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Retrograde Carbon Monoxide Is Required for Induction of Long-Term Potentiation in Rat Superior Cervical Ganglion

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Carbon monoxide (CO), produced in the body by the enzyme heme oxygenase (HO), has been suggested as a retrograde synaptic messenger with a prominent role in the long-term potentiation (LTP) of certain areas of the brain. LTP of sympathetic ganglia is 5-HT_3 receptor-dependent and has been shown to require nitric oxide for the maintenance, but not for the induction, phase. We investigated the possibility of CO being required for the induction of ganglionic LTP. Pretreatment of rat isolated superior cervical ganglia with oxyhemoglobin (25–100 μM) completely blocked LTP. In the same ganglia, prolonged washout of oxyhemoglobin did not uncover any potentiation of the compound action potential. Oxyhemoglobin had no significant effect on the maintenance phase in ganglia with established LTP. Pretreatment of ganglia with the HO inhibitor zinc protoporphyrin-IX (ZnPP) (10 μM) completely and irreversibly prevented the expression of tetanus-evoked LTP. However, in the same ganglia, after superfusion of CO in the presence of ZnPP, tetanic stimulation readily evoked LTP. No effect was seen on the maintenance phase when ZnPP was superfused on ganglia with established LTP. Pretreatment of ganglia with the 5-HT_3 receptor antagonist ondansetron (0.4 μM) alone completely and irreversibly blocked LTP. However, in the presence of CO, ondansetron did not block LTP. These results suggest that activation of 5-HT_3 receptors may be involved in the production of CO. The results also suggest that CO, probably originating outside the presynaptic nerve terminal, is involved in the induction of LTP.

Key words: long-term potentiation; oxyhemoglobin; Zn-protoporphyrin-IX; ondansetron; L-NOARG; 5-HT_3 receptor; nitric oxide; heme oxygenase

In the mammalian sympathetic ganglia, a brief tetanic stimulation of the preganglionic nerve induces long-term potentiation (LTP) that is manifested as a long-lasting enhancement of the nicotinic pathway as measured by intracellular and extracellular techniques (Briggs and McAfee, 1988). This has been demonstrated *in vivo* (Alonso-deFlorida et al., 1991; Bachoo and Polosa, 1992; Bachoo et al., 1992), as well as *in vitro* (Brown and McAfee, 1982; Briggs et al., 1985, 1988; Minota et al., 1991; Alkadhi et al., 1996; Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999). This LTP is independent of the activation of either cholinergic or adrenergic receptors and may be attributable to an increase in acetylcholine release as measured by biochemical assay (Briggs et al., 1985). Although the role of ganglionic LTP in the physiology of autonomic ganglia is not understood, recent a report showed that ganglionic LTP may be linked to the development of stress-induced hypertension (Alkadhi et al., 1998).

Recently, we have shown that activation of serotonin 5-HT_3 receptors is necessary for both induction and maintenance of tetanus-induced ganglionic LTP (Alkadhi et al., 1996). Activation of 5-HT_3 receptor, which is primarily a calcium ionophore (Loomis et al., 1994), appears to be a primary extracellular trigger for the induction of ganglionic LTP, much like the requirement for activation of NMDA receptors in hippocampal LTP.

In the mammalian superior cervical ganglion (SCG) (Dun et al., 1993; Sheng et al., 1993; Morris et al., 1993; Okamura et al., 1995; Klimaschewski et al., 1996a; Mazet et al., 1996), as well as in the avian ciliary ganglion (Scott and Bennett, 1993), nitric oxide (NO) synthase has been demonstrated primarily in the preganglionic nerve terminals. Compliant with these findings is the recent demonstration that NO is required only for the maintenance and not for initiation of ganglionic LTP (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999). Therefore, a second similar messenger may be required for the process of induction of LTP. Carbon monoxide (CO) is also a membrane-permeable gas that has been suggested as an intercellular messenger with a possible role in LTP in the CNS (Stevens and Wang, 1993; Zhuo et al., 1993). It is produced by the enzyme heme oxygenase-2 (HO2) when it transforms heme to biliverdin. In sympathetic ganglia, HO2 is reported to be present only in cell bodies and some dendrites of postganglionic principal neurons, but none was found in preganglionic nerve terminals (Vollerthun et al., 1995). Because CO is, in many ways, similar to NO, we examined the possibility of involvement of CO in the induction and maintenance of LTP in the SCG of the rat.

