Blocking Induction of Tetrahydrobiopterin to Block Induction of Nitric Oxide Synthesis

Published date: July 25, 2012

Technology description

Invention

These patents are directed to the methods to treat acute hypotension in conditions such as shock, as well as methods to immunosuppress patients who receive transplants. Use of the methods blocks the enzymes required for the production of tetrahydrobiopterin (BH4), which in turn is an essential cofactor for iNOS, which in turn produces nitric oxide (NO) in blood vessels and immune cells. That nitric oxide dilates blood vessels and is part of the immune response. Hence, use of the method allows prevention of the pathological production of NO. Further, because BH4 is a cofactor for the enzymes that produce dopamine, norepinephrine, epinephrine, and serotonin, co-administration of agents that overcome potential deficits in those important signaling molecules are considered as well.

Background

Nitric oxide (NO) is an inter-and intra-cellular signaling molecule that mediates critical roles in key processes as diverse as the regulation of vascular tone and blood pressure, neuronal signaling, host-defense, and stimulation-secretion coupling.

Investigators at the Weill Cornell Medical College pioneered the cloning and study of NO synthases and the role of NO in the cardiovascular system. One of their clinical foci has been indications in which NO is toxically over-produced, leading to profound vasodilation, vascular collapse, and death.

Septic shock is a prime example. It is one of the leading cause of death in ICU's in the U.S., afflicting 250,000-350,000 people annually with mortality estimates ranging from 40%-60%. Our research has led to the concept that a key step in sepsis is the induction by LPS and cytokines of the gene encoding a specific isoform of NOS that produces unregulated and toxic quantities of NO.

Cornell has obtained a broad and deep portfolio of intellectual property around this work, most of which is directed to compositions and methods for administering analogs of arginine, its precursors, or metabolites to interfere with NO signalling.

These patents are directed to specifically blocking the production of nitric oxide by the inducible form of nitric oxide synthase (iNOS), rather than constitutive NO production. It is thought that in sepsis or cytokine-induced shock, overproduction of nitric oxide by iNOS plays an important role in the observed life-threatening low blood pressure, or hypotension. Furthermore, it is thought that overproduction of nitric oxide by iNOS is a basis for insensitivity to pressor agents such as adrenergic

agonists, used in the treatment of septic or cytokine-induced shock in patients. Moreover, it is thought that overproduction of nitric oxide by iNOS is involved in inflammation driven by an immune response. The approach the inventors took, was blocking the enzymes that generate an essential cofactor for iNOS, called tetrahydrobiopterin (BH4). Such antagonism would be specific for iNOS, and not affect constitutive NO synthesis. When BH4 is synthesized de novo, the rate-limiting enzyme is GTP cyclohydrolase. There is also a pterin salvage pathway for BH4 synthesis; the key enzyme here is dihydrofolate reductase. Agents that target one or both pathways, singly or in combination, are claimed. These agents may be used in combination with other agents, such as pressors.

Agents

guanosine triphosphate cyclohydrolase I inhibitors, for example:

substituted pyrimidines, for example

hydroxyl, amino and halogen substituted pyrimidines, for example:

2,5-diamino-6-hydroxypyrimidine

4,5-diamino-6hydroxypyrimidine

4,5-diaminopyrimidine

4,6-diamino-2hydroxypyrimidine.

4-phenyl(hydro)pyridines, including 4-phenylpyridine, 4-phenylpiperidine and 4-phenyltetrahydropyridine

oxidized pterins, for example:

neopterin, xanthopterin, isoxanthopterin and biopterin.

reduced pterins that are not substrates for the pterin salvage pathway, for example:

7,8-dihydro-D-neopterin

(6R,S)-5,6,7,8-tetrahydro-D-neopterin

7,8-dihydrofolic acid

5,6,7,8-tetrahydrofolic acid.

reduced pterins that are substrates for the pterin salvage pathway, for example:

7,8-dihydro-L-biopterin

L-sepiapterin

6-pyruvoyl tetrahydrobiopterin synthase inhibitors

sepiapterin reductase inhibitors, for example:

N-acetylserotonin, N-acetyldopamine, N-acetyl-m-tyramine, N-chloroacetyldopamine, N-chloroacetylserotonin, N-methoxyacetyldopamine and N-methoxyacetylserotonin.

dihydrofolate reductase inhibitors, for example:

Methotrexate

Aminopterin

10-propargyl-5,8-dideazafolate

2,4-diamino,5-(3',4'-dichlorophenyl),6-methylpyrimidine

trimetrexate

pyrimethamine

trimethoprim

pyritrexim 5,10-dideazatetrahydrofolate
10-ethyl,10-deaza-aminopterin

Institution

Cornell University

Inventors

Steven Gross