8% saline. (L: left site; R: right site).
**Fig. 2.** Responses of bilateral paw withdrawal reflexes elicited by mechanical (panel A) and heat (panel B) stimuli before and after the unilateral i.m. injection of 0.1 ml of either 0.9% IT saline (S.) or 5.8% HT saline. *P<0.05 and **P<0.05 compared with the baseline response. #P<0.05 compared with male rats (B: baseline response before i.m. injection of saline; ipsi: ipsilateral; cont.: contralateral).

**Fig. 3.** Responses of bilateral paw withdrawal reflexes elicited by mechanical (panel A) and heat (panel B) stimuli before and after the unilateral i.m. injection of 0.2 ml of either 0.9% IT saline (S.) or 5.8% HT saline. *P<0.05, **P<0.001, and #P<0.05 compared with the baseline response. #&P<0.05 and &&P<0.001 compared with male rats (B: baseline response before the i.m. injection of saline; ipsi: ipsilateral; cont.: contralateral).
No significant changes in heat evoked withdrawal reflex were found after the i.m. injection of 0.1 ml HT saline in rats of both sexes (Fig. 2B).

The i.m. injection of 0.2 ml IT saline did not influence mechanically and heat evoked withdrawal reflexes in male rats, whereas long-term (>7 d) mechanical hyperalgesia was bilaterally found in female rats (P<0.05, Fig. 3A). Following the i.m. injection of 0.2 ml HT saline, long-lasting mechanical hyperalgesia was bilaterally observed in both the male and female rats (P<0.05), while female rats showed more pronounced mechanical hyperalgesia compared with that of in male rats (ipsilateral: F(9, 162) = 2.25, P<0.05; contralateral: F(9, 162) = 2.32, P<0.05, two-way ANOVA, Fig. 3A).

In contrast to no significant changes in paw withdrawal thermal latency subjected to the i.m. injection with 0.2 ml HT saline in female rats (P>0.05), significant prolonged heat evoked paw withdrawal latency (heat hypoalgesia) was found 1 d after the i.m. injection of 0.2 ml HT saline in male rats (P<0.001). The heat evoked paw withdrawal latency increased from 11.5±0.6 s (ipsilateral) and 10.5±0.5 s (contralateral) (baseline response) to 17.4±0.6 s and 17.5±0.7 s, and it lasted for more than 1 week. Significant sex-related differences in heat evoked response after the injection with 0.2 ml HT saline were observed (ipsilateral: F(6, 108) = 22.5, P<0.001; contralateral: F(6, 108) = 23.2, P<0.001, two-way ANOVA) (Fig. 3B).

During the 0.4 ml IT saline i.pl. injected muscle nociception, significant mechanical hyperalgesia was bilaterally observed in male rats as well as in female rats (P<0.05). This mechanical hyperalgesia lasted 7 d over time in female rats, but only around 1 d in male rats (ipsilateral: F(6, 108) = 2.31, P<0.05; contralateral: F(6, 108) = 2.33, P<0.05, two-way ANOVA, Fig. 4A). One day after the i.m. injection of 0.4 ml IT saline, heat hypalgesia was significantly found in both the male and female rats, and gradually returned to the baseline level within 7 d (P<0.05). After the i.m. injection of 0.4 ml HT saline, long lasting (7 d) mechanical hyperalgesia was observed bilaterally in rats regardless of sex (P<0.05). During 0.4 ml HT saline induced muscle nociception, heat hypoalgesia in male rats was greater in magnitude and longer in duration than that of in female rats (P<0.05) (ipsilateral: F(6, 108) = 2.38, P<0.05; contralateral: F(6, 108) = 2.43, P<0.05, two-way ANOVA) (Fig. 4B).
noxious stimuli, i.e. intensity and modality (Fillingim, 2002). Related differences in pain and anesthesia vary, to some extent, across withdrawal responses to noxious stimuli with specific modalities. Compared with male rats, in the current study female rats exhibited mechanical hyperalgesia and heat hypoalgesia exposed to lower dose and higher dose of saline injection, respectively. Thus, one may speculate that the actions of sex hormones at the periphery probably modulating the effects of nerve growth factor (NGF) and protein kinase C (PKC) receptors might be different between males and females in responsible of such sex-associated differences (Kaplan et al., 1991; Dina et al., 2001).