MATERIALS AND METHODS

Preparation of ganglia. All procedures involving animals were performed in accordance with the *NIH Guide for the Care and Use of Laboratory Animals*. Sprague Dawley male rats (200–250 gm) were anesthetized with pentobarbital (50 mg/kg, i.p.). Ganglia were rapidly excised and carefully desheathed in oxygenated (95% O_2, 5% CO_2) Locke's solution, pH 7.4, containing (in mM): NaCl 136, KCl 5.6, $CaCl_2$ 2.2, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 16, glucose 11, and choline chloride 0.02.

Electrophysiological recording. For recording postganglionic compound action potentials (CAPs), ganglia were placed in a constant temperature (32 ± 1°C) chamber (3 ml), and the preganglionic (cervical sympathetic) and postganglionic (internal carotid) nerves were gently drawn into capillary stimulating and recording suction electrodes, respectively. The

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ganglion was continuously superfused with Locke's solution at a rate of 1.3 ml/min. The CAPs were evoked by supramaximal stimulation of the preganglionic nerve using 0.3 msec square wave pulses at 0.017 Hz. The CAPs were amplified (Grass Instruments P5 preamplifier), displayed on a digital storage oscilloscope, and plotted on paper for later measurement.

Protocol. After stabilization of the CAP, hexamethonium (0.4 mM) was included in the Locke's solution perfusate to partially block the nicotinic pathway to obtain submaximal CAPs. This concentration of hexamethonium produces >50% reduction in the amplitude of the CAP. Enhanced synaptic efficacy is best evaluated in submaximal postsynaptic responses, but submaximal preganglionic nerve stimulation may result in an increase in recruitment of presynaptic fibers, which may lead to an apparent increase in synaptic efficacy. However, no recruitment was observed when supramaximal stimulation was used (Brown and McAfee, 1982). We used a method modified from Briggs et al. (1985), in which submaximal responses were obtained with supramaximal preganglionic nerve stimulation. This was done by partial blockade of the response to supramaximal stimulation with hexamethonium. Another stabilization period (30–60 min) was allowed for the CAP in the new hexamethonium-induced submaximal amplitude before a brief tetanus (supramaximal pulses of 0.3 msec duration at 20 Hz for 20 sec) was applied. Immediately after tetanus, the amplitude of the CAP was measured at 2 min intervals for the first 10 min and then every 5 min thereafter. Changes in amplitude of CAP were expressed as percent of the mean CAP amplitude recorded during a 15 min period immediately before tetanus.

Preparation and sources of drugs. Drugs used in this study were obtained from Research Biochemicals (Natick, MA). Zinc protoporphyrin-9 (ZnPP) was dissolved in either DMF (*N*,*N*-dimethylformamide) or, in the majority of the experiments, weak alkaline solution. Stock solutions of drugs were made with distilled water. Oxyhemoglobin (Hb) stock solution was prepared as previously described (Martin et al., 1985). The CO stock solution was prepared by bubbling CO (100%) into 10 ml of distilled water for 30 min under a fume hood. The final perfusate was prepared by adding 20 μl of the saturated CO solution to 20 ml of Locke's solution (estimated, 0.2–2.0 μM) (Zhuo et al., 1993).

Statistical analysis. In comparing values under different conditions, a test of significance was made by using the paired *t* test, unpaired *t* test, or ANOVA as appropriate using the GB-Stat 6.5.2 computer program (Dynamic Microsystems Inc., Silver Spring, MD); *p* values of 0.05 or less were considered significant.

RESULTS

Because we have shown previously that NO is not required for induction of ganglionic LTP (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999), the alternative would have to be an agent that also has a strong affinity for and is readily taken up by Hb. Therefore, we investigated the role of CO in the induction of ganglionic LTP.

