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Changes in Concentrations of Dopamine, Serotonin, and Their Metabolites Induced by Carbon Monoxide (CO) in the Rat Striatum as Determined by In Vivo Microdialysis

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HIRAMATSU, M., S. YOKOYAMA, T. NABESHIMA AND T. KAMEYAMA. *Changes in concentrations of dopamine, serotonin, and their metabolites induced by carbon monoxide (CO) in the rat striatum as determined by in vivo microdialysis.* PHARMACOL BIOCHEM BEHAV **48**(1) 9–15, 1994.—Striatal microdialysis was performed in rats exposed to carbon monoxide (CO). Extracellular changes of dopamine, serotonin, and their metabolites were monitored before and after CO exposure at 15-min intervals by HPLC analysis. After CO exposure, extracellular dopamine increased (3.8 times that of baseline), whereas 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) decreased (by 20–25% of baseline). The decrease in HVA at individual time points, however, was not significant. After a transient increment of the dopamine, it was cleared from the extracellular fluid within 45 min and reached a stable level. Serotonin and 5-hydroxyindoleacetic acid (5-HIAA) showed a pattern different to that of dopamine and its acid metabolites, i.e., the changes in extracellular levels were small. Pretreatment with dizocilpine (MK-801), a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, 45 min before CO exposure antagonized the changes in the extracellular concentration of DOPAC. However, the change in dopamine levels was not antagonized by pretreatment with MK-801. MK-801 itself had no effect on the levels of monoamines. Therefore, NMDA receptors may not have an important role for regulating striatal dopamine neurons in hypoxic condition.

Carbon monoxide CO In vivo microdialysis Dopamine Serotonin MK-801 Dizocilpine Excitatory amino acid NMDA receptor

HYPOXIC and ischemic conditions can induce massive increases of neurotransmitters in the extracellular space of the brain. For example, extracellular concentrations of amino acid transmitters such as glutamate, γ-aminobutyric acid (GABA), aspartate, and taurine, increase under ischemic conditions in the hippocampus (2,10,13,20). Exposure to hypoxia increased dopamine levels in striatal dialysates (1). Similarly, during ischemia, dopamine rise dramatically in the extracellular fluid of the striatum (3,9,12,19,29,37). In contrast, a decrease of extracellular cortical acetylcholine has been reported following occlusion of the middle cerebral artery (35). Changes in extracellular neurotransmitters in the hippocampus, cortex, and striatum of laboratory animals have received much attention, because these structures are particularly susceptible to the effects of hypoxia and ischemia (30,38).

Exposure to hypoxia including carbon monoxide (CO) and ischemia produce behavioral disturbances such as memory loss, blockade of the conditioned avoidance response, and of amphetamine-induced stimulation of locomotor activity in experimental anmals (4,5,16,25,40). Akiyama et al. (1) have suggested that the hypoxia-induced behavioral disturbances are the result of decreased activity of catecholaminergic neu-

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ron by blockade of dopamine reuptake which induces the increase in extracellular dopamine. The increase in extracellular neurotransmitter concentrations has also been implicated in the pathogenesis of ischemic cell damage; for example, a neurotoxic role for excitatory amino acids in ischemia- and CO-induced cell loss in the hippocampus has been suggested (18,34). Similarly, there is evidence that dopamine is involved in ischemia-induced cell damage in the striatum. Depletion of striatal dopamine prior to ischemia reduces the degree of neuronal damage (7,11,12,43). The mechanisms by which excessive extracellular dopamine might cause brain damage, however, are not well understood.

In the present study we used in vivo microdialysis to characterize extracellular changes of dopamine, serotonin, and their metabolites after CO exposure in the striatum of the rat. To study the involvement of the NMDA receptor, a second group of rats was pretreated with MK-801 to block NMDA receptors.

METHOD

Microdialysis and subsequent chemical analysis by HPLC were performed essentially as described elsewhere (15).