However, the current results are not in line with this notion as no significant differences in mechanically and heat evoked behavioral responses before the i.m. injection of saline were found between male and female rats. Additionally, our previous study showed that exposed to the muscle nociception neither mechanical hyperalgesia nor heat hypoalgesia exists after the kainic acid lesion of RVM (rostroventral medulla) (You et al., 2010). It is suggested that the activities of descending modulations from the supraspinal structures are probably different upon the occurrence of mechanical hyperalgesia and heat hypoalgesia in rats of both sexes.

With regard to the effects of estrous cycle on pain/nociception, the contradictory results were reported. In contrast to no variation in thermal pain tolerance and mechanical pain threshold observed in relation to estrous cycle in mice (Sanoja and Cervero, 2008), others showed that the estrus cycles might significantly affect behavioral responses to noxious stimuli (Frye et al., 1993; Kayser et al., 1996). Using vaginal smears approach, it is accepted that the estrus cycle in rats is a short-term, 4–5-day period containing cycle phases (Maeda et al., 2000). According to the present experimental protocol, our study was continuously performed throughout 1–2 weeks for the investigation of early onset mechanical hyperalgesia and late occurrence of heat hypoalgesia. Thus, the precise analysis of influence of estrous cycle on i.m. administration of different doses of saline induced muscle nociception was impossible and not taken into consideration.

**Discussion**

The present study demonstrated a sex-related difference in endogenous descending modulations: facilitation and inhibition, of mechanically and heat evoked nociceptive withdrawal reflex during the i.m. saline induced experimental muscle nociception. I.m. injection of saline dose-dependently elicits secondary/contralateral mechanical hyperalgesia and heat hypoalgesia, which are differently modulated by descending NA and 5-HT pathways, in rats of both sexes.

**Sex differences in noxious mechanically and heat evoked withdrawal reflexes following i.m. saline induced muscle nociception**

It is widely accepted that magnitude and significance of sex-related difference in pain and anesthesia vary, to some extent, across noxious stimuli, i.e. intensity and modality (Fillingim, 2002). Pronounced sex differences in pain could be observed during the exposure to electrical and pressure stimuli rather than heat stimuli (Riley et al., 1998). The present study reports a significant role of sex-related different modulations on both mechanically and heat evoked withdrawal reflexes during the i.m. saline induced muscle nociception. The onset and magnitude of the occurrence of mechanical hyperalgesia and heat hypoalgesia were different across the entire investigation in rats of both sexes. Similarly sex-related differences in pain modulation between men and women were also found in other study exhibiting heat stimuli inhibit wind-up (temporal summation) of second pain only in healthy men but not in women (Staud et al., 2003). It is thus suggested that sex difference in pain and its endogenous modulation among females relative to males are not restricted only in response to noxious stimuli with specific modalities.

In the present study, the ipsilateral (secondary) and contralateral mechanical hyperalgesia and heat hypoalgesia occurred differently following the IT or HT saline intramuscularly induced muscle nociception. Interestingly, unilateral i.m. injection with 0.2–0.4 ml IT saline brought the fact of the bilateral mechanical hyperalgesia in female and male rats respectively. This is consistent with others showing that contraalateral mechanical hyperalgesia evoked by repeated, but not single, unilateral subcutaneous injection of 0.15 ml IT saline in ipsilateral hind paw (Levine et al., 1985). Growing evidence shows the involvement of central components in the contralateral hypersensitization (Audette et al., 2004; Owen et al., 2010; Sluka et al., 2001). Of particular importance, we also observed a long lasting mechanical hyperalgesia and heat hypoalgesia from forepaws during muscle nociception occurred in the ipsilateral hind paw, showing diffused descending facilitatory and inhibitory modulations (You et al., 2010). Thus, supraspinal, but not peripheral and spinal, actions are predominantly involved in the phenomena of the bilateral behavioral hyper- or hypoactivities in rats of different sexes.