Effect of oxyhemoglobin

Being a membrane-impermeable molecule known to have a high affinity for both CO and NO, Hb is expected to capture either of these two gases in the extracellular fluid. However, previously, we have shown that inhibitors of NO synthase reversibly blocked tetanus-induced ganglionic LTP, indicating the involvement of NO in maintenance, but not induction, of LTP (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999). If CO is involved in the induction of ganglionic LTP by permeating from the extracellular space, then the presence of Hb will prevent induction. In a series of experiments, tetanic stimulation of ganglia superfused with Hb failed to express LTP. Washout of Hb in these ganglia did not result in any significant increase in the amplitude of CAP (Fig. 1*A*, 10 ganglia). In all of these experiments, Hb had no significant effect on baseline CAP. However, in another series, when a second tetanic stimulation was applied after removal of Hb, LTP was expressed (Fig. 2, five ganglia). In contrast with its effect on LTP, Hb did not seem to affect post-tetanic potentiation [(PTP) potentiation seen within 4 min after tetanus] or the decremental short-term potentiation (STP) that lasts 10–20 min after tetanus (Figs. 1, 2). Superfusion of Hb during the maintenance phase of established LTP had no significant effect on the magnitude of this response (Fig. 1*B*, seven ganglia). These results indicate the involvement of an intercellular messenger in the induction of ganglionic LTP.

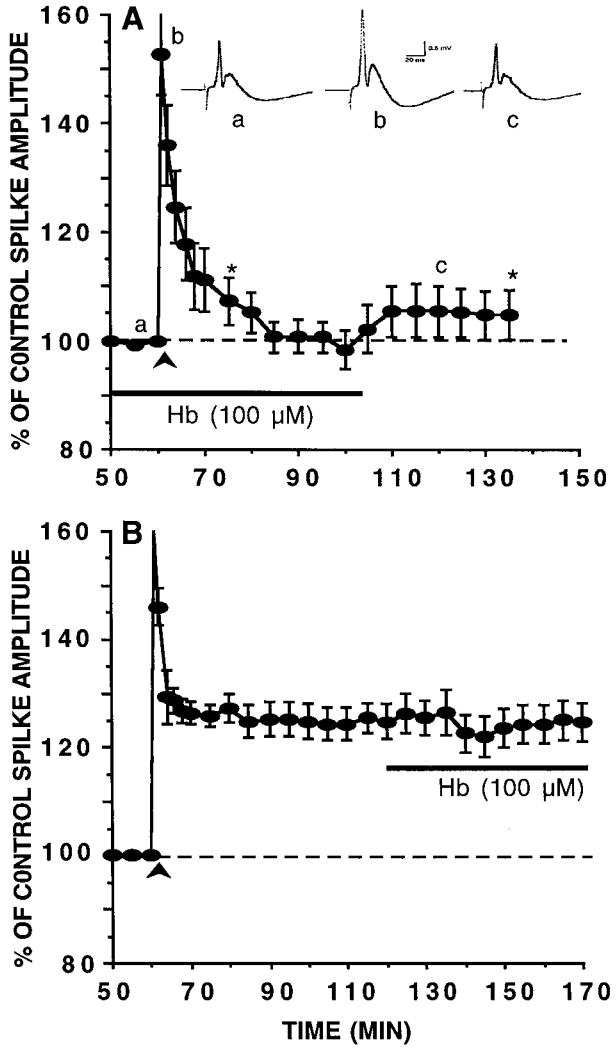

Figure 1. Effect of the membrane-impermeable, NO–CO scavenger oxyhemoglobin on LTP of the rat SCG. *A*, In ganglia pretreated with Hb (100 μM; *solid horizontal line*), tetanus failed to induce LTP. No significant recovery of LTP was seen on washout of oxyhemoglobin 40 min after tetanus. Each *point* is the mean ± SEM from 10 ganglia. When not shown, error bars are within the *symbols*. *Inset*, Records of CAPs from a representative ganglion taken at times indicated on the graph. Calibration: 0.4 mV, 20 msec. *Points* between the *two asterisks* are not significantly different from baseline. *B*, Superfusion of oxyhemoglobin on ganglia during the maintenance phase of established LTP produced no significant effect on this phase of LTP. Each *point* is the mean ± SEM from seven ganglia.

Inhibition of nitric oxide synthase

We have shown previously that NO synthase inhibitors reversibly blocked the expression of LTP, indicating requirement of NO for maintenance, but not induction, of LTP (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999). Figure 3 represents two new series of experiments to confirm previous results. Superfusion of ganglia with L-NOARG before tetanus prevented the expression of LTP for as long as the inhibitor was in contact with the ganglia without affecting PTP or STP. However, when the inhibitor was

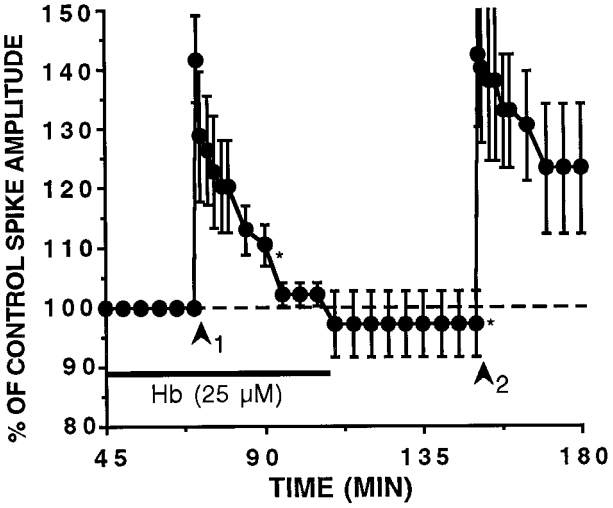

Figure 2. Washout of oxyhemoglobin restored the ability of tetanus to generate LTP. The presence of Hb (25 μM) prevented tetanus-induced LTP (*arrowhead 1*). However, after washout of oxyhemoglobin, a second tetanus (*arrowhead 2*) readily evoked LTP. Each *point* is the mean ± SEM from five ganglia. *Points* between the *two asterisks* are not significantly different from baseline.

washed out, a robust LTP was revealed (Fig. 3*A*, eight ganglia). Additionally, L-NOARG readily and reversibly inhibited established LTP (Fig. 3*B*, four ganglia).

Inhibition of heme oxygenase

To investigate a possible role for CO in the induction of ganglionic LTP, we blocked the production of CO in the ganglion. Pretreatment of ganglia with the HO2 inhibitor ZnPP caused an irreversible inhibition of expression of LTP (Fig. 4*A*, 13 ganglia). As with Hb, ZnPP did not seem to block the PTP or STP (Figs. 4, 5). Again, as with Hb, ZnPP had no effect on established LTP when superfused during the maintenance phase (Fig. 4*B*, five ganglia). These results suggest that CO may be required for the induction phase but not the maintenance phase of ganglionic LTP.

Furthermore, Zn-PP did not affect the CAPs of ganglia in which transmission was potentiated by pretreatment with the guanylate cyclase stimulator sodium nitroprusside (four ganglia; data not shown).

Effect of exogenous carbon monoxide

If, in fact, CO is required for induction, then in ganglia in which HO2 is blocked by ZnPP, the presence of exogenous CO would be expected to obviate the need for a viable HO2 for induction of LTP. In a series of experiments in which ganglia were pretreated with ZnPP failed to express LTP, CO was superfused in the presence of the inhibitor. The gas had no significant effect on the CAP when applied after the first train. However, when a second train was applied, a robust LTP was expressed (Fig. 5, five ganglia). Applied alone, CO had no significant on the CAP (evoked repetitively at 0.017 Hz) of naïve ganglia (three ganglia; data not shown)

If CO is the retrograde messenger required for the induction of LTP and if its production is secondary to activation of 5-HT_3 receptors, then if supplied exogenously, its action should not need activation of 5-HT_3 receptors. We superfused CO solution on ganglia pretreated with the 5-HT_3 receptor antagonist ondansetron (0.4 μM), which, by itself, irreversibly blocks the induction of LTP by tetanic stimulation (Fig. 6*A*). In the presence of both

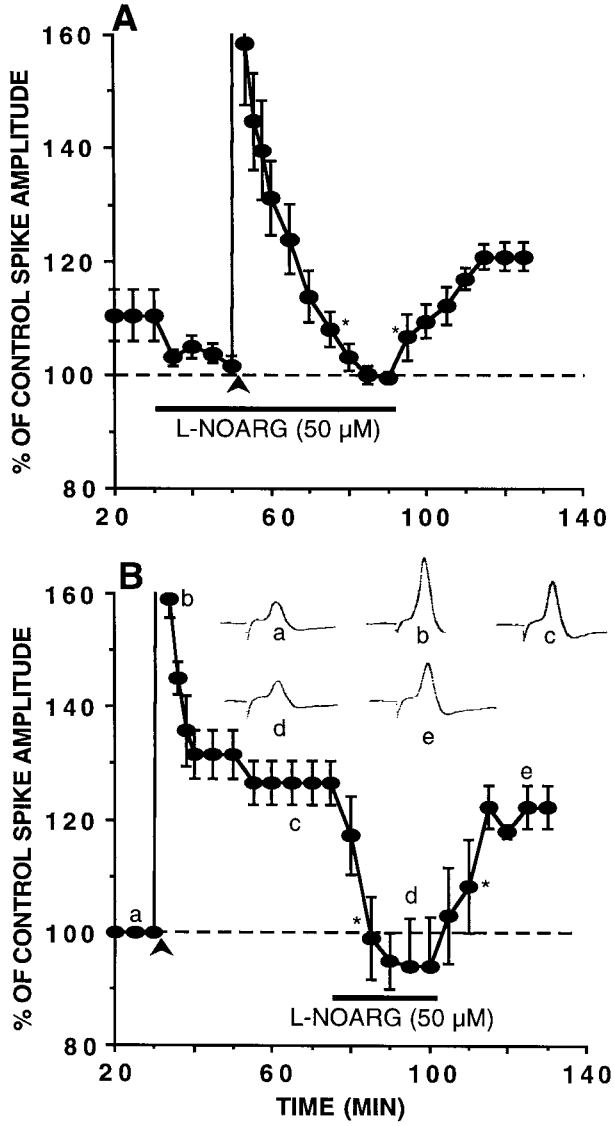

Figure 3. Removal of the NO synthase inhibitor L-NOARG resulted in reversal of inhibition of ganglionic LTP. *A*, LTP blocked by L-NOARG (50 μM; *solid horizontal line*) was fully restored when the inhibitor was washed out. Each *point* is the mean ± SEM from eight ganglia. *B*, Superfusion of L-NOARG (50 μM; *solid horizontal line*) on established LTP resulted in complete, but reversible, inhibition of ganglionic transmission enhancement. *Inset*, Records of CAPs from a representative ganglion taken at times indicated on the graph. Calibration: 0.4 mV, 20 msec. Each *point* is the mean ± SEM from four ganglia. *Points* between the *two asterisks* are not significantly different from baseline in both series.

ondansetron and CO, tetanic stimulation readily evoked LTP (Fig. 6*B*).

DISCUSSION

The present results strongly suggest that CO may be required for the induction, but not maintenance, phase of LTP in the SCG of rat. Neither Hb nor ZnPP affects PTP or STP, which shows that these treatments specifically block the induction of ganglionic LTP. Furthermore, baseline ganglionic transmission does not seem to require CO because neither ZnPP nor exogenous CO has any significant effect on the CAP, indicating that CO plays a role only in LTP. If CO were acting as a retrograde synaptic messenger, then its action would be limited to the time up to the

