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Evidence that the NH_2-terminus of substance P modulates *N*-methyl-D-aspartate-induced activity by an action involving σ receptors

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Abstract

Behaviors induced in mice by intrathecal injections of either *N*-methyl-D-aspartate (NMDA) or kainic acid are modulated by NH_2-terminal fragments of substance P, such as substance P-(1–7). The action of substance P-(1–7) on kainic acid depends on σ receptor activity. The present study was designed to test the hypothesis that σ receptor activity is also necessary for modulation of NMDA by substance P-(1–7). Intrathecal injection of mice with NMDA results in a brief burst of biting and scratching behaviors which decrease in intensity when NMDA is injected repeatedly at 2 min intervals. Pretreatment with 1,3-di-*O*-tolylguanidine (DTG), a ligand at both σ_1 and σ_2 sites, converted NMDA-induced desensitization to sensitization, thereby enhancing tonic NMDA receptor activity. Although haloperidol (30 min) alone was without effect, the potentiation of NMDA-induced activity by DTG was abolished by haloperidol but unaffected by an equimolar dose of either spiperone or thiothixine, two dopamine receptor antagonists. When mice received substance P-(1–7), NMDA-induced behaviors were initially inhibited but then potentiated. Pretreatment with haloperidol prevented both inhibitory and potentiative effects of substance P-(1–7) whereas thiothixine did not, suggesting inhibitory as well as potentiative modulation of NMDA by σ receptor activity. Endogenous σ_1 receptor activity may enhance NMDA receptor activity as a treatment regimen that down-regulates σ_1 binding also inhibited responses to NMDA. In contrast, pretreatment with haloperidol just 5 min prior to challenge, which blocks both σ_1 and σ_2 receptor activity, increased responses to NMDA suggesting an inhibitory effect of σ_2 receptor activity. In summary, modulation of NMDA by substance P-(1–7) appears to depend on activity at σ sites as substance P-(1–7) mimicked the potentiative effects of DTG, while haloperidol inhibited the effects of both DTG and substance P-(1–7).

Keywords: Spinal cord, mouse; DTG (1,3-di(2-tolyl)guanidine); Haloperidol

1. Introduction

Despite much research in recent years, the function of the σ receptor remains largely unknown and the endogenous σ receptor ligand unidentified (Quirion et al., 1984). Originally thought to be an opiate receptor (Martin et al., 1976), and later to be the same structure as the phencyclidine (PCP) receptor (Zukin and Zukin, 1983), it is now believed that PCP and σ receptors are two distinct entities (Largent et al., 1986), and multiple σ receptor subtypes appear to exist (Walker et al., 1988; Quirion et al., 1992).

The results of recent electrophysiologic studies suggest a functional relationship between the σ receptor and activity at the *N*-methyl-D-aspartic acid (NMDA) subtype of excitatory amino acid receptor. For example, the high-affinity σ ligand 1,3-di-*O*-tolylguanidine (DTG) (Weber et al., 1986) potentiates the excitatory effect of NMDA in the rat hippocampus (Monnet et al., 1990). This potentiation can be reversed by haloperidol, suggesting that DTG-like compounds are σ receptor agonists while haloperidol-like compounds are σ receptor antagonists.

The excitatory amino acids, glutamate and aspartate, are well known neurotransmitters in the dorsal horn of the spinal cord (Salt and Hill, 1983; Besson and Chaouch, 1987; Schneider and Perl, 1988) where they appear to play a critical role in the transmission of nociceptive information (Wanaka et al., 1987; DeBiasi and Rustioni, 1988; Tracey et al., 1991). Intrathecal injection of excitatory amino acid receptor agonists produce a stereotypical, caudally directed biting and scratching behavior in mice (Hyl-

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den and Wilcox, 1983; Aanonsen and Wilcox, 1986). This response provides a reproducible and easily quantifiable means for monitoring the actions of excitatory amino acids at these receptor populations in the spinal cord.