Animals

Male Sprague–Dawley rats (280–350 g) were housed in a room with controlled lighting (12 h : 12 D cycle) and temperature (23°C) and accessed to food and water ad lib. Experimental protocols concerning the use of laboratory animals were approved by the committee of Meijo University and followed the guidelines of the Japanese Pharmacological Society (Folia Pharmacol. Jpn. 99:35A, 1992) and the interministerial decree from May 25th, 1987 (the Ministry of Education).

Construction of the Dialysis Probes

The dialysis probes were constructed in the method of Hiramatsu and Cho (15). In brief, the infusion and effluent tubes were made from fused silica tubing (o.d., 170 μm, i.d., 120 μm, Scientific Instrument Services Inc., NJ), which were attached to short lengths of stainless steel tubing. These tubes were fixed with epoxy resin glue. Dialysis membrane (cellulose acetate, 5,000 molecular cut-off, i.d., 230 μm, wall thickness, 10 μm, Bioresearch Center, Nagoya) was then attached to the needle and trimmed to 4 mm. The tip of the dialysis membrane and its junction with the needle were sealed with epoxy cement.

Surgical Procedure

Rats were anesthetized with pentobarbital-Na (40 mg/kg, IP) and placed in a stereotaxic frame (Narishige, Tokyo). Using coordinates chosen according to the stereotaxic atlas of Paxinos and Watson (28), a guide cannula was implanted so that the tip was just above the striatum (A: 1.0, L: 3.0, V: 4.0 relative to the bregma) of each rat. The animals were allowed to recover from the procedure for 5 to 8 days prior to experimentation. In the experiment, the dialysis probe was inserted through the guide cannula and the 4-mm length of dialysis membrane was entered into the striatum.

CO Exposure

Due to technical difficulties during carbon monoxide (CO) exposure, rats were treated with α-chloralose (55 mg/kg, IP) at a dose sufficient to produce anesthesia for approximately 3 h after control samples (baseline) were stable. A cylindrical mask (26 mm in diameter × 46 mm) connected to tube for supplying CO gas was set up in front of nose of rat. The animals were allowed to breathe spontaneously. Exposure of rats continuously to CO gas for more than 40 s resulted in some deaths. Therefore, pure CO gas (flow rate: 10 cc/min) was exposed to the rats three times (30, 30, 10 s) at intervals of 90 s 45 min after treatment with α-chloralose.

Sampling Procedure

The dialysis probe was perfused with physiological Ringer's solution (composition in mM: NaCl 147; KCl 4; $CaCl_2$ 2.3) at the rate of 2 μl/min, using microbore tubing (Cole-Palmer Instrument, IL) with an i.d. of 0.19 mm and an o.d. of 2.0 mm, connected to a microinfusion pump (Syringe Infusion Pump 22, Harvard Apparatus, MA) via a single channel liquid swivel. The infusion and effluent cannulae were passed through or attached to a tether, which was attached to the animal by a rodent collar (Bioanalytical Systems Inc., Tokyo). This arrangement allowed the animal to move freely within the cage. The rats were placed in individual cages (22 cm in diameter and 25 cm high) and allowed to adapt for at least 60 min before the experiment was started. The dummy cannula was replaced with dialysis probes, which were fixed to the guide cannula with wax. The perfusate was collected in a small (250 μl) disposable microcentrifuge tube that was secured to the middle of the tether. The collecting tube contained 20 μl of 0.2 N perchloric acid. The total dead volume from the tip of the probe to the collection tube was usually 10 μl but was always measured to adjust the delay in collecting samples after administration of the drugs. About 3 h after the probe was inserted, samples (30 μl) were collected at 15-min intervals and at least four control samples were stable and then α-chloralose and MK-801 were administered. Perfusate samples from the brain were taken up to 195 min after the treatment with drugs or saline.

