CONTROLLING NITROGEN OXIDE CONCENTRATIONS TO MODULATE SKELETAL MUSCLE CONTRACTION

This application is a continuation-in-part of U.S. Ser. No. 08/276,105, filed Jul. 15, 1994, (pending).

Nitric oxide (NO) is an important endogenous modulator of smooth muscle function (Ignarro, *FASEB J.*, Vol. 3, pgs. 31–36 (1989); Moncada, Palmer, et al., *Pharmcol. Rev.*, Vol. 43, pg. 109 (1991)). NO activates a cