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# Biological Functions of Nitric Oxide in the Brain and Brain Stem

**Zahra Rezaei[1], Sohrab Hajizadeh[2*], Zahra Piri[1]**

[1]Department of Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran
[2]Department of Physiology, Medical School, Tarbiat Modares University, Tehran, Iran

**Abstract**

Nitric oxide (NO) is a small biological arbitrator and signaling molecule that has numerous significant biological roles in our body. Most of the neurons produce NO by neuronal nitric oxide synthase (nNOS). NO has been involved in the regulation of neurogenesis, synaptic plasticity, learning, and memory. Also, it contributes to the regulation of circulation and synapses, cerebral map formation, and neuropeptides. In the current review, we focused on previous research that has demonstrated structural aspects, subcellular localization, and some factors that adjust nNOS function. Furthermore, we have characterized the effect of nNOS in the brain in some physiological situations, particularly long-term potentiation and depression (LTP and LTD) and neural plasticity during development . Moreover, the effect of NO on neuropeptidergic neurons, including orexin, in reward systems was reviewed. Also, this study has focused on the NO involvement in brain circulation, the excitability of neurons, and the homeostatic balance of excitatory and inhibitory signaling in the brain.

**Keywords**: Nervous system, Nitric oxide, Brain, Brain stem

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## Introduction

Nitric oxide (NO) is a small biological mediator that plays many significant biological roles in our body (1). Though it is a short-lived messenger with two main roles in our body: adjustment and cytotoxicity. Low levels of NO show regulatory and cytoprotective properties, while high levels will be destructive by producing cytotoxic effects (2). NO, as a neuromodulator, regulates sleep, neural secretion (3), synaptic plasticity (4), body temperature, neural development (5), and gene expression (6).

Diverse NOS types have been demonstrated to adjust diverse physiological roles. Different types of NO synthases including neuronal, inducible, and endothelial ones have been explained in Table 1. NO creation from neuronal nitric oxide synthase (nNOS) in the central nervous system is related to an extensive array of cerebral proficiencies and efficient controls, including neurosecretion, cognitive roles, cerebral circulation, neurogenesis, synaptic plasticity, appetite, sleep, and body temperature (7).

In preceding research, injection of sodium nitroprusside, as an NO donor, inside the nucleus raphe magnus (NRM), the thermoregulation center in rats, prohibited thermal constriction of vessels of rat tail in cold exposure. Furthermore, intra-NRM injection of lidocaine reduced the blood flow in hypothermia (13,14). In sum, NO modifies skin blood flow in the NRM of rats in hypothermia (14).

In addition, in the nucleus tractus solitarius (NTS) nitric oxidergic neurons have been established to adjust blood pressure. Baroreceptor fibers inside the NTS synapse with the rosteroventrolateral part of the medulla through nitric oxidergic fibers. It was reported that NTS inactivation increased diastolic pressure (15,16). Moreover, released NO inside the cerebellum produces dilation of vessels by exciting stellate cells that express nNOS (17).

Raphe magnus is a center of regulation of the cardiovascular system. Raphe projections to the medulla cause an extra substrate for inducing autonomous activity over changes of preganglionic neurons of the parasympathetic system, premotor neurons of the sympathetic system, and visceral sensory inputs. Electrical or chemical stimulation can induce both depressor and pressor reactions with little indication of any functional organization within different raphe nuclei (18). Raphe regulates skin blood flow via sympathetic activation (14,19).

## nNOS regulating factors

Phosphorylation of nNOS is vital for the enzyme activity that is controlled by some kinases and phosphatases such as calmodulin-dependent kinases, PKA, PKC, and phosphatase 1, which are modified by extracellular and intracellular factors (20).