HPLC Analysis

The perfusates were assayed for dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) by high performance liquid chromatography (HPLC) with electrochemical detection. The mobile phase consisted of 0.075 M citrate buffer, pH 3.5 (pH adjusting by using acetic acid), containing 10% methanol, 1% tetrahydrofran, and 50 mg/l ethylenediamine tetraammonium (EDTA-2Na), 55 mg/l sodium octylsulfate was delivered by a pump (TriRotor V, Japan Spectroscopic Co., Ltd., Tokyo) at the flow rate of 0.5 ml/min. To protect the analytical column from impurities of the mobile phase and samples, a precolumn (3 × 50 mm, Richrosorb 5C18, Applied Biosystems, Inc., CA) was placed between the pump and injector. These compounds were separated by reverse phase chromatography using Biophase ODS IV 3 μm (4 × 110 mm, Bioanalytical Systems Inc.). Electrochemical measurements were made using a glassy carbon working electrode set at +0.75 V vs. Ag/AgCl reference electrode (LC-4B, Bioanalytical Systems, Inc.). The sample tubes containing total 50 μl sample were setted in an autoinjector and 40 μl of the perfusate samples were injected directly onto the HPLC column without any preparation. Signals were recorded with a Chromatogram 11 recording integrator (System Instruments Inc., Tokyo), and the peak height of each compound was determined by comparison with the control sample from each animal before treatment.

Under the HPLC conditions employed, the retention time for dopamine was 5.3 min, for DOPAC, 6.3 min, for 5-HT, 7.8 min, for 5-HIAA, 8.8 min, and for HVA, 11.5 min. Baseline resolution of all compounds was achieved and a chromatographic run took 14 min. As a result, by selecting dialysate collection times of 15 min, the collection and HPLC analysis could be conducted immediately and continuously with the autoinjector. The concentrations of the neurotransmitters in the dialysate were very small compared to their metabolites. Basal concentrations for all groups were closely similar and average basal concentrations of samples of dialysate were: dopamine 7.5 nM; DOPAC, 1420 nM, HVA, 780 nM, 5-HT, 2 nM, and 5-HIAA, 360 nM.

Drugs

MK-801, which was a kind gift from Dr. A. K. Cho (Department of Pharmacology, UCLA), was dissolved in saline and injected subcutaneously. α-Chloralose (Sigma, St. Louis, MO) was suspended in 5% gum arabicum solution and injected intraperitoneally. All HPLC assay reagents were of an analytical grade.

Data Analysis

Data were shown by the mean ± SE of the percent of baseline level which was obtained from each rat before drug treatments. To compare the effect of CO exposure with α-chloralose-treated group, the data was analyzed by two-way repeated measures analysis of variance. Statistical analysis of the data for individual time points was carried out using one-way analysis of variance followed by Dunnett's test.

RESULTS

Effect of CO Exposure on the Extracellular Levels of Dopamine and Its Metabolites

The dialysate concentrations of dopamine did not change following administration of α-chloralose, and dopamine and its main metabolites, DOPAC and HVA, were relatively stable during the preparative procedures prior to CO exposure. Repeated measures analysis of variance of the effect of CO exposure on the dialysate concentrations of dopamine, DOPAC, and HVA indicated that there were significant effects of treatment; dopamine, $F1, 104 = 48.6, p < 0.001$, DOPAC, $F1, 104 = 32.9, p < 0.001$, and HVA, $F1, 104 = 6.4, p < 0.05$, respectively. In the first 15-min sample after CO exposure, extracellular dopamine increased about fourfold over the baseline (Fig. 1). After transient release, dopamine levels decreased rapidly, returning within 45 min to baseline levels, and stabilized at the baseline. DOPAC and HVA, however, showed different patterns after CO exposure. They decreased to 75–80% of the baseline levels at the second 15-min sampling period, and there was no significant difference from the control levels at the time points of 70–150 min after CO exposure (Fig. 2). HVA followed a pattern similar to that of DOPAC, but to a lesser extent (Fig. 2). However, there was no significant decrease when compared the individual time points.