Repeated administration of NMDA leads to a decrease in the intensity of caudally directed biting and scratching behaviors, a phenomenon which we refer to herein as behavioral desensitization (Sun and Larson, 1991). Biting and scratching behaviors induced in mice by a single intrathecal injection of NMDA have been reported to be unaffected when coinjected with σ ligands (Delander and Wahl, 1989). However, our preliminary data indicated that σ ligands can increase as well as decrease behaviors induced by NMDA (Hornfeldt and Larson, 1991) depending on the time of injection and prior exposure to NMDA. In a fashion similar to that of DTG, substance P-(1–7), a commonly occurring NH_2-terminal metabolic fragment of substance P, initially inhibits and then enhances the intensity of behaviors induced by repeated injections of NMDA (Hornfeldt et al., 1994). Substance P-(1–7) thus changes NMDA-induced behavioral desensitization to sensitization. These effects appear to be dependent upon the activation state of the NMDA receptor and occur via novel, non-neurokinin activity (Igwe et al., 1990c). In a similar fashion, when drugs are applied iontophoretically to single nociceptive-sensitive neurons in the rat spinal cord, substance P-(1–7) inhibits and then potentiates NMDA-induced depolarizations in electrophysiological studies of single cell recordings (Budai et al., 1992).

Using the behavioral approach described above, we have previously shown that caudally directed biting and scratching behaviors induced in mice by the intrathecal injection of kainic acid, a non-NMDA excitatory amino acid agonist, is potentiated by pretreatment with DTG (Larson and Sun, 1993). This potentiation is prevented by pretreatment with haloperidol but not with spiperone, a structurally similar butyrophenone that antagonizes dopamine receptors but lacks σ receptor activity. Substance P-(1–7) mimics the ability of DTG to potentiate kainic acid-induced activity in the mouse spinal cord (Larson and Sun, 1993). Like DTG, the effect of substance P-(1–7) is blocked by haloperidol, but not spiperone, implicating a σ receptor in the mediation of substance P-(1–7)-induced activity. In view of the high concentration of substance P-(1–7) necessary to compete for [^{3}H]DTG binding in the mouse spinal cord (k_i = 24 μM) (Mousseau and Larson, 1994), it is unlikely that substance P-(1–7) interacts directly with σ sites, but may activate them indirectly, perhaps by promoting the release of another neuroactive compound.

As σ ligands have been shown to modulate NMDA activity in other areas of the CNS (Walker et al., 1988), we hypothesized that the modulatory effect of substance P-(1–7) on NMDA-induced activity in the mouse spinal cord might similarly involve σ receptor activity. Such an effect would be redundant with the modulation of non-NMDA receptor activity in the spinal cord by substance P-(1–7) via a σ-sensitive pathway. The following experiments were conducted to compare the effects of the σ receptor ligand, DTG, to those of substance P-(1–7) on NMDA-induced activity in the mouse spinal cord and to determine whether the effects of both substance P-(1–7) and DTG are selectively sensitive to haloperidol compared to selective dopamine receptor antagonists, such as spiperone and thiothixine, consistent with the activity of σ receptors. Based on the possible involvement of both substance P and NMDA-type activity in pain transmission at the spinal cord level, clarification of the mechanism underlying the ability of substance P NH_2-terminal metabolites to modulate NMDA activity in vivo would be an important step in our understanding of pain transmission.

2. Materials and methods

2.1. Animals

Male Swiss-Webster mice, 20–25 g (Sasco, Omaha, NE) were housed four per cage and allowed to acclimate with free access to food and water for at least 24 h prior to experiments. Animals were used in accordance with guidelines of the University of Minnesota Animal Care and Use Committee and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW publication (NIH) 78-23, revised 1978).

2.2. Drugs and chemicals

All drugs were administered by intrathecal injection unless otherwise indicated. Intrathecal injections were made at approximately the L5-L6 intervertebral space using a 0.5 in, 30 gauge disposable needle mounted on a 50 μl Luer-tip syringe (Hamilton, Reno, NV). For all injections, drugs were dissolved in 0.85% saline and delivered in 5 μl volumes.