*Corresponding Author: Sohrab Hajizadeh, Email: hajizads@modares.ac.ir

**Table 1.** Different types of nitric oxide synthase

| Type | Place of function | Controlling factor | Functions | References |
|---|---|---|---|---|
| Neuronal nitric oxide synthase | Cerebral cortex, nucleus accumbens, striatum, amygdala, CA1, dentate gyrus, paraventricular nuclei, raphe magnus, nucleus of the solitary tract, cerebellum | Phosphorylation CaM/$Ca^{2+}$ PDZ domains | Synaptic plasticity, learning, memory neurogenesis central blood pressure regulation, fine-tuning synchronous network activity in the developing hippocampus, coupling between increased neuronal activity and local blood flow | (8) |
| Inducible nitric oxide synthase | Glial cells, Macrophages | CaM/$Ca^{2+}$ | Blood pressure regulation, inflammation, infection, and the onset $Ca^{+2}$-independent Immune system, Pain | (9-11) |
| Endothelial nitric oxide synthase | CA2 and CA3, granule cells of the dentate gyrus Vascular endothelial cells | Phosphorylation, CaM/ $Ca^{2+}$ | $Ca^{+2}$-dependent Vasodilation, Pain, Prevention of atherosclerosis Vasoprotection | (9,10,12) |

Calmodulin acts as an allosteric activator of NOS that simplifies electron current transferring from NADPH to the reductase domain flavins and from the reductase domain to the heme center. Calmodulin binding is brought about by a surge in intracellular $Ca^{2+}$(21,22).

Hsp90 can intensify the binding of calmodulin to nNOS that activate nNOS. Therefore, nNOS–HSP90 binding augments the production of NO. However, in skeletal muscles, caveolin-3 diminishes NO synthesis by inhibition of Ca-CaM binding, and so this inhibition is reversed by Ca-CaM (1).

Another factor is NOSIP (nitric oxide synthase interacting protein) which inhibits the production of NO (23). NOSIP and nNOS are located in different areas of the central and peripheral nervous systems. NOSIP negatively affects nNOS activity in a neuroepithelioma cell line stably expressing nNOS (23).

**Nitric oxide and regulation of synapses in development**

Nitric oxide can control the synchronization of metabolic states, electrical coupling, and direction of transcriptional activity among linked neurons (24). Gap junctions allow neurons to connect with others more quickly. Hence, NO controls the electrical synapses through gap junction coupling between neurons (25).

Gap junctions associate electrical and metabolic synapses between glutamatergic and GABAergic neurons of the neocortex. The synchronization among excitatory and inhibitory signaling is important for preserving the equilibrium between excitatory and inhibitory signaling in the brain. nNOS is the most dominant NO-producing interneurons of the hippocampal neurons. It can decrease glutamate (26) or GABA release (27) presynaptically through second messenger cGMP. NO is a weak polar molecule that can diffuse simply through cell membranes. Though NO shows a high reactivity in a few micrometers, it may display synapse specificity for regulating presynaptic roles (28).

According to some studies, the release of neurotransmitters in the synapses including acetylcholine, glutamate, GABA, and catecholamines is moderated by NO in the striatum, hypothalamus, locus coeruleus, and hippocampus (26).

Some glutamatergic synapses during postnatal development are silent because they consist of N-methyl-D-aspartate (NMDA) receptors that mainly induce hyperpolarization and inhibitory roles (29). In the locus coeruleus neurons that receive glutamatergic innervation from paragigantocellularis nucleus (30-32), injection of NO donor potentiates the memory induction (33). Coordinated injection of nitroprusside and glutamate proved a reverse outcome, and so the neurons showed depolarization and excitation (34). These consequences revealed that NO participates in changing inhibitory reactions to glutamate, and it may be intermediated by NMDA receptors (29).

**Nitric oxide and orexin neuropeptide synthesis regulation**

The previous reports showed that NO makes degeneration of orexinergic neurons of the hypothalamus through inhibition of protein disulfide isomerase (35). Orexin peptides are formed in the lateral portion of the hypothalamus that affects postsynaptic neurons through two G-protein-coupled receptors (36,37). In the *rostral ventrolateral medulla* (*RVLM*), orexin might contribute to the central directive of cardiovascular functions, and both of its receptors are vitally involved in this process. The cardiovascular roles of orexin in the RVLM can be produced by nNOS-derived NO, which triggers guanylate cyclase-associated signaling pathways (38). It is discovered that the continuing inhibition of orexin 1 receptors may alter the phospholipase Cβ3 (PLCβ3) in the hippocampus, and hence may inhibit the formation of memory (39). Orexin may enhance the PLCβ3 level in most regions of the rat hippocampus (40). In addition, the blockade of orexin receptor 1 is involved in the progress of morphine addiction through the reduction of cAMP-response element-binding protein and PLCβ3 (41). Furthermore, it was revealed that the continued inhibition of the orexin receptor might contribute to formalin-induced nociceptive behaviors (42).