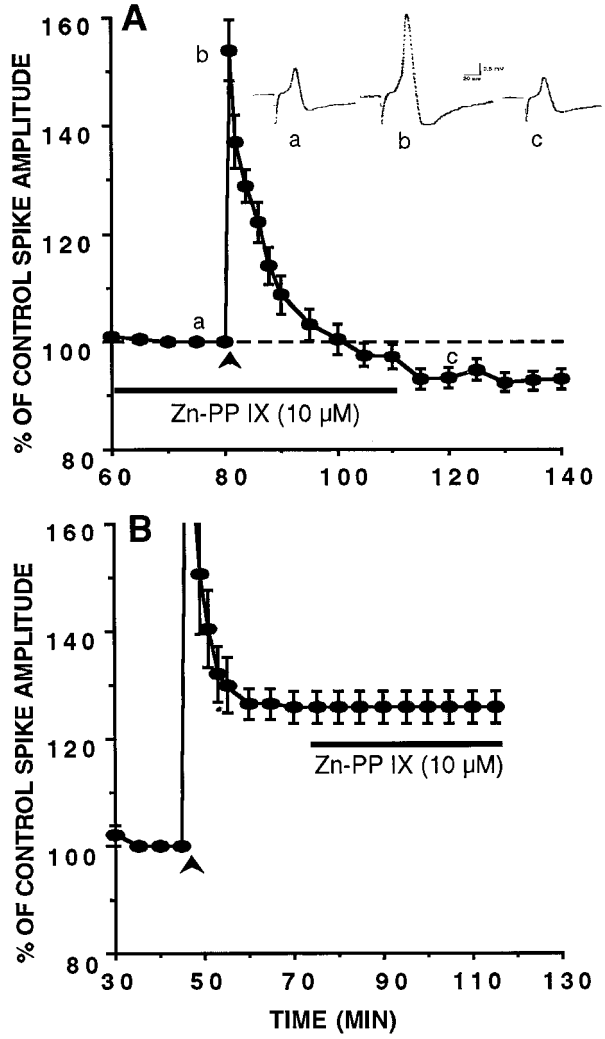

Figure 4. Effect of inhibition of the CO-generating enzyme HO2 on ganglionic LTP. *A*, Superfusion of the HO2 inhibitor ZnPP (10 μM; *solid horizontal line*) before tetanus completely and irreversibly blocked expression of LTP. *Inset*, Records of CAPs from a representative ganglion taken at times indicated on the graph. Calibration: 0.4 mV, 20 msec. Each *point* is the mean ± SEM from 13 ganglia. *B*, ZnPP produced no significant effect on ganglionic transmission when superfused during the maintenance phase of established LTP. Each *point* is the mean ± SEM from four ganglia.

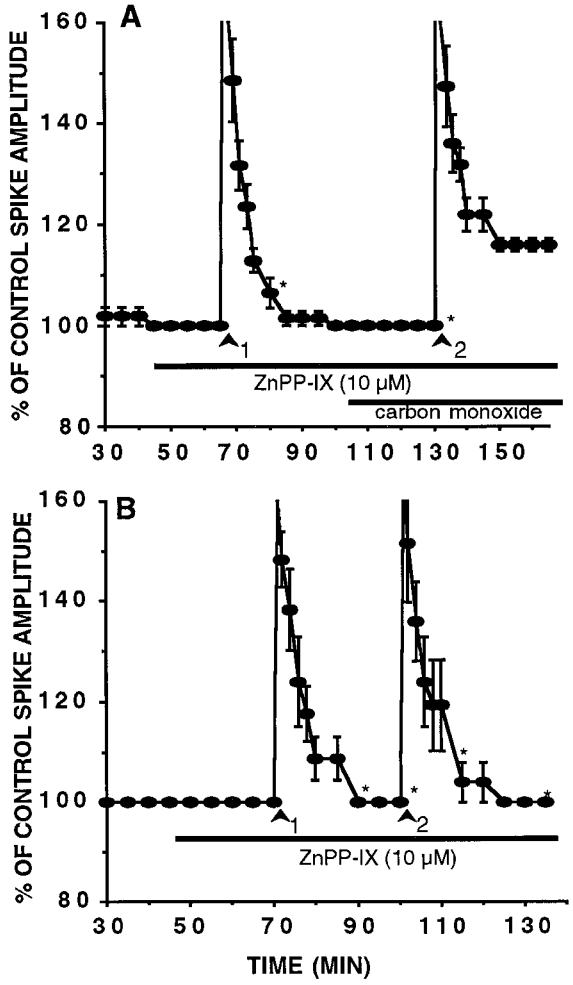

Figure 5. The presence of CO renders ZnPP ineffective in blocking ganglionic LTP. *A*, ZnPP (*solid horizontal line*) given before tetanus (*arrowhead 1*) completely blocked ganglionic LTP. In the same ganglia, after superfusion of CO solution (0.2–2.0 μM; *solid horizontal line*) and in the presence of ZnPP, a second tetanus (*arrowhead 2*) evoked a robust LTP. Each *point* is the mean ± SEM from five ganglia. *B*, A similar series in which two tetani were used in the presence of ZnPP but without CO is shown for comparison. Each *point* is the mean ± SEM from three ganglia. After each tetanus, *points* between the *two asterisks* are not significantly different from baseline in both series.

end of the tetanus required to induce LTP. Consistent with this notion, our results showed that the HO2 inhibitor had no effect on established LTP and therefore was not involved in the maintenance phase. A similar retrograde messenger role for CO has been suggested for the induction of LTP in the hippocampus based on results from effects of the HO2 inhibitor ZnPP (Stevens and Wang, 1993; Zhuo et al., 1993; Ikegaya et al., 1994; Poss et al., 1995).

It appears that both gases are involved in ganglionic LTP; CO is required for the induction phase, and NO is required for the expression–maintenance phase. That NO is required for maintenance, but not induction, of ganglionic LTP is demonstrated by the present and previous results. When an inhibitor of NO synthase was applied before or after tetanus, although it seemed to have completely blocked LTP, full recovery of LTP resulted when the drug was removed (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999). In contrast, washout of HO2 inhibitor, applied before tetanus, did not result in recovery. Furthermore, the lack of action of ZnPP on established LTP suggests that it is unlikely that CO is involved in the expression–maintenance phase of LTP.

Another indication for the respective roles of NO and CO in ganglionic LTP is the localization of the enzymes responsible for production of these gases. There seems to be a specific differential distribution of the enzymes HO2 and NO synthase in autonomic ganglia. In these ganglia, the enzyme HO2 exists in the perikarya and dendrites of principal neurons but not in axons or presynaptic nerve terminals (Vollerthun et al., 1995, 1996; Zakhary et al., 1996; Magnusson et al., 2000). In contrast, NO synthase exists in sympathetic preganglionic neurons (Blottner and Baumgarten, 1992; Dun et al., 1992; Valtschanoff et al., 1992) and has been localized mainly within preganglionic nerve terminals in sympathetic ganglia (Dun et al., 1993; Morris et al., 1993; Saito et al., 1994; Anderson et al., 1995; Okamura et al., 1995; Klimaschewski et al., 1996b).

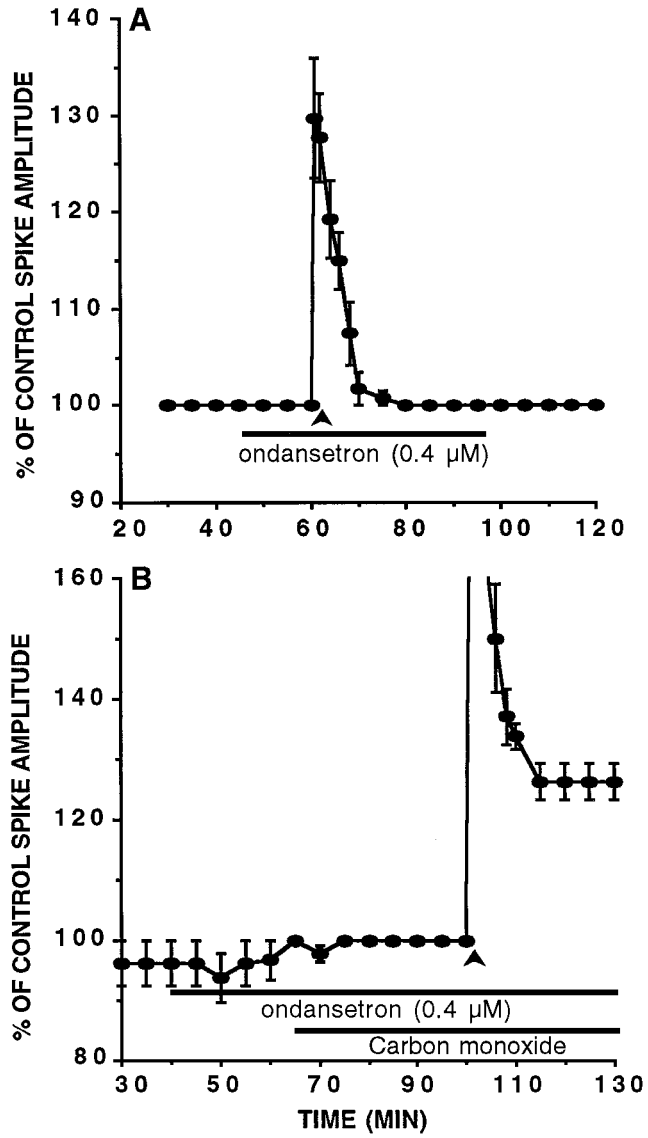

Figure 6. The 5-HT_3 receptor antagonist ondansetron did not block ganglionic LTP in the presence of CO. *A*, Ondansetron (0.4 μM; *solid horizontal line*) completely and irreversibly blocked LTP of the SCG. Each *point* is the mean ± SEM from four ganglia. *B*, In the presence of CO (0.2–2.0 μM; *solid horizontal line*), ondansetron failed to inhibit LTP. Each *point* is the mean ± SEM from four ganglia.

