**REVIEW**

Role of Nitric Oxide in Central Synaptic Transmission: Effects on Neurotransmitter Release

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ABSTRACT—Nitric oxide (NO), an unstable radical formed via oxidative deamination of L-arginine by NO synthase, has the activity to evoke release of several neurotransmitters including acetylcholine, catecholamines and neuroactive amino acids. N-methyl-D-aspartate (NMDA) receptor stimulation also causes neurotransmitter release through NO formation, which is supported by the data that extracellular hemoglobin completely abolishes the stimulatory effect of NMDA on neurotransmitter release. In addition, NO formed by NMDA receptor activation exhibits its stimulatory action on neurotransmitter release extracellularly. A product formed by the reaction of NO and superoxide, peroxynitrite, is also considered to be partly involved in NO-evoked neurotransmitter release. The removal of Ca²⁺ or Na⁺ significantly reduces the release of GABA evoked by an NO generator, S-nitroso-N-acetylpenicillamine (SNAP), and simultaneous withdrawal of these ions completely abolishes the SNAP-induced release of GABA. Either in the presence or absence of Ca²⁺, GABA transport inhibitors such as nipecotic acid dose-dependently suppress the SNAP-induced GABA release in the presence of Na⁺. These results indicate that NO-evoked neurotransmitter release is mediated by two distinct release systems, a Ca²⁺-dependent system and the reverse process of a Na⁺-dependent carrier-mediated transport system.

**Keywords:** Nitric oxide, Neurotransmitter release, NMDA receptor, NO generator

Nitric oxide (NO) is an unstable radical and has properties as a potent oxidant. Although NO was first identified as an endothelium-derived relaxing factor (EDRF) (1), the data that NO activates guanylate cyclase (2) and an EDRF-like substance is released (3) in the central nervous system (CNS) have been reported. In addition, recent investigations have revealed the presence of NO synthase (EC 1. 14. 23. -) in the central nervous system (CNS) have been reported. In addition, recent investigations have revealed the presence of NO synthase (EC 1.14.23.-) in the central nervous system (CNS). This enzyme is dependent on Ca²⁺ and calmodulin, and requires flavin adenine dinucleotide, flavin mononucleotide, NADPH and tetrahydrobioppterin as cofactors (4); This enzyme catalyzes the oxidative deamination of L-arginine to form NO and L-citrulline. The amino acid sequence of this enzyme was also confirmed (5). In the CNS, this enzyme is abundant in the cerebellum and the olfactory bulb. NO synthase is also distributed in the superior and inferior colliculi, dentate gyrus, striatum, islands of Calleja and superficial layers of the cerebral cortex. All of the basket cells and granule cells in the cerebellum possess NO synthase, while only 1–2% of neurons in the cerebral cortex and hippocampus contain NO synthase (5, 6).

NO, serving as a neurotransmitter and/or a second messenger, is involved in long-term potentiation in the hippocampus and long-term depression in the cerebellum, and it has been proposed to induce neuronal injury (7–9). In addition to these functional roles of NO in the CNS, data suggesting that NO evokes neurotransmitter release have been accumulating. In this review, we describe the role of NO in neurotransmitter release and review the pharmacological profile of NO-evoked release of neurotransmitter.

**Role of NO in neurotransmitter release**

Recent investigations have confirmed that NO is a factor that evokes the release of several neurotransmitters. These data are dominantly obtained from experiments employing N-methyl-D-aspartate (NMDA) receptor activation or direct application of several NO generators including sodium nitroprusside (SNP) and S-nitroso-N-acetylpenicillamine (SNAP) to produce NO.

NMDA receptor activation induces the release of
norepinephrine from hypothalamic slices (10) and dopamine from the striatum (11-13). The releases of other neurotransmitters such as GABA and acetylcholine (ACh) are also evoked from cerebral cortical and striatal neurons by NMDA receptor stimulation (14-16). These releases of neurotransmitters induced by NMDA are significantly inhibited by the presence of Mg$^{2+}$ and MK-801, a noncompetitive antagonist specific for NMDA receptors, indicating that the releases of neurotransmitters evoked by NMDA are certainly events subsequent to the activation of NMDA receptors by NMDA. Although several investigators have not referred to NO produced by NMDA receptor stimulation, NMDA-induced neurotransmitter release is assumed to be mediated by NO production resulting from NMDA receptor stimulation, because an increase in Ca$^{2+}$ influx, triggered by the activation of NMDA receptors, stimulates the activity of Ca$^{2+}$-dependent NO synthease (17). The data that hemoglobin having an activity to scavenge NO significantly suppresses the increase in neurotransmitter release induced by NMDA receptor stimulation (16, 18) are also considered to support this idea. The experimental result that NO synthase inhibitors including N-nitro-l-arginine and N$^{\omega}$-methyl-l-arginine reduce the NMDA-evoked increase in neurotransmitter release to the basal level may indicate that the induction of neurotransmitter release by NMDA receptor stimulation is due to NO formed by NMDA receptor stimulation (16, 18).