N-Methyl-D-aspartate (NMDA), haloperidol, spiperone and (±)-pentazocine were purchased from Sigma Chemical Co. (St. Louis, MO); 1,3-di-*O*-tolylguanidine (DTG), and thiothixine were obtained from Research Biochemicals (Natick, MA) and substance P-(1–7) was purchased from Peninsula Laboratories (Belmont, CA).

The doses of DTG and substance P-(1–7) were chosen based on the ability of these drugs, when injected intrathecally in mice, to influence the behavioral response to an intrathecal injection of kainic acid (Larson and Sun, 1993). Substance P-(1–7) produces two effects on NMDA-induced behaviors (Hornfeldt et al., 1994) depending on the time of administration. For this reason, substance P-(1–7) was injected with the first injection of NMDA, a time that reveals both the inhibitory as well as the potentiative effect of substance P-(1–7) on NMDA-induced activity. The

effects of DTG, on the other hand, were found to be predominantly potentiative regardless of the time of administration. DTG was, therefore, administered at a time that appeared to elicit its optimal effects. The dose of haloperidol was chosen based on its ability to inhibit the action of DTG on kainic acid-induced activity in the mouse spinal cord (Larson and Sun, 1993).

2.3. Behavioral testing

Mice were injected with 0.2 nmol of NMDA and placed in a large glass cylinder containing 2 cm of bedding. The total number of caudally directed biting and scratching behaviors occurring over the subsequent 2 min interval were counted. Each bite or scratch was counted as a single behavior. During episodes of continuous biting or scratching behavior, each second of continuous biting or scratching was counted as a single behavior. Mice were then reinjected with 0.2 nmol of NMDA and behaviors similarly recorded for a total of three to four injections. This dose of NMDA used was chosen as a single injection of this dose reliably produced the same number of biting and scratching behaviors that were of a magnitude that readily permitted measurement of inhibition or potentiation of behaviors. Repeated injections of vehicle failed to produce biting and scratching behaviors and had no effect on the animals normal exploratory behavior. Pretreatment with vehicle alone produced no effect on subsequent NMDA-induced behaviors.

2.4. Statistical analysis

Statistical analysis of data was performed using Student's t test for unpaired data for single comparisons of first and fourth injections of NMDA. Analysis of variance (ANOVA) was used for multiple comparisons between treatment groups. A level of significance was established at $P < 0.05$.

3. Results

Four intrathecal injections of mice with 0.2 nmol of NMDA at 2 min intervals resulted in a gradual decrease in the intensity of caudally directed biting and scratching behaviors evoked by each of four injections (Fig. 1A), as previously described (Sun and Larson, 1991). When animals were pretreated with a bolus of DTG (5 nmol) at 30 min (Fig. 1) prior to the first injection of NMDA, no change occurred in the intensity of behaviors following the first injection of NMDA. However, DTG pretreatment converted NMDA-induced behavioral desensitization to sensitization, as indicated by an increased number of behaviors in response to the latter of four injections of NMDA (Fig. 1).