In both the CNS and autonomic ganglia, exogenous NO, by itself, can produce prolonged enhancement of synaptic transmission without the need for tetanic stimulation (Bohme et al., 1991; Scott and Bennett, 1993; Southam et al., 1996). In contrast, exogenous CO in sympathetic ganglia (present results), as well as in hippocampal slices (Zhuo et al., 1993), must be accompanied by tetanic activation of presynaptic nerve fibers to produce enhancement of synaptic transmission. Thus, CO seems to be necessary but not sufficient to initiate long-term enhancement.

Although the molecular mechanisms for activation of HO2 are not known, there is evidence suggesting that this enzyme may be activated by interaction of neurotransmitters with their respective receptors (Glaum and Miller, 1993; Nathanson et al., 1995). Thus, it is possible that the production of CO in ganglia is induced by activation of the Ca^{2+} ionophore 5-HT_3 receptors. Consistent with this possibility is the finding that, in the presence of 5-HT_3 receptor antagonists that completely and irreversibly inhibit LTP (Alkadhi et al., 1996), exogenously applied CO followed by tetanic stimulation evokes a robust LTP. This indicates that CO works downstream from 5-HT_3 receptors in sympathetic ganglia. We suggest that, as a result of activation of these receptor–channels, Ca^{2+} enters into specific postsynaptic regions where it activates PKC, which, in turn, rapidly phosphorylates and activates HO2 for the production of CO required for the induction of LTP in the ganglion (Doré et al., 1999).

Because both gases have strong affinity for Hb, the finding that Hb blocks the induction of LTP is equally compliant with either CO or NO functioning as a retrograde messenger. Therefore, for LTP induction, one could argue that NO, rather than CO, could have come from outside the nerve terminal to initiate changes that lead to sensitization of the NO synthase to produce more NO, on demand within the terminal, for the maintenance phase. Based on this hypothesis, application of Hb during maintenance phase would have no effect. However, this alternative explanation is unlikely, because the reversibility of the blocking effect of NO synthase inhibitors when applied either before or after tetanic stimulation (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999) indicates that the LTP induction process is not blocked by these inhibitors. In contrast, the HO2 inhibitor ZnPP, when applied before tetanus, completely and irreversibly prevented the induction of ganglionic LTP. Together, these results indicate that CO, and not NO, is required for the induction of ganglionic LTP.

The inhibitor ZnPP has been reported to have other effects, unrelated to inhibition of the enzyme OH. First, the drug has been reported to inhibit NO synthase in the hippocampus. This is unlikely to be the case in the present experiments, because reports show that ZnPP inhibits NO synthase only at much higher concentrations (up to 1000-fold) than L-NOARG (East and Garthwaite, 1991; Meffert et al., 1994; Prabhakar et al., 1995). Second, because of the reported ability of ZnPP to inhibit soluble guanylate cyclase (Luo and Vincent, 1994; Zakhary et al., 1996), it is possible that the effect of ZnPP may be independent of CO but is attributable to direct inhibition of guanylate cyclase. However, it has been shown that, at the level of the concentration used in the present study, ZnPP is unlikely to produce inhibition of guanylate cyclase (Luo and Vincent, 1994; Zakhary et al., 1996). Furthermore, the present experiments clearly showed that ZnPP has no effect on previously established LTP, which requires activation of guanylate cyclase as has been demonstrated previously (K. A. Alkadhi, unpublished observation) (Briggs, 1992; Scott and Bennett, 1993; Southam et al., 1996). Additionally, failure of ZnPP to inhibit sodium nitroprusside-induced enhancement of ganglionic transmission indicates that guanylate cyclase is not inhibited by ZnPP in our experiments (Verma et al., 1993).

In conclusion, we present evidence indicating that CO may be involved in the induction of ganglionic LTP and that the production of CO is downstream from 5-HT_3 receptors, which suggest that activation of 5-HT_3 receptor may be involved in the production of CO.

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