**Neurogenesis neuronal developmental effects of NO**

Nitric oxide has been involved in neurogenesis and also in the progressive stages, including synaptogenesis and formation of the neural map in neuronal differentiation (43).

Neurogenesis is detected throughout the development of the brain and likewise in brain damages such as stroke and seizures. Though adult neurogenesis is controlled by numerous endogenous neurotransmitters like glutamate, serotonin, and NO, it is revealed that NO performs as a paracrine messenger in newly formed neurons; NO contributes to the regulation of differentiation and proliferation in mouse brain neural progenitor cells (43).

It has been proposed that neuronal NO negatively regulates neurogenesis (44). NO regulates the extent of the undifferentiated precursor pool and increases the differentiation of neurons in two main neurogenesis places in the adult brain, the sub-granular zone and the sub-ventricular zone of the dentate gyrus. So, it is an inhibitor of neurogenesis physiologically (45).

Some studies have shown that regulatory effects of NO take place through EGF downstream signaling pathway and augment Ras-GTP activity, which might produce a proliferation of cells by the trigger of mitogen-activated protein kinase ERK1/2 (46). Exogenous NO may negatively cause the proliferation of neural stem cells (NSCs) and hence downregulates the expression of nNOS in NSCs via dropping cAMP-response element-binding protein phosphorylation (44).

**Effect of NO on the excitability of neurons**

The excitability of neurons is regulated through the location, expression, and action of voltage-dependent ion channels inside the plasma membrane. $Na^+$and $Ca^{2+}$channels comprise two main channels that induce action potential, while the vital controllers of excitability are voltage-dependent potassium channels (47). The pattern of action potential firing depends on the interaction of voltage-dependent ion channels. The action potential is the essential signaling mechanism that activates the synaptic transmission in axon terminals. Synaptic transmission is classified according to the calcium amount entering the presynaptic terminal (48). Alterations of the voltage-gated $Na^+$and $K^+$channels elucidate the dynamic shift of a neuron between the low and high-frequency firing (49).

Continued duration of open channel was detected for the gathered channels, which shows the changes in activation gating (50,51). Selective permeation of sodium ions through voltage-dependent sodium channels is important to the induction of action potentials in excitable cells like neurons. Depolarization of the neuron leads to activation and inactivation of sodium channels within milliseconds. The entry of sodium ions over the integral membrane proteins containing the channel depolarizes the membrane more and recruits the rising phase of the action potential (52). The main function of sodium channels is to permit the propagation of action potentials (53).

The conductance of ion channels is regulated by $K^+$channels (54), $Ca^{2+}$channels (55), and hyperpolarization-activated cyclic nucleotide-gated channels (56). The effect of NO on ion channels in glutamatergic synapses has been shown in Figure 1.

**Effects of NO on learning and memory**

Long-term potentiation (LTP) and long-term depression (LTD) are processes of strengthening and weakening