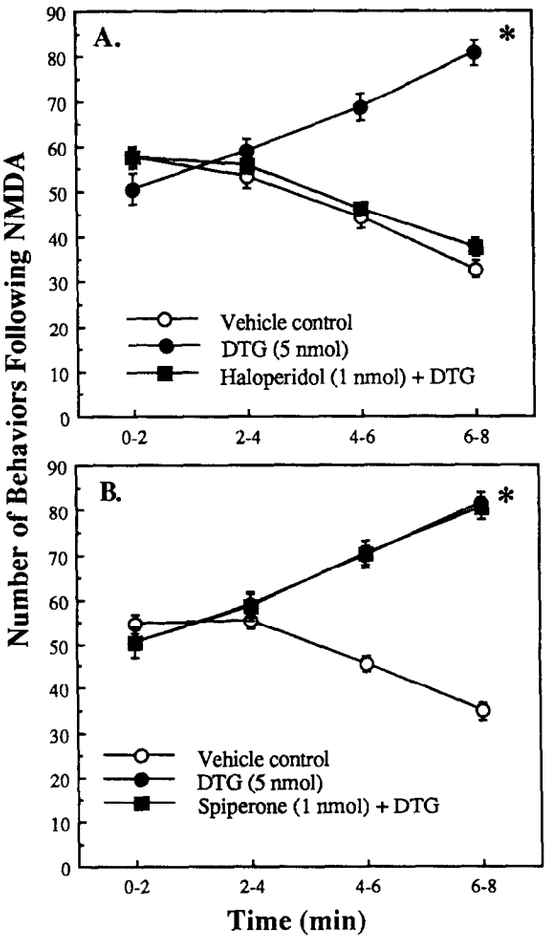

Fig. 1. The effect of DTG on NMDA-induced activity. Throughout the figures, each point represents the mean ± S.E. intensity of caudally directed biting and scratching behaviors evoked by each of four intrathecal injections of 0.2 nmol of NMDA at 2 min intervals in groups of at least six mice. Statistically significant differences are indicated by * when $P < 0.05$ using the Student's unpaired two-tailed t test. A: DTG (5 nmol) was injected intrathecally 5 min prior to the first injection of NMDA. Haloperidol (1 nmol), injected 30 min prior to NMDA, did not alter the response to NMDA (data not shown) but completely reversed the effect of DTG. B: Spiperone (1 nmol) alone had no effect on NMDA activity (data not shown) and pretreatment with spiperone 30 min prior to NMDA had no effect on DTG-induced facilitation of NMDA activity, resulting in data that are superimposed with those following treatment with DTG only.

Pretreatment with haloperidol (1 nmol) 30 min prior to NMDA had no effect on the number of NMDA-induced behaviors, however haloperidol abolished the potentiative effect of DTG (Fig. 1A). Spiperone, like haloperidol, is a butyrophenone with a similar spectrum of dopamine antagonistic actions as haloperidol but lacks an affinity for σ sites. Pretreatment with spiperone (1 nmol) 30 min prior to administration of DTG, had no effect on NMDA-induced behaviors and failed to reverse the facilitation of NMDA receptor activity brought about by pretreatment with DTG (Fig. 1B). An equivalent dose of thiothixine, a dopamine antagonist that is structurally unrelated to spiperone, also