Effect of CO Exposure on the Extracellular Levels of Serotonin and Its Metabolite

The dialysate concentration of 5-HT decreased by treatment with α-chloralose, $F1, 104 = 10.0, p < 0.05$. Extracellular levels of 5-HT increased after CO exposure when compared with α-chloralose control group; the maximum output

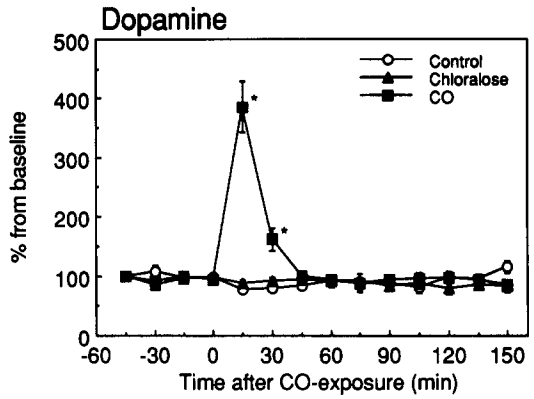

FIG. 1. Effect of CO exposure on the extracellular levels of dopamine in the striatum. Each rat was exposed to CO three times as described in the Method section. α-Chloralose (55 mg/kg, IP) was administered 45 min before CO exposure. Each sample was collected for 195 min with 15-min intervals. Data show the percentage from the basal preinjection peak height for dopamine. $*p < 0.05$ vs. corresponding time of α-chloralose-treated group at each time interval (ANOVA followed by Dunnett's test, $n = 5$).

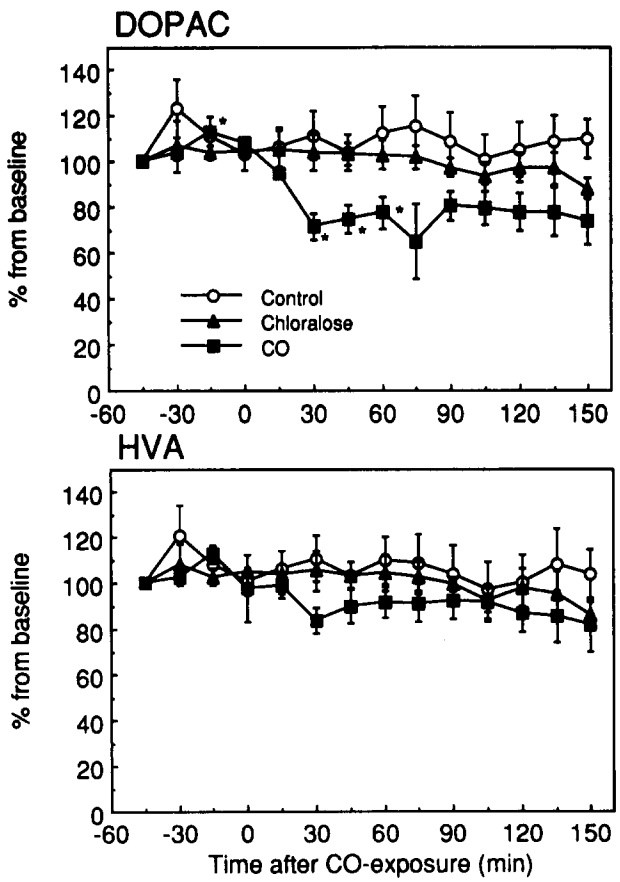

FIG. 2. Effect of CO exposure on the extracellular levels of DOPAC and HVA in the striatum. $*p < 0.05$ vs. corresponding time of α-chloralose-treated group at each time interval (ANOVA followed by Dunnett's test, $n = 5$). For further details see the legend for Fig. 1.

was 140% of the baseline level and persisted for about 2 h (Fig. 3). Repeated measures analysis of variance of the effect of CO exposure on the dialysate concentrations of 5-HT indicated that there was significant effect of treatment for 5-HT, $F1, 104 = 56.1, p < 0.001$. Changes in 5-HIAA levels were different from the acid metabolites of dopamine. The decrease of 5-HIAA release was less pronounced and not significant, $F1, 104 = 2.4, p > 0.12$ (Fig. 3).