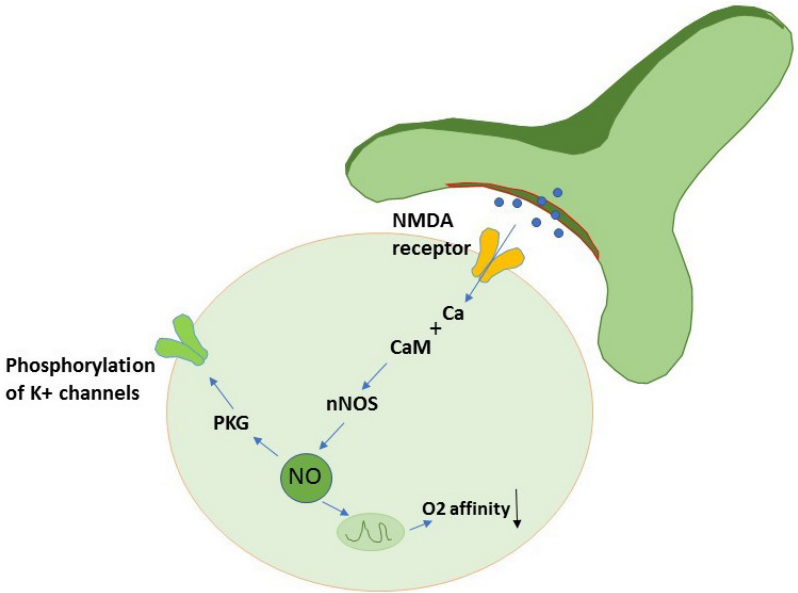


**Figure 1.** The effect of NO in glutamatergic synapses on ion channels. NMDA receptor activity produces NO that phosphorylates the potassium channels

the synapses, respectively (57), and are supposed to have a central effect on the modification of cortical circuits (58,59). Moreover, LTP may reduce or inhibit coordinated activity in inhibitory synapses of cortical neurons (59). The effect of NO on LTP in glutamatergic synapses has been shown in Figure 2.

Nitric oxide can be released from activated CA1 pyramidal neurons in the hippocampus. Previous studies have also recognized the presence of nNOS protein trace in populations of GABAergic interneurons (60-62). Some studies proved NO roles in modulations of synaptic plasticity, including production of LTP in the hippocampus and cerebral cortex and production of LTD in the striatum and cerebellum (63-67).

Nitric oxide generation is accomplished in presynaptic terminals that activate postsynaptic actions or interneurons, persuading LTD in the cerebellum and striatum. Furthermore, NO can act like a retrograde messenger that is produced in postsynaptic neurons and have some effects on presynaptic terminals to induce LTP in the hippocampus and cortical area (68,69).

Nitric oxide synthase is expressed as a result of the postsynaptic NMDA receptors activation in pyramidal cells of the adult hippocampus. The resulting NO like a retrograde messenger regulates the production of LTP at the Schaffer collateral/CA1 synapses (70,71). However, NO is formed in parallel fiber terminals of cerebellar interneurons and diffuses into the postsynaptic Purkinje cell, finally leading to the LTD induction (72). While NO shows irregular postsynaptic actions in the hippocampus (73) and can make an acute augmentation of synaptic efficacy, it shows the presynaptic action for longer times (74,75). NO may lead to the synchronous network activity

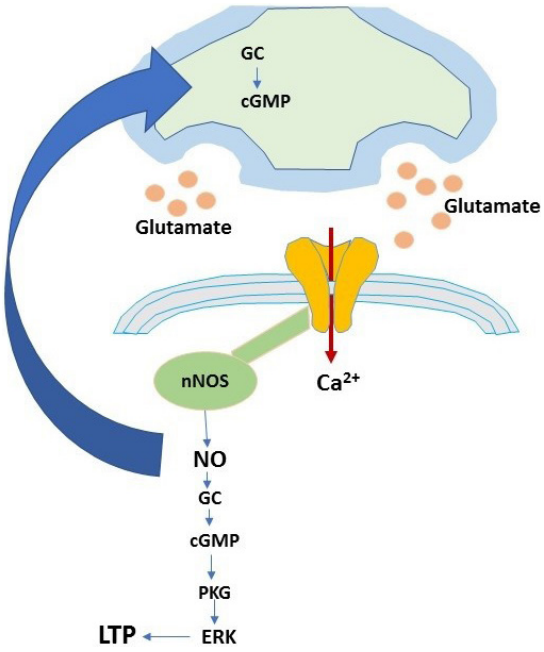


**Figure 2.** The impact of NO on LTP in glutamatergic synapses

in the hippocampus during development because NO signaling diminishes the GABAergic and glutamatergic postsynaptic currents (27). Interruption of this balance results in pathological disorders such as autism, epilepsy, and schizophrenia (75,76).