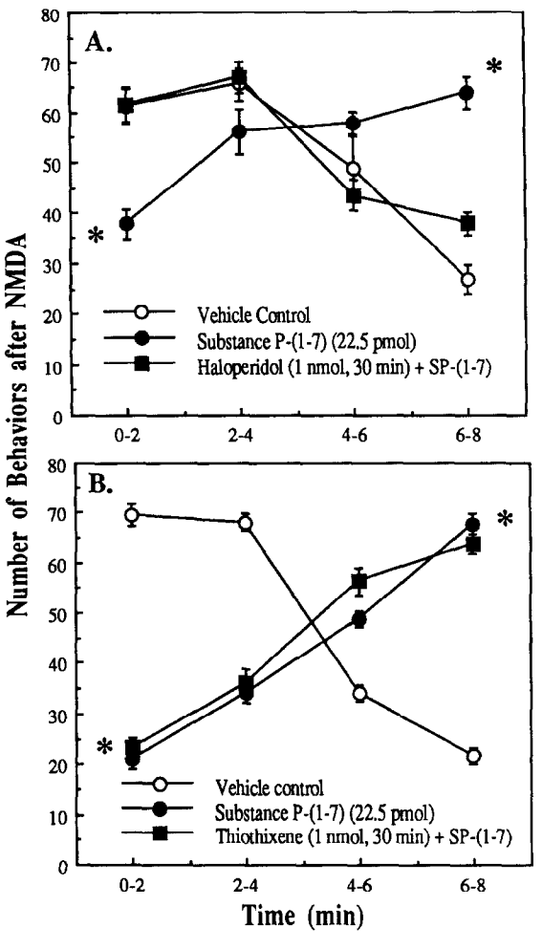

Fig. 2. The effect of substance P-(1–7) on NMDA activity. A: Mice received the first injection of NMDA (0.2 nmol) coadministered with 22.5 pmol of the substance P metabolite, substance P-(1–7). Pretreatment with haloperidol (1 nmol), 30 min prior to NMDA plus substance P-(1–7), resulted in reversal of both the inhibitory and potentiative effects of substance P-(1–7). B: Unlike haloperidol, pretreatment with the relatively selective dopamine receptor antagonist thiothixine (1 nmol), 30 min prior to NMDA plus substance P-(1–7), failed to reverse either the inhibitory or potentiative effects of substance P-(1–7). Details as in Fig. 1.

failed to alter this effect of DTG on NMDA receptor activity (data not shown).

When mice received the substance P NH_2-terminal heptapeptide, substance P-(1–7) (22.5 pmol), coadministered with the first injection of NMDA, the number of behaviors were initially attenuated followed by an increase in behaviors in response to subsequent injections of NMDA (Fig. 2A), reversing NMDA desensitization to sensitization in a fashion similar to the effect of DTG. To determine if these effects of substance P-(1–7) were mediated via an action involving a σ receptor, mice were pretreated with haloperidol (1 nmol) 30 min prior to receiving NMDA and substance P-(1–7). Haloperidol prevented both the inhibitory and potentiative effects of substance P-(1–7) on NMDA (Fig. 2A). An identical pretreatment schedule with an equimolar dose of the dopamine antagonist thiothixene failed to affect either the inhibitory or potentiative action of substance P-(1–7) on NMDA-induced behaviors (Fig. 2B).

The ability of haloperidol to reverse both the inhibitory as well as the potentiative effects of substance P-(1–7) on NMDA suggested two modulatory effects of this compound, both of which appear to be mediated by haloperidol-sensitive, σ receptor populations. To explore the possibility of a dual regulation of NMDA by two distinct populations of σ receptors, we used treatments that have been reported to differentiate between σ_1 and σ_2 sites (Reynolds et al., 1983). Chronic exposure to haloperidol for 7 days has been reported to down-regulate σ_1 to a greater degree than σ_2 binding sites as indicated by a decreased B_{max} for [^{3}H](+)-pentazocine binding in the absence of an effect on the B_{max} of [^{3}H]DTG binding

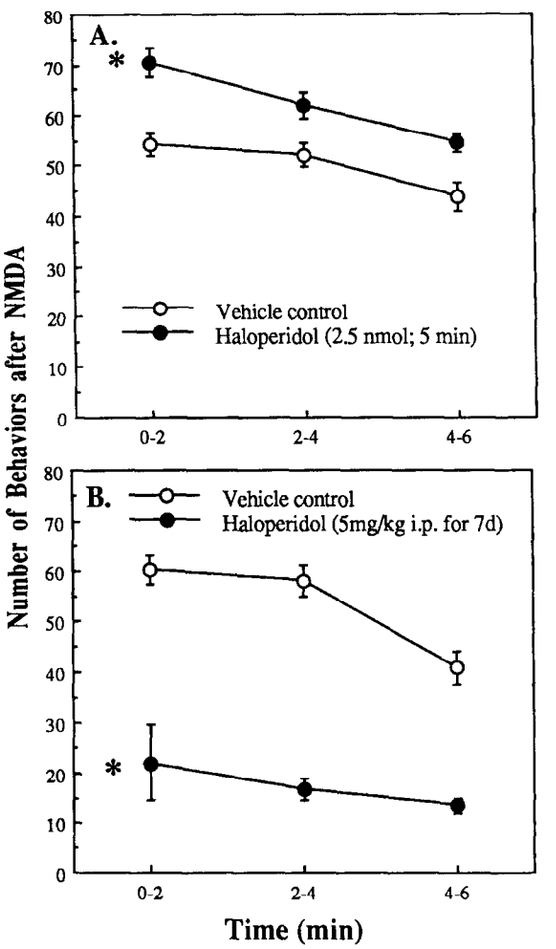

Fig. 3. The effect of haloperidol on NMDA activity. A: Pretreatment with haloperidol intrathecally (2.5 nmol) 5 min prior to the first injection of NMDA resulted in a significant potentiation of biting and scratching behaviors. B: Mice were pretreated with haloperidol (5 mg/kg i.p.) once daily for 1 week, a schedule that has been shown to inhibit σ_1 ligand binding density (see text). The last injection was given 24 h prior to challenge with NMDA.