Effect of MK-801 Pretreatment on CO Exposure-Induced Changes of Dopamine, Serotonin, and Their Metabolites

MK-801 (1 mg/kg, SC), administered 45 min prior to the CO exposure, showed no changes in the concentrations of dopamine, 5-HT, and their metabolites (Figs. 4–6). In the MK-801-pretreated rats, CO exposure induced a smaller increase of dopamine and 5-HT compared with the control rats. However, there was no significant difference in those levels between CO-exposed and MK-801 plus CO-exposed groups. The decrease of DOPAC levels after CO exposure was blocked by pretreatment with MK-801 and the level was returned to the control level (Fig. 5). HVA levels were increased in the MK-801 pretreated group 2 h after CO exposure compared with the CO-exposed group (Fig. 5). There was no significant difference in the 5-HT and 5-HIAA levels between the MK-801-treated CO-exposed rats and control rats, although MK-

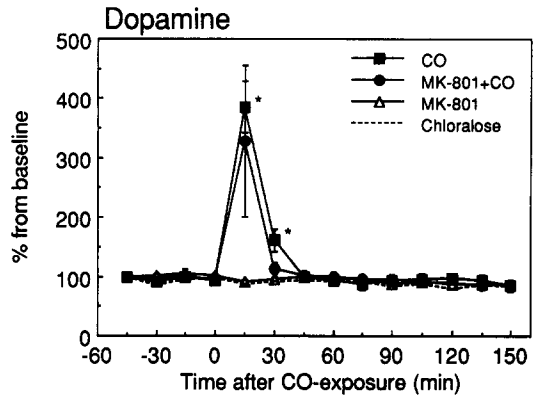

FIG. 4. Effect of MK-801 on the CO-induced changes in levels of dopamine in the striatum. MK-801 (1 mg/kg, SC) was administered 45 min before CO exposure. *$p < 0.05$ vs. corresponding time of α-chloralose-treated group at each time interval (ANOVA followed by Dunnett's test, $n = 5$). For further details see the legend for Fig. 1.

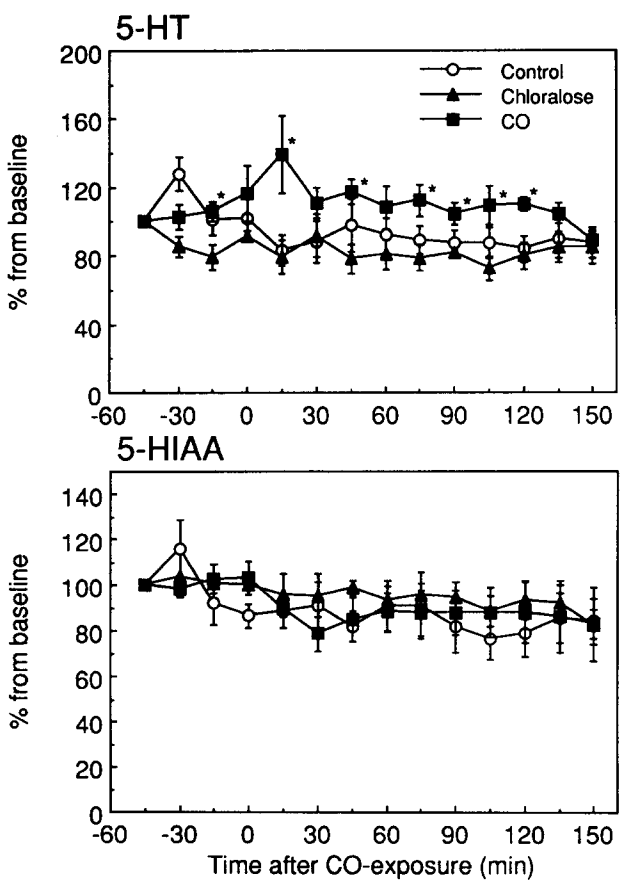

FIG. 3. Effect of CO exposure on the extracellular levels of 5-HT and 5-HIAA in the striatum. *$p < 0.05$ vs. corresponding time of α-chloralose-treated group at each time interval (ANOVA followed by Dunnett's test, $n = 5$). For further details see the legend for Fig. 1.