![Supraspinal nociception discriminator and its contribution on spinally-organized nociception in rats of both sexes](image-url)
It has been demonstrated that the supraspinal structures may function to discriminate between afferent noxious inputs mediated by A-β and C fibers, either facilitating A-β fiber mediated responses or inhibiting C-fiber mediated activities (Lumb, 2002; McMullan and Lumb, 2006; You et al., 2010). Due to the early onset of mechanical hyperalgesia and the late occurrence of heat hypoalgesia during the muscle nociception, the data from our serial studies suggest that supraspinal discriminator has different triggering thresholds that determine its actions: a lower threshold for the facilitation of A-β fiber mediated responses and a higher threshold for the induction of descending inhibition of C-fiber mediated activities. The most important finding from the current study is that the lower doses of saline elicited bilateral mechanical hyperalgesia in female, but not male, rats. In contrast, the heat hypoalgesia in female rats tended to be evoked by the i.m. injection of higher doses of saline. These findings expand our previous observations (You et al., 2010), and further suggest that between male and female rats the supraspinal nociception discriminator may have different triggering thresholds in initiating facilitatory or inhibitory effects. The triggering threshold for descending facilitation in male rats is supposed to be higher than that of in female rats, whereas the triggering threshold for descending inhibition in male rats is probably lower than that of in females (Fig. 7). Future studies on this relation of different triggering thresholds between descending facilitation and inhibition among males and females may open a new window and extend our better understanding of the reason of sex-associated differences in experimental and clinical pain and anesthesia.

**Sex-related difference of NA and 5-HT in descending control of pain**

In the present study, after the neurotoxic lesion with 6-OHDA, i.m. injection of 0.4 ml HT saline failed to elicit any significant changes in heat evoked paw withdrawal latency, whereas mechanical hyperalgesia was not significantly influenced in rats of both sexes throughout the observation period. This result is in line with others (Sagen et al., 1983; Tjalsen et al., 1991), showing that endogenous NA is involved in the descending inhibitory control of pain in rats regardless of sex.

Interestingly, the i.t. pretreatment with 5,7-DHT either prevented the occurrence of heat hypoalgesia in male rats, or blocked the mechanical hyperalgesia in female rats. Evidence suggests that the spinal 5-HT system concerning receptor expression and distribution, and innervation, are different in male and female rats (Kojima and Sano, 1984; Zhang et al., 1997; Fonseca et al., 2001). Thus, one may propose that the different effects of i.t. treatment with 5,7-DHT on mechanical hyperalgesia and heat hypoalgesia might be related to the difference of spinal 5-HT system in male and female rats. However, the current study does not support this notion as male and female rats neither differed in terms of spinal 5-HT level, nor did they show different spinal 5-HT depletions due to the i.t. 5,7-DHT treatment. The data thus suggest a sex-associated difference of descending 5-HT facilitatory/inhibitory actions on spinally-organized nociception.

**Conclusion**

A significant sex-related difference in ipsilateral secondary and contralateral mechanical hyperalgesia and heat hypoalgesia in muscle nociception was found. We hypothesize here that the triggering thresholds of endogenous descending facilitation and inhibition may be different among males and females. Furthermore, descending NA and 5-HT pathways differently participated in mechanical hyperalgesia and heat hypoalgesia governed by descending modulation in male and female rats.

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Fig. 7. Schematic drawing of the descending modulation (M.) from supraspinal nociception discriminator with different triggering thresholds showing either facilitatory or inhibitory actions on spinally-organized nociception in rats of both sexes. Involvement of different neurotransmitters is also summarized. “+” represents enhance. “−” represents inhibit. “?” represents uncertainty.


