

Nitric oxide synthase (E.C. 1.14.13.39)

Overview: The nomenclature suggested by NC-IUPHAR of NOS I, II and III has not gained wide acceptance. Nitric oxide synthases [NOS, L-arginine, NADPH₂ : oxygen oxidoreductase (nitric-oxide-forming)] utilize L-arginine (not D-arginine) and molecular oxygen to generate nitric oxide and L-citrulline. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca²⁺/calmodulin and thus appears to be constitutively active. All the three isoforms are homodimers and require tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all three isoforms, with an IC₅₀ value in the micromolar range.

Nomenclature	Endothelial NOS	Inducible NOS	Neuronal NOS
Preferred abbreviation	eNOS	iNOS	nNOS
Other names	NOS III, NOS-3, ecNOS	NOS II, NOS-2	NOS I, NOS-1, brain NOS
Ensembl ID	ENSG00000164867	ENSG00000007171	ENSG00000089250
Selective inhibitors	–	1400W (8.2, Garvey <i>et al.</i> , 1997), 2-amino-4-methylpyridine (7.4, Faraci <i>et al.</i> , 1996), PIBTU (7.3, Garvey <i>et al.</i> , 1994), NIL (5.5, Moore <i>et al.</i> , 1994), aminoguanidine (Corbett and McDaniel, 1992)	3-Bromo-7NI (6.1–6.5, Bland-Ward and Moore, 1995), 7NI (5.3, Babbedge <i>et al.</i> , 1993)

The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes (Mayer & Hemmens, 1997). NADPH : O₂ oxidoreductase catalyses the formation of superoxide anion/H₂O₂ in the absence of arginine and tetrahydrobiopterin.

Abbreviations: 1400W, N-(3-(aminomethyl) benzyl)acetamidine; NADPH, reduced nicotinamide adenosine dinucleotide phosphate; 7NI, 7-nitroindazole; NIL, L-N⁶-(1-iminoethyl)lysine; PIBTU, 13-phenylen-bis(1,2-ethanediy)bis-thiourea

Further Reading

- Cary SP, Winger JA, Derbyshire ER, Marletta MA (2006). Nitric oxide signaling: no longer simply on or off. *Trends Biochem Sci* 31: 231–239.
- Dudzinski DM, Igarashi J, Greif D, Michel T (2006). The regulation and pharmacology of endothelial nitric oxide synthase. *Annu Rev Pharmacol Toxicol* 46: 235–276.
- Fish JE, Marsden PA (2006). Endothelial nitric oxide synthase: insight into cell-specific gene regulation in the vascular endothelium. *Cell Mol Life Sci* 63: 144–162.
- Forstermann U, Munzel T (2006). Endothelial nitric oxide synthase in vascular disease: from marvel to menace. *Circulation* 113: 1708–1714.
- Fukumura D, Kashiwagi S, Jain RK (2006). The role of nitric oxide in tumour progression. *Nat Rev Cancer* 6: 521–534.
- Jones SP, Bolli R (2006). The ubiquitous role of nitric oxide in cardioprotection. *J Mol Cell Cardiol* 40: 16–23.
- Kukreja RC, Xi L (2007). eNOS phosphorylation: a pivotal molecular switch in vasodilation and cardioprotection? *J Mol Cell Cardiol* 42: 280–282.
- Moncada S, Higgs A, Furchgott R (1997). International Union of Pharmacology Nomenclature in Nitric Oxide Research. *Pharmacol Rev* 49: 137–142.
- Moncada S, Higgs EA (2006). Nitric oxide and the vascular endothelium. *Handb Exp Pharmacol* 213–254.
- Mount PF, Kemp BE, Power DA (2007). Regulation of endothelial and myocardial NO synthesis by multi-site eNOS phosphorylation. *J Mol Cell Cardiol* 42: 271–279.
- Oess S, Icking A, Fulton D, Govers R, Muller-Esterl W (2006). Subcellular targeting and trafficking of nitric oxide synthases. *Biochem J* 396: 401–409.
- Redington AE (2006). Modulation of nitric oxide pathways: therapeutic potential in asthma and chronic obstructive pulmonary disease. *Eur J Pharmacol* 533: 263–276.
- Rivero A (2006). Nitric oxide: an antiparasitic molecule of invertebrates. *Trends Parasitol* 22: 219–225.
- Toda N, Ayajiki K, Okamura T (2009). Cerebral blood flow regulation by nitric oxide: recent advances. *Pharmacol Rev* 61: 62–97.
- Tousoulis D, Boger RH, Antoniadis C, Siasos G, Stefanadi E, Stefanadis C (2007). Mechanisms of disease: L-arginine in coronary atherosclerosis—a clinical perspective. *Nat Clin Pract Cardiovasc Med* 4: 274–283.

References

- Babbedge RC *et al.* (1993). *Br J Pharmacol* 110: 225–228.
- Bland-Ward PA, Moore PK (1995). *Life Sci* 57: PL131–PL135.
- Corbett JA, McDaniel ML (1992). *Diabetes* 41: 897–903.
- Faraci WS *et al.* (1996). *Br J Pharmacol* 119: 1101–1108.
- Garvey EP *et al.* (1994). *J Biol Chem* 269: 26669–26676.
- Garvey EP *et al.* (1997). *J Biol Chem* 272: 4959–4963.
- Mayer B, Hemmens B (1997). *Trends Biochem Sci* 22: 477–481.
- Moore WM *et al.* (1994). *J Med Chem* 37: 3886–3888.