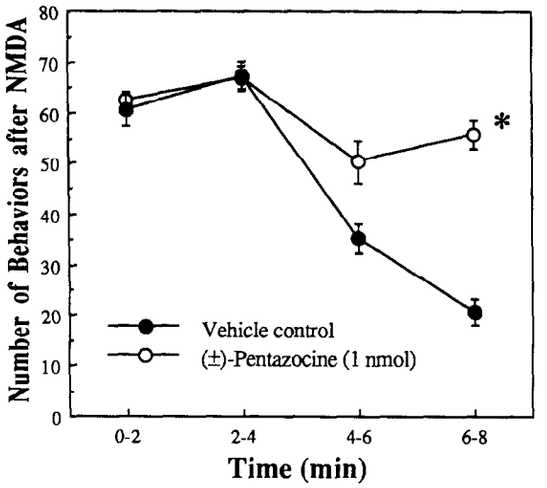

Fig. 4. Effect of (±)-pentazocine on NMDA behaviors. Pretreatment with (±)-pentazocine (1 nmol) had no effect on the behaviors produced 30 min later by the first injection of NMDA (0.2 nmol) but significantly inhibited desensitization to the behavioral response to latter injections of NMDA. Details as in Fig. 1A.

(Reynolds et al., 1983). Mice were thus pretreated with intraperitoneal injections of haloperidol (5 mg/kg) daily for 1 week prior to challenge with NMDA to determine whether a σ_1 receptor population is necessary for the modulation of NMDA receptor activity. 24 h after the last injection of haloperidol, there was a significant inhibition of behaviors in response to the injection of NMDA compared to vehicle-injected control mice (Fig. 3B). Treatment of haloperidol pretreated mice with substance P-(1–7) failed to alter the response to NMDA (data not shown). In contrast, 24 h after a single injection of haloperidol (5 mg/kg intraperitoneally) or 30 min after a single injection of haloperidol (1 nmol; intrathecally) there was no effect on the number of NMDA-induced behaviors and the modulatory effect of substance P-(1–7) was no different than that shown in Fig. 2A. When administered at a dose of 2.5 nmol just 5 min prior to testing, haloperidol potentiated rather than inhibited responses to each injection of NMDA (Fig. 3A).

Pretreatment with (±)-pentazocine (1 nmol), a relatively selective σ_1 receptor agonist (Quirion et al., 1992), had no effect on the behaviors induced 30 min later by the first dose of NMDA but significantly inhibited the rate of behavioral desensitization to NMDA (Fig. 4), in a fashion similar to the effect of DTG.

4. Discussion

We have previously found that behaviors induced in mice by intrathecally injected kainic acid are modulated by DTG in a fashion similar to that following treatment with substance P-(1–7) (Larson and Sun, 1993). The effect of substance P-(1–7) on kainic acid-induced activity is prevented by haloperidol but not spiperone, suggesting that substance P-(1–7) depends on σ, and not dopaminergic activity for its modulatory action. The present study shows that, at a dose that has been previously found to enhance kainic acid-induced activity (Larson and Sun, 1993), DTG also potentiates the behavioral response to repeated intrathecal injections of NMDA. It further suggests that σ sites are also involved in the modulatory action of substance P-(1–7) on NMDA-induced activity, just as they appear to be involved in kainic acid-induced activity (Larson and Sun, 1993). Our data, illustrating the modulation of NMDA by σ activity in the spinal cord, is consistent with previous reports documenting this interaction in other parts of the CNS as well as in the spinal cord. For example, iontophoretic application of σ ligands enhance the excitatory effects of NMDA in the rat hippocampus following administration of DTG (Monnet et al., 1990; Malouf et al., 1988). A similar effect is seen following (+)-3-[3-hydroxyphenyl]-*N*-(1-propyl)piperidine (3-PPP) in rat spinal cord neurons (Church and Lodge, 1990).