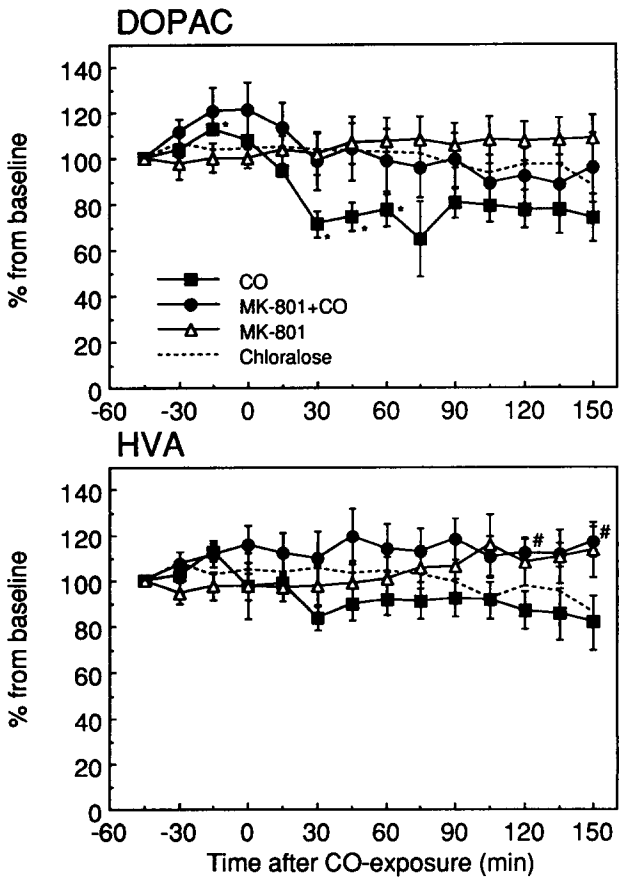

FIG. 5. Effect of MK-801 on the CO-induced changes in levels of DOPAC and HVA in the striatum. MK-801 (1 mg/kg, SC) was administered 45 min before CO exposure. *$p < 0.05$ vs. corresponding time of α-chloralose-treated group at each time interval; #$p < 0.05$ vs. CO-exposed group (ANOVA followed by Dunnett's test, $n = 5$).