**Effects of NO on cerebral maps formation**

Neuronal nitric oxide synthase and NO show a central role in brain development through the regulation of synapse formation and patterning, (24,27,77,78). They involve in the procedure of the activity-dependent modification of axonal growth, stabilization, and consolidation of the developed synapses (79,80).

Also, they involve in neuronal communication and activating a shift from proliferation to differentiation of cells during neurogenesis (78,81,82). The underlying signaling of map formation in the development of the brain is difficult to know. Some structures of the embryo-like signaling centers of the boundaries of the tissues release signaling proteins. These proteins regulate zonal growth and specify local character in the tissue.

Several models have been proposed for map formation. In one of the models, signaling proteins diffuse through the tissue and create a gradient that exhibits the positional information (83). In another model in the developing spinal cord, Wingless-tnt (WNT) 1 and 3a produce a gradient of proteins based on their concentration, one of which synchronizes the growth of tissue (84).

Nitric oxide as a neurotransmitter involves in the development of cerebral maps. It causes synaptic enhancement or abolition of immature synaptic connections at retino-thalamic and retino-collicular planes in the visual system (85). Evidence shows that NO plays an important role in creating patterned neocortical maps. For example, nNOS knockout mice show the normal organization of the somatosensory cortex and barrel field plasticity (86,87).

Nonetheless, NO involves in launching and refining neocortical connectivity, since NO may promote thalamocortical development and contributes to the consolidation of synaptic strength in layer IV of the primary somatosensory cortex (24).

As formerly described, NO similarly may affect the gap junction coupling of neurons (88,89). In glutamatergic or GABAergic neurons of the developing neocortex, metabolic and electrical communication is completed by gap junctions. Therefore, the regulatory effects of NO in the regulation of gap junctions permit it to affect electrical coupling, coordination of metabolic states, and transcriptional activity between associated neurons during the development of the brain (24). Despite this evidence, detecting the specific roles that NO and nNOS play in the development of the brain requires additional research.

Both excitatory and inhibitory effects of NO in different

areas of the brainstem are caused by direct actions of NO on neurons and/or by NO-mediated alteration in local cerebral blood flow. Through cyclic 3′, 5′-guanosine monophosphate (cGMP)-dependent mechanisms, NO modulates neuronal activity. In the ventrolateral medulla (VLM) and the nucleus of the solitary tract (NTS), which are located in the lower brain stem, NO modifies several central and reflex-activated neuronal pathways. NO-mediated modulation of autonomic function is strictly reduced in cardiovascular diseases (90). Microinjection of superoxide dismutase into the RVLM reduced sympathetic activity, whereas peroxynitrite, an important mediator of NO-related oxidative stress, had excitotoxic impacts (91). Antagonism of neuronal NOS shows a new therapeutic method to counteract neurohumoral activation in hypertension and heart failure (92).

**NO involvement in brain vessels and blood circulation**

When NO donor is injected into cortical slices causes vasodilation, this effect may likewise promote electrical stimulation through nNOS expressing interneurons of the cortex in that zone (93). Relation between the vasodilatory and neuronal activity of interneurons expressing nNOS has also been detected in other brain areas, like the cerebellum (17). By this adjustment of brain blood perfusion, most nNOS interneurons co-release neuropeptide Y (NPY) which is a strong vasoconstrictor (94). Hence, it seems that both nerve growth factors of the cortex and hippocampus which co-express NPY and nNOS may show dual regulatory roles over cerebral blood flow. Neuropeptide Y is probably released at axon terminals and regulates the tonicity of blood vessels distant from the cell body, whereas NO is produced by the somatodendritic section and affects more proximally through volume transmission (24).

Parasympathetic nerves send nitroxidergic innervation to the blood vessels of forebrain cerebral area. Released NO from parasympathetic nerves makes vasodilatation of cerebral vessels during hypertension (95). NO exhibits a main effect in the regulation of cerebral blood flow (CBF) at rest and during physiological and pathological stresses. eNOS-NO shows an important role in autoregulation, while nNOS-derived NO is critical for neurovascular coupling (96). NO is a vital moderator of cerebral vasodilatation in response to alteration of the physiological parameters during hypercapnia and hyperoxia; however, the role of NO in the regulation of evoked cerebral blood flow remains to be elucidated (97). NO provides a potential target for new therapeutic opportunities against several neuroendocrine and behavioural abnormalities (98).