This behavioral model, using intrathecal injections of excitatory agonists in the mouse spinal cord, provides a simple and direct method of studying the modulation of NMDA-mediated activity in the intact, unanesthetized animal. Using this model, the influence of σ receptor ligands such as DTG, a σ_1 and σ_2 ligand, and (±)-pentazocine, a σ_1 ligand, provide evidence that the behavioral response to NMDA is modulated by σ receptor activity. Pretreatment with haloperidol, a σ and dopamine receptor antagonist, completely blocked the action of DTG on NMDA (Fig. 1A) at a dose that has been previously shown to inhibit the action of DTG on kainic acid-induced behaviors (Larson and Sun, 1993). That haloperidol produced its effects by an interaction with σ rather than dopamine receptor populations is evidenced by the failure of equimolar doses of either spiperone or thiothixine to alter the modulation by DTG on NMDA-induced behaviors. Based on the selectivity of these antagonists, these data indicate an activation of σ, rather than dopaminergic sites by DTG. The ability of haloperidol to inhibit the action of DTG, at a dose that has no effect on NMDA-induced behaviors, is consistent with the notion that DTG acts as a σ receptor agonist while haloperidol acts as a σ receptor antagonist (Monnet et al., 1990).

The present report further indicates that modulation of NMDA by the substance P NH_2-terminus involves activity at σ sites. In support of this, substance P-(1–7) mimics the facilitating effects of (±)-pentazocine and DTG. The potentiative effects of DTG and (±)-pentazocine are, therefore, likely mediated by σ_1 receptor activity as σ_1 binding sites are their common target. Both the excitatory as well as the initial inhibitory actions of substance P NH_2-terminal activity on NMDA appear to be mediated by σ receptor activity as haloperidol, at a dose that was sufficient to inhibit DTG-induced changes, also inhibited the actions of substance P-(1–7). An equimolar dose of

thiothixine did not alter the influence of substance P-(1–7) on NMDA, eliminating the possibility of a dopaminergic mechanism.

Two approaches were used to differentiate σ_1 receptor mediated activity from other σ receptor populations in the spinal cord. Chronic treatment with haloperidol, which has been reported to selectively down-regulate the number of (±)-pentazocine-labeled σ_1 binding sites (Itzhak and Alerhand, 1989; Matsumoto et al., 1989; Reynolds et al., 1983), dramatically decreased the behavioral response of mice to intrathecally injected NMDA. The decrease in NMDA-induced activity correlates with decreased σ_1 binding, suggesting that an endogenous, tonically occurring σ_1 influence normally facilitates the behavioral response to NMDA. Consistent with this, (±)-pentazocine, which has a high selectivity for σ_1 sites, potentiated NMDA-induced activity in normal animals. The failure of acute injections of haloperidol to inhibit NMDA in a fashion similar to that following chronic haloperidol would further suggest that the effect of chronically administered haloperidol does not merely persist for 24 h.

There also appears to be a σ-mediated influence that tonically inhibits NMDA-induced activity in the spinal cord. In support of this, potentiation of NMDA by a high dose of haloperidol (Fig. 3A) may reflect the blockade of an endogenously mediated inhibitory effect elicited via σ_2 sites. The existence of two opposing σ receptor populations is consistent with the dual action of substance P-(1–7) on NMDA. It is of interest that D-substance P-(1–7) and haloperidol each share the ability to shift the magnitude of NMDA-induced responses when injected just 5 min prior to injection of the first injection of NMDA (Hornfeldt et al., 1994).

