IUPHAR/BPS Guide to Pharmacology CITE
https://doi.org/10.2218/gtopdb/F253/2019.4

Nitric oxide synthases (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

Nitric oxide synthases (NOS, E.C. 1.14.13.39) are a family of oxidoreductases that synthesize nitric oxide (NO.) via the NADPH and oxygen-dependent consumption of L-arginine with the resultant by-product, L-citrulline. There are 3 NOS isoforms and they are related by their capacity to produce NO, highly conserved organization of functional domains and significant homology at the amino acid level. NOS isoforms are functionally distinguished by the cell type where they are expressed, intracellular targeting and transcriptional and post-translation mechanisms regulating enzyme activity. The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [11] has not gained wide acceptance, and the 3 isoforms are more commonly referred to as neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) which reflect the location of expression (nNOS and eNOS) and inducible expression (iNOS). All are dimeric enzymes that shuttle electrons from NADPH, which binds to a C-terminal reductase domain, through the flavins FAD and FMN to the oxygenase domain of the other monomer to enable the BH4-dependent reduction of heme bound oxygen for insertion into the substrate, L-arginine. Electron flow from reductase to oxygenase domain is controlled by calmodulin binding to canonical calmodulin binding motif located between these domains. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+}/calmodulin with great avidity and is essentially calcium-independent and constitutively active. Efficient stimulus-dependent coupling of nNOS and eNOS is achieved *via* subcellular targeting through respective N-terminal PDZ and fatty acid acylation domains whereas iNOS is largely cytosolic and function is independent of intracellular location. nNOS is primarily expressed in the brain and neuronal tissue, iNOS in immune cells such as macrophages and eNOS in the endothelial layer of the vasculature although exceptions in other cells have been documented. L-NAME and related modified arginine analogues are inhibitors of all three isoforms, with IC_{50} values in the micromolar range.

Contents

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Database links

Nitric oxide synthases

http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=253

Enzymes

eNOS(Endothelial NOS)

http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1249

iNOS(Inducible NOS)

http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1250

nNOS(Neuronal NOS)

http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1251

References

1. Adams JL, Smothers J, Srinivasan R and Hoos A. (2015) Big opportunities for small molecules in immuno-oncology. *Nat Rev Drug Discov* **14**: 603-22 [PMID:26228631]
2. Babbedge RC, Bland-Ward PA, Hart SL and Moore PK. (1993) Inhibition of rat cerebellar nitric oxide synthase by 7-nitro indazole and related substituted indazoles. *Br. J. Pharmacol.* **110**: 225-8 [PMID:7693279]
3. Bland-Ward PA and Moore PK. (1995) 7-Nitro indazole derivatives are potent inhibitors of brain, endothelium and inducible isoforms of nitric oxide synthase. *Life Sci.* **57**: PL131-5 [PMID:7544863]
4. Collins JL, Shearer BG, Oplinger JA, Lee S, Garvey EP, Salter M, Duffy C, Burnette TC and Furfine ES. (1998) N-Phenylamidines as selective inhibitors of human neuronal nitric oxide synthase: structure-activity studies and demonstration of in vivo activity. *J. Med. Chem.* **41**: 2858-71 [PMID:9667974]
5. Connolly S, Aberg A, Arvai A, Beaton HG, Cheshire DR, Cook AR, Cooper S, Cox D, Hamley P and Mallinder P *et al.*. (2004) 2-aminopyridines as highly selective inducible nitric oxide synthase inhibitors. Differential binding modes dependent on nitrogen substitution. *J. Med. Chem.* **47**: 3320-3 [PMID:15163211]
6. Corbett JA and McDaniel ML. (1992) Does nitric oxide mediate autoimmune destruction of beta-cells? Possible therapeutic interventions in IDDM. *Diabetes* **41**: 897-903 [PMID:1378415]
7. Faraci WS, Nagel AA, Verdries KA, Vincent LA, Xu H, Nichols LE, Labasi JM, Salter ED and Pettipher ER. (1996) 2-Amino-4-methylpyridine as a potent inhibitor of inducible NO synthase activity in vitro and in vivo. *Br. J. Pharmacol.* **119**: 1101-8 [PMID:8937711]
8. Garvey EP, Oplinger JA, Furfine ES, Kiff RJ, Laszlo F, Whittle BJ and Knowles RG. (1997) 1400W is a slow, tight binding, and highly selective inhibitor of inducible nitric-oxide synthase in vitro and in vivo. *J. Biol. Chem.* **272**: 4959-63 [PMID:9030556]
9. Garvey EP, Oplinger JA, Tanoury GJ, Sherman PA, Fowler M, Marshall S, Harmon MF, Paith JE and Furfine ES. (1994) Potent and selective inhibition of human nitric oxide synthases. Inhibition by non-amino acid isothioureas. *J. Biol. Chem.* **269**: 26669-76 [PMID:7523409]
10. Mayer B and Hemmens B. (1997) Biosynthesis and action of nitric oxide in mammalian cells.*Trends*

Biochem. Sci. **22**: 477-81 [PMID:9433128]

11. Moncada S, Higgs A and Furchgott R. (1997) International Union of Pharmacology Nomenclature in Nitric Oxide Research. *Pharmacol. Rev.* **49**: 137-42 [PMID:9228663]
12. Moore WM, Webber RK, Jerome GM, Tjoeng FS, Misko TP and Currie MG. (1994) L-N6-(1-iminoethyl)lysine: a selective inhibitor of inducible nitric oxide synthase. *J. Med. Chem.* **37**: 3886-8 [PMID:7525961]
13. Wang HY, Qin Y, Li H, Roman LJ, Martásek P, Poulos TL and Silverman RB. (2016) Potent and Selective Human Neuronal Nitric Oxide Synthase Inhibition by Optimization of the 2-Aminopyridine-Based Scaffold with a Pyridine Linker. *J. Med. Chem.* **59**: 4913-25 [PMID:27050842]
14. Zhang HQ, Fast W, Marletta MA, Martasek P and Silverman RB. (1997) Potent and selective inhibition of neuronal nitric oxide synthase by N omega-propyl-L-arginine. *J. Med. Chem.* **40**: 3869-70 [PMID:9397167]