Nitric oxide (NO)

Nitric oxide (nitrogen oxide, nitrogen monoxide) is a molecular, chemical compound with chemical formula of NO that is a colorless gas under standard conditions.

Nitric oxide is a free radical—i.e., its bonding structure includes an unpaired electron —and it is in the class of heteronuclear diatomic molecules that are of historic theoretical interest (for the insights they gave in formulating early modern theories of bonding). It is a practically important intermediate in the chemical industry and day-to-day life, for instance appearing as a by-product of incomplete combustion of fuels burned in fossil fuel power plants and automobile engines, and it is produced naturally during the electrical discharges of lightning in thunderstorms.

There is contradictory evidence in the literature on the role of nitric oxide in the pathophysiology of traumatic brain injury (TBI). These contradictory perspectives are likely due to different Nitric oxide synthase (NOS) isoforms - endothelial (eNOS), inducible (iNOS) and neuronal (nNOS) which are expressed in the central nervous system. Of these, the role of nNOS in acute injury remains less clear.

A study of Madan et al., from the Baylor College of Medicine, Houston, aimed to employ a genetic approach by overexpressing arginase isoforms specifically in neurons using a Thy-1 promoter to manipulate cell autonomous NO production in the context of TBI. The hypothesis was that increased arginase would divert arginine from pathological NO production.

They generated 2 mouse lines that overexpress arginase I (a cytoplasmic enzyme) or arginase II (a mitochondrial enzyme) in neurons of FVB mice.

They found that two-weeks after induction of controlled cortical injury, overexpressing arginase I but not arginase II in neurons significantly reduced contusion size and contusion index compared to wild-type (WT) mice. This study establishes enhanced neuronal arginase levels as a strategy to affect the course of TBI and provides support for the potential role of neuronal NO production in this condition [1)].

Delayed ischemic neurological deficit (DIND) due to symptomatic vasospasm is a major cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH), most likely because of a decreased availability of nitric oxide (NO) in the cerebral microcirculation [2)].

Experimental studies

Studies show that inhaled nitric oxide (iNO) prevents impairment of cerebral autoregulation and histopathology after FPI in pigs. Unrelated studies indicated an association between ERK and increased IL-6 after FPI. However, the role of IL-6 in central nervous system (CNS) pathology is not well understood. We investigated whether iNO protects autoregulation and limits histopathology after FPI in pigs due to modulation of brain injury associated upregulation of ET-1, ERK MAPK, and IL-6.

Lateral FPI was produced in anesthetized pigs equipped with a closed cranial window and iNO administered at 30 min or 2 h post injury.

CSF ET-1, ERK MAPK, and IL-6 were increased by FPI, but release was blocked by iNO administered at 30 min or 2 h after TBI. The IL-6 antagonist LMT-28 prevented impairment of cerebral autoregulation and hippocampal CA1 and CA3 neuronal necrosis after FPI. Papaverine induced dilation was unchanged by FPI and LMT-28. Protection lasted for at least 2 h after iNO administration was stopped.

These data indicate that iNO protects cerebral autoregulation and reduces hippocampal necrosis after traumatic brain injury through inhibition of ET-1, ERK MAPK, and IL-6 upregulation in pigs [3].

1)
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2)
Ehlert A, Schmidt C, Wölfer J, Manthei G, Jacobs AH, Brüning R, Heindel W, Ringelstein EB, Stummer W, Pluta RM, Hesselmann V. Molsidomine for the prevention of vasospasm-related delayed ischemic neurological deficits and delayed brain infarction and the improvement of clinical outcome after subarachnoid hemorrhage: a single-center clinical observational study. J Neurosurg. 2016 Jan;124(1):51-8. doi: 10.3171/2014.12.JNS13846. Epub 2015 Jul 10. PubMed PMID: 26162034.
3)
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