D-Substance P-(1–7), the D-isomer of substance P-(1–7), inhibits [^{3}H]substance P-(1–7) binding (Igwe et al., 1990c) and activity in the mouse spinal cord (Igwe et al., 1990a,b). We have previously shown that D-substance P-(1–7) selectively antagonizes the inhibitory, but not the potentiative effect of substance P-(1–7) on NMDA (Hornfeldt et al., 1994). The ability of D-substance P-(1–7) to antagonize the inhibitory effect of substance P-(1–7) is also exhibited by haloperidol in the present study (Fig. 2A). In contrast, the facilitatory effect of substance P-(1–7) is sensitive to haloperidol pretreatment but not to D-substance P-(1–7). Facilitation of NMDA activity by substance P-(1–7) may thus be brought about by activation of a different population of σ receptor subtypes than that responsible for the inhibitory effect.

Similar to their actions on NMDA, the potentiative effects of substance P-(1–7) on KA-induced behaviors are prevented by D-substance P-(1–7) and haloperidol at doses that, when given alone, have no effect on NMDA-induced activity (Larson and Sun, 1993). Although D-substance P-(1–7) and haloperidol share a common action on these two excitatory amino acids, the two compounds do not likely share a common receptor. The relatively high concentration of substance P-(1–7) required to effectively compete with [^{3}H]DTG binding (Mousseau and Larson, 1994) would suggest that activation of σ sites by substance P-(1–7) is indirect, possibly involving the release of endogenously occurring σ ligands, rather than a direct interaction between substance P NH_2-terminal fragments and σ recognition sites. Although the inhibitory effect of substance P-(1–7) may be mediated by a small population of σ_2 sites, the identity of the substance P-(1–7) receptors initiating this effect is not clear as there are two substance P-(1–7) binding sites in the spinal cord (Igwe et al., 1990a).

Interactions between SP and NMDA are important in pain transmission at the level of the spinal cord (Dougherty and Willis, 1991; Mjellem-Joly et al., 1991; Dougherty and Willis, 1992). Although a role for σ sites in nociception has not been intensively investigated, the tendency for σ binding populations to down-regulate in response to altered levels of activity make the system sufficiently plastic to account for the development of hyperalgesia. Haloperidol has been shown to possess some analgesic properties (Maltbie et al., 1979; Raft et al., 1979) as well as an ability to potentiate opiate analgesia via an antagonistic action at σ receptors (Chien and Pasternak, 1995). In contrast, (+)-pentazocine has been found to inhibit morphine-induced antinociception via a mechanism involving σ receptors (Chien and Pasternak, 1993). It would thus appear that the synergistic interaction between haloperidol and morphine observed clinically may result from the inhibition by haloperidol of σ sites that inhibit opioid receptor activity. The mechanism behind the inhibition of opioid activity may be the tendency for σ receptor agonists to facilitate NMDA (present study) and kainic acid (Larson and Sun, 1993) activity.

In light of the proposed role of NMDA in pain and hyperalgesia, it would be of interest to determine whether these actions of substance P NH_2-terminal fragments modulate NMDA activity along nociceptive pathways. Recent evidence suggests the existence of NMDA receptors located on primary afferent terminals in the spinal cord (Liu et al., 1994). This points to the possibility that NMDA activity plays a role in the release of excitatory amino acids and/or substance P from primary afferent C-fibers during pain transmission. An accumulation of substance P NH_2-terminal metabolites following noxious stimulation may, therefore, alter the efficacy of excitatory amino acids at NMDA sites at presynaptic as well as postsynaptic sites. The dense localization of σ binding sites in the spinal cord and especially in dorsal root ganglion cells (Aanonsen and Seybold, 1989) is consistent with an anatomically feasible interaction between NMDA and σ sites.

In summary, the interaction between NMDA and σ ligands mimics those shown to occur between NMDA and substance P-(1–7). Based on their sensitivity to haloperidol, our results indicate that NH_2-terminal fragment of substance P exert its opposing effects via activity along

pathways containing σ sites, and may thereby modulate sensory information in dorsal horn neurons. σ_1 receptor activity appears to enhance while σ_2 inhibits NMDA-induced activity.

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