NO formed by the activation of NMDA receptors is initially localized in the intracellular space, because NO synthase is soluble and is located in the cytoplasm. On the other hand, hemoglobin is a macromolecule with a molecular weight of approximately 60 kDa. In our study, we have employed 5 min as an incubation period to measure neurotransmitter release (16, 19, 20). During such a short period, it is not likely that the hemoglobin molecule is incorporated into neurons. In addition, NO with a neutral charge has been assumed to have free diffusibility in aqueous medium and across cell membranes (21). Therefore, it is reasonable to assume that NO produced intracellularly by NMDA receptor stimulation diffuses out through neuronal membranes and then extracellularly exhibits its stimulatory action to induce neurotransmitter release.

NMDA receptor stimulation is known to depolarize neuronal membranes and consequently to increase Ca$^{2+}$ influx into neurons in association with the opening of voltage-dependent Ca$^{2+}$ channels. The increase in Ca$^{2+}$ influx is assumed to contribute to the initiation of Ca$^{2+}$-dependent exocytotic release of neurotransmitter. However, it is unlikely that such an event occurs because hemoglobin completely abolishes the stimulatory effect of NMDA receptor activation on neurotransmitter release (16, 18). Namely, neurotransmitter release evoked by NMDA receptor activation is considered to be due to NO formation subsequent to the activation of NO synthase rather than Ca$^{2+}$ influx itself via the opening of voltage-dependent Ca$^{2+}$ channels, although the possibility that the latter event mediated by NO participates in neurotransmitter release evoked by NMDA receptor stimulation has not yet been clarified.

Direct application of NO generators to preparations from the brain also releases neurotransmitters. SNP has been reported to evoke the releases of dopamine (22) and acetylcholine (23) from striatal slices, acetylcholine (16, 19) from cerebral cortical neurons, and GABA from striatal (23) and cerebrocortical neurons (20). SNAP also induces the release of acetylcholine from the striatum (23) and cerebral cortical neurons (19) and that of GABA from cerebral cortical neurons (20). Similarly, other NO generators such as hydroxylamine induce the increased releases of norepinephrine and acetylcholine (24). In these investigations described above, that NO liberated from NO generators is a primary factor to induce the release of neurotransmitters is confirmed by the evidence that hemoglobin abolishes the stimulatory actions of NO generators on neurotransmitter release.

In addition to the application of NO generators and NMDA receptor stimulation to induce neurotransmitter release, endogenous NO has also been reported to participate in neurotransmitter release. To examine the role of endogenous NO in neurotransmitter release, NO synthase inhibitors have usually been employed. NO synthase inhibitors inhibit neurotransmitter release from the brain (22, 25) as well as the peripheral nervous system (26, 27). Based on these reported data, it is certain that NO serves as a factor to evoke neurotransmitter release in the CNS.

Participation of peroxynitrite, a NO-related substance, in NO-induced neurotransmitter release