**Pathophysiological functions of nNOS**

Abnormal NO signaling contributes to some neurodegenerative pathologies including excitotoxicity following stroke, Alzheimer's and Parkinson's diseases and multiple sclerosis. Under these conditions, NO can contribute to excitotoxicity, perhaps by peroxynitrite activation of PARP and/or mitochondrial permeability transition. High levels of NO can also yield energy depletion, caused by inhibition of mitochondrial respiration and glycolysis. Some disorders of smooth muscle tone in the gastrointestinal tract (e.g. gastroesophageal reflux disease) may also be derived from an extreme NO production by nNOS in peripheral nitrergic nerves (99).

A central mode of inactivation of NO is its reaction with the superoxide anion which forms the potent oxidant peroxynitrite. This can make oxidative damage, nitration, and S-nitrosylation of biomolecules including proteins, lipids, and DNA (100). Nitrosative stress caused by oxidant peroxynitrite contributes to DNA single-strand breakage, followed by poly (ADP-ribose) polymerase activation (101).

Previous study results demonstrated that demyelination was mainly prevented in mice lacking nNOS. Protection enhances mature oligodendrocyte survival and diminishes apoptosis. In eNOS-/- mice, demyelination increased to the same level as in the wild type, but they showed a slight delay in spontaneous remyelination (102).

nNOS as a $Ca2^{+}$-sensitive enzyme exhibits a major role in excitotoxicity. In primary cortical neuronal cultures of nNOS-/- mice, these neurons exhibit resistant to NMDA neurotoxicity and to oxygen-glucose deprivation compared with wild-type cultures. These studies in vitro show that nNOS-derived NO is the principal source of neurotoxicity in neurons (1).

Ischemia activates a pronounced augmentation in citrulline immunoreactivity, but more so in a large population of the neuronal isoform of NO synthase in the peri-infarct rather than the infarcted tissue. In contrast, 3-nitrotyrosine (a marker for peroxynitrite formation) is confined to the infarcted tissue and is not present in the peri-infarct tissue. In addition, nitric oxide production is induced in a number of immune cells, including neutrophils and macrophage/monocyte lineage (103).

Moreover, overexpression of nNOS was shown in basal ganglia and the respiratory burst of circulating neutrophils of Parkinson's disease patients. At the same time, NO production and protein tyrosine nitration were also significantly enhanced. Based on these observations, it is conceivable that nNOS exhibits a key role in the pathogenesis of Parkinson's disease. Therefore, a better perception of nNOS involved in Parkinson's disease is required (99).

All three isoforms of NOS are elevated in Alzheimer's disease, indicating an important role for NO in the pathomechanism of Alzheimer's disease. Given an impressive amount of isoform-specific NOS inhibitors could be useful for Alzheimer's disease treatment (99).

## Conclusion

Nitric oxide contributes to the regulation of the neurons in the circulatory system, brain blood flow, neurogenesis, neuron excitability, modulation of electrical and chemical synapses in development, cerebral map formation, and neurovascular coupling for regulating neocortical blood flow. Moreover, NO involves in the homeostatic balance of excitatory and inhibitory signaling in the brain, LTP, LTD, neuronal plasticity, learning and memory, and control of the blood flow in the central nervous system.

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**Author Contributions**

**Conceptualization:** Zahra Rezaei, Zahra Piri.
**Investigation:** Zahra Rezaei.
**Methodology:** Zahra Rezaei.
**Project administration:** Sohrab Hajizadeh.
**Resources:** Zahra Piri.
**Supervision:** Sohrab Hajizadeh.
**Validation:** Zahra Rezaei.
**Visualization:** Sohrab Hajizadeh.
**Writing – original draft:** Zahra Rezaei.
**Writing – review & editing:** Sohrab Hajizadeh.

**Conflict of interest**

No conflict of interest is declared.

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