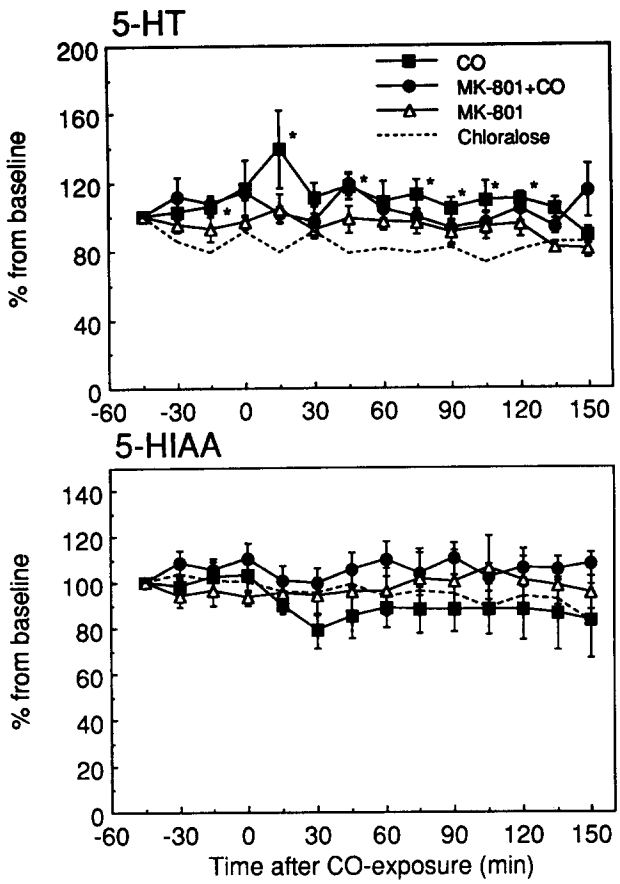

FIG. 6. Effect of MK-801 on the CO-induced changes in levels of 5-HT and 5-HIAA in the striatum. MK-801 (1 mg/kg, SC) was administered 45 min before CO exposure. *$p < 0.05$ vs. α-chloralose group (ANOVA followed by Dunnett's test, $n = 5$).

801 failed to block the significant increase of 5-HT levels induced by CO exposure (Fig. 6).

DISCUSSION

The mechanism by which hypoxia causes increased levels of catecholamines in the extracellular space probably reflects both an increased release of dopamine into the extracellular space as well as a decreased removal of dopamine from the extracellular space. The synaptic release of catecholamines can be driven by increased extracellular potassium levels. Extracellular potassium levels are known to increase rapidly during ischemia, reaching levels of up to 60 mM within 3–4 min (14). Furthermore, normal synaptic release is dependent on intracellular calcium levels. Ischemia is known to cause a rapid calcium influx (36) which, in turn, might be expected to drive synaptic catecholamine release by mass action following CO exposure. However, an increase of the extracellular dopamine levels during ischemia was resistant to tetrodotoxin, suggesting that the increase was independent of action potential. It is well known that removal of catecholamines from the extracellular space is largely due to neuronal reuptake, which is an adenosine triphosphate (ATP)-dependent process (8). Hypoxia is known to cause ATP depletion within 5 min (14); therefore, within 5 min, dopamine reuptake from the extracellular space is blocked and the dopamine level in the extracellular space might increase following CO exposure. It has been reported that the extracellular dopamine levels increased after treatment with nomifensine, a dopamine reuptake blocker, and after addition of pretreatment with nomifensine (100 mg/kg, IP), exposure to hypoxia no further increased in the extracellular dopamine levels was observed (1). Because this dose of nomifensine completely inhibits dopamine reuptake (1), the extracellular dopamine levels after pretreatment with nomifensine can be regarded as a good parameter of dopamine release. Therefore, CO-induced increase in the extracellular dopamine levels may also be involved the result of inhibition of the dopamine reuptake mechanism.

Amphetamine derivatives also increase the efflux of dopamine and reduce level of DOPAC and HVA (15,44). To account for these actions, Zetterström et al. (44) proposed that the release of newly synthesized dopamine reduces its oxidation by monoamine oxidase (MAO). In their view, a significant proportion of DOPAC originates from the intraneuronal metabolism of dopamine before it is released, an idea supported by the fact that nomifensine did not change the levels of extracellular DOPAC in the striatum, although the levels of extracellular dopamine were increased. There is also a possibility that DOPAC levels decrease after CO exposure because in the hypoxic condition, the MAO activities themselves may also be reduced. However, if these comprise the main mechanism, extracellular 5-HT levels should be increased, and 5-HIAA levels should be decreased as well. In the present study, the CO-induced 5-HT release was much less compared with dopamine release and there was no significant difference in 5-HIAA levels between the control and CO-exposed animals. Therefore, other mechanisms causing the increase of dopamine levels and the decrease of DOPAC levels might exist.

Roberts and Anderson first showed that glutamate stimulates the release of exogenous [^{3}H]dopamine from rat striatal slices in vitro, and that this effect was not observed in kainic acid-lesioned slices, or in striatal synaptosomes (31,32). Stimulation of the motor and visual cortices also results in the release of striatal [^{3}H]dopamine synthesized from labeled tyrosine in the cat caudate nucleus in vivo, an effect presumably related to activation of glutamatergic cortico-striatal projections (26). As described in the introductory paragraphs, ischemic conditions also induce massive increases of glutamate in the extracellular fluid of the brain. Our result indicates that extracellular dopamine increases about fourfold over the baseline after CO exposure. Therefore, the present finding may also suggest the glutamate-evoked liberation of striatal dopamine.

Krebs et al. (21,22) have indicated that striatal dopaminergic nerve terminals possess NMDA receptors and that these presynaptic receptors are involved in a facilitative control of dopamine release. Moreover, Carter et al. (6) have reported that both NMDA and kainate stimulate dopamine release in the striatum and that the effects of NMDA are fully antagonized by coinfusion of 2-APV, as well as being tetrodotoxin sensitive, whereas the effects of kainate are only partially blocked by doses of 2-APV. These data suggest that the effects of NMDA are mediated entirely by NMDA receptor stimulation, whereas the effects of kainate may be partially realized by tetrodotoxin-insensitive stimulation of kainate receptors on dopamine terminals, and partially by liberation of an NMDA receptor agonist. Recently, Imperato et al. (17) have reported that the dopaminergic system within the striatum is under glutaminergic control through kainate and quisqualate receptors, while the NMDA receptors do not appear to be involved.

Therefore, we examined whether the increase of extracellular levels of dopamine and decrease of DOPAC levels following CO exposure were blocked by pretreatment with MK-801, an NMDA receptor antagonist.

In the present study, systemic administration of MK-801 could not antagonize the dopamine release while the reduction of DOPAC was reversed by pretreatment with MK-801. Perhaps the most interesting conclusion from these studies is that NMDA or non-NMDA receptor stimulation can affect striatal dopamine release via different routes. In vivo, only one transmitter (glutamate) is generally believed to be able to stimulate both these receptors, although the conditions necessary to allow NMDA receptor stimulation are rather rigidly defined [for review see Mayer and Westbrook (24)]. It is worth noting that we observed no stimulation of endogenous striatal dopamine release with MK-801 itself. This finding is consistent with the data that systemic injection of phencyclidine (3 mg/kg, IP) caused no stimulation of endogenous striatal dopamine release (6). Phencyclidine and MK-801, however, antagonized the NMDA-evoked release of dopamine in rat striatal slices (39). As mentioned above, an increase of the dopamine levels during ischemia was resistant to tetrodotoxin (1). Therefore, it cannot rule out the possibility that the increase of dopamine does not relate to the activation of NMDA receptors. This may explain why MK-801 could not fully antagonize the dopamine release.

The massive increase in excitatory amino acids plays a very important role in the pathogenesis of ischemic cell damage (34). Studies by Weinberger and Cohen (41,42) demonstrated that catecholamine nerve terminals exhibited greater damage during brain ischemia than did GABA, glutamate, or 5-HT nerve terminals. A potential role for released catecholamines in ischemic tissue damage has been suggested (3,23) and is supported by observations that depletion of catecholamines by the administration of α-methyl-p-tyrosine protects dopamine, 5-HT, and glutamate nerve terminals from ischemia-induced injury (43). Although dopamine is involved in ischemia-induced cell damage in the striatum, it is not clear whether massive excitatory amino acids released in the striatum are mainly involved in hypoxia-induced cell damage. In the present experiment, 5-HT was released much less than dopamine. This is consistent with the previous finding that serotonergic neurons are relatively resistant to brain ischemia (42). These results may also indicate that the serotonergic neurons do not interact with excitatory amino acid neurons in the striatum.

In summary, the present results provide further arguments in favor of a role of corticostriatal glutamatergic neurons in the direct presynaptic facilitative control of dopamine release. Imperato et al. (17) have reported that perfusion of the striatum with Ringer's solution containing only high concentration of NMDA releases dopamine in the striatum and that this effect was not antagonized by CPP, a competitive NMDA antagonist. On the other hand, there is now strong evidence from release studies that not only quisqualate/kainate but also NMDA functional receptors are located presynaptically on dopamine nerve terminals (21,22). However, it remains to be determined how these NMDA receptors are activated in physiological conditions and whether or not events similar to long-term potentiation can be initiated at a presynaptic level.

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