In biological tissues, NO reacts with transition metal ions included in metalloproteins to form complexes and with O$_2$ to be converted to nitrogen dioxide (NO$_2$·) (28). Similarly, NO rapidly reacts with superoxide in aqueous solution with a rate constant of 6.7±0.9 x 10$^9$ M$^{-1}$sec$^{-1}$ to form peroxynitrite (OONO⁻) (29, 30) (Fig. 1). The pKa value of peroxynitrite is 6.8 (31), and its half-life at pH 7.4 is less than 1.9 sec (32). The half-life of peroxynitrite is considered to be longer than that of NO (33). Under physiological conditions, peroxynitrite is easily protonated to form peroxynitrous acid. After protonation, peroxynitrous acid is decomposed to hydroxyl radical (·OH) and NO$_2$· or to NO$_3$⁻ and H$^+$ (31) (Fig. 1). When hydroxyl radical is removed by hydroxyl radical scavengers, more nitrogen dioxide is formed (34).
Under experimental conditions where there is an adequate supply of oxygen, the formation of superoxide might be expected, and it is supposed that NO may react with superoxide to form peroxynitrite. According to this working hypothesis, the neurotransmitter release evoked by NO is considered to be partially mediated by peroxynitrite formed from NO and superoxide during release experiments. Therefore, the authors performed an experiment to examine the functional role of superoxide on NMDA- and NO generator-evoked releases of [³H]GABA and endogenous acetylcholine by the removal of superoxide with superoxide scavengers such as Cu²⁺, Zn²⁺ superoxide dismutase (SOD) and ceruloplasmin. These superoxide scavengers dose-dependently inhibited the NMDA- and NO generators-evoked release of acetylcholine (16, 19) (Fig. 2). Similar effects of the superoxide scavengers on [³H]GABA release were observed (20). These data are assumed to indicate that the formation of peroxynitrite is essential to the NO-induced neurotransmitter release. On the other hand, Beckman and his co-workers reported that peroxynitrite reacts with SOD (35). Even if this is the case, it is suggested that peroxynitrite is involved in NO-evoked neurotransmitter release, because in the experiments described above, superoxide scavengers have been added into the experimental system before the application of NO generators, which implicated that the superoxide is removed prior to the formation of peroxynitrite from NO and superoxide. To clarify the possible involvement of peroxynitrite in the NO-evoked release of neurotransmitter, we have examined whether or not peroxynitrite has an activity to evoke neurotransmitter release by the direct application of synthesized peroxynitrite to cerebral cortical neurons. Synthesized peroxynitrite induced the release of both [³H]GABA and
acetylcholine from cerebral cortical neurons in a dose-dependent manner (Fig. 3). Based on these results, it is reasonable to conclude that the NO-evoked neurotransmitter release is partly mediated by peroxynitrite formed by the reaction of NO with superoxide.

At present, the mechanisms underlying the induction of neurotransmitter release by peroxynitrite are not yet clarified. Peroxynitrite is a potent oxidant and shows a variety of biological actions: Peroxynitrite oxidizes thiols contained in proteins, non-proteins (36, 37) and deoxyribose (32), and it induces the peroxidation of membrane lipids (31) and lipoproteins (38). In addition, the nitration of tyrosine and phenylalanine is attributed to the actions of peroxynitrite (35, 39). These biochemical effects of
effect (34), to decrease sodium uptake in rat colonic membrane (40) and to increase Ca\(^{2+}\) efflux from mitochondria (41). Taking these data together, it is likely that peroxynitrite evokes neurotransmitter release by the modification of physiological properties of neuronal membranes and/or intracellular proteins that regulate processes of neurotransmitter release.

Mechanisms underlying neurotransmitter release evoked by NO

In general, neurotransmitter release is considered to be mediated by a Ca\(^{2+}\)-dependent exocytotic mechanism. In addition to this release system, recent lines of evidence have revealed that the reverse process of the Na\(^{+}\)-dependent carrier-mediated transport system is also involved in the release of neurotransmitters (42, 43). Although recent investigations confirm that NO certainly evokes neurotransmitter release as mentioned above, little data on the mechanisms of this NO-induced neurotransmitter release are available. We will now show which of the above-described release systems are involved in the release of GABA evoked by NO liberated from NO generators.

The removal of Ca\(^{2+}\) significantly decreased the release of [\(^3\)H]GABA evoked by SNAP from cerebral cortical neurons (44). The extent of Ca\(^{2+}\)-independent release of [\(^3\)H]GABA was approximately 50\% of the release in the presence of Ca\(^{2+}\). This Ca\(^{2+}\)-dependent release may be driven by ordinary exocytotic process. On the other hand, Na\(^{+}\) withdrawal from incubation buffer by equi-

Fig. 4. Effects of Ca\(^{2+}\) and/or Na\(^{+}\) on S-nitroso-N-acetylpenicillamine (SNAP)-induced release of [\(^3\)H]GABA from cerebral cortical neurons in primary culture. Each value represents the mean ± S.E.M. (n = 4) and is expressed as a percent of the basal release. **P < 0.01, compared with the value determined in the presence of both Ca\(^{2+}\) and Na\(^{+}\) (Bonferroni’s test). In the case of Na\(^{+}\) removal from the incubation buffer, Na\(^{+}\) was replaced by equimolar choline. ##P < 0.01, compared with the value obtained in the absence of both Ca\(^{2+}\) and Na\(^{+}\) (Bonferroni’s test).

Fig. 5. Effects of GABA uptake inhibitors, nipecotic acid (NA) and 1-[2-(((diphenylmethylene)amino)oxy)ethyl]-1,2,5,6-tetrahydro-3-pyridine carboxylic acid (NO-711), on S-nitroso-N-acetylpenicillamine (SNAP)-induced [\(^3\)H]GABA release from cerebral cortical neurons in primary culture. The concentration of SNAP was 5 µM. Each value represents the mean ± S.E.M. (n = 4) and is expressed as a percent of the basal release. *P < 0.05, **P < 0.01, compared with each value determined in the presence of SNAP alone (Dunnett’s test).
molar replacement of Na\(^+\) with choline also reduced the SNAP-induced \(^{3}\text{H}\)GABA release by about 50\% in the presence of Ca\(^{2+}\). In the absence of both Ca\(^{2+}\) and Na\(^+\) in the incubation buffer, SNAP did not show any stimulatory effects on \(^{3}\text{H}\)GABA release (Fig. 4) (44). These data indicate that NO induces \(^{3}\text{H}\)GABA release through two different mechanisms, the Ca\(^{2+}\)-dependent exocytotic release system and the Na\(^+\)-dependent release mechanism.

Since the Na\(^+\)-dependent release system involved in neurotransmitter release is supposed to be the reverse process of the Na\(^+\)-dependent carrier-mediated uptake system, we have attempted to clarify this possibility by examining the effects of GABA transport inhibitors, nipecotic acid and 1-(2-(((diphenylethylene)-amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridine-carboxlic acid (NO-711). These inhibitors dose-dependently inhibited the SNAP-evoked \(^{3}\text{H}\)GABA release (Fig. 5), which was observed either in the presence or absence of Ca\(^{2+}\) (44). Such inhibition of the NO-induced \(^{3}\text{H}\)GABA release, therefore, is assumed to be independent of Ca\(^{2+}\). These data indicate that a part of the NO-evoked \(^{3}\text{H}\)GABA release occurs via the reverse process of the Na\(^+\)-dependent carrier-mediated GABA uptake system. The release of neurotransmitter through such a system has been reported in the releases of GABA by electrical stimulation (45) and high potassium (46–48); dopamine, by high glutamate (49); and serotonin, by high potassium (50).

The concentrations of nipecotic acid and NO-711 showing the maximal inhibitory effects on the \(^{3}\text{H}\)GABA release induced by SNAP were 1 \(\mu\text{M}\) and 0.1 \(\mu\text{M}\), respectively. On the other hand, the \(K_{i}\) values of nipecotic acid and NO-711 to inhibit \(^{3}\text{H}\)GABA uptake were found to be approximately 25 \(\mu\text{M}\) and 0.9 \(\mu\text{M}\), respectively. It is
noteworthy that the $K_i$ values of these inhibitors for inhibiting $[^3H]GABA$ uptake are $10-25$ times higher than those exhibiting the maximal reduction of the SNAP-induced $[^3H]GABA$ release. A part of the NO-evoked $[^3H]GABA$ release is dependent on $Na^+$, and this $Na^+$-dependent release of $[^3H]GABA$ is inhibited by the inhibitors of carrier-mediated GABA transport, indicating that NO-evoked $[^3H]GABA$ release is partially operated by the reverse process of the $Na^+$-dependent carrier-mediated GABA transport system.

In conclusion, NMDA receptor stimulation evokes neurotransmitter release via the formation of NO following the activation of $Ca^{2+}$-dependent NO synthase. NO produced by NMDA receptor stimulation diffuses out through the neuronal membrane into the intercellular space and then evokes the release extracellularly. Similarly, NO generators induce the release of neurotransmitter by the liberation of NO from their molecules. Under an adequate oxygen supply, NO rapidly reacts with superoxide to form peroxynitrite, which has a potent oxidative property. The formed peroxynitrite also induces the release of neurotransmitter, which is partly involved in the NO-evoked neurotransmitter release (Fig. 6).

The NO-induced release of GABA is reduced in the absence of $Ca^{2+}$ and/or $Na^+$. The portion of $Na^+$-dependent GABA release evoked by NO is dose-dependently suppressed by GABA transport inhibitors such as nipeotic acid and NO-711. These results indicate that NO-evoked GABA release occurs through the $Ca^{2+}$-dependent release system and the reverse process of the $Na^+$-dependent carrier-mediated GABA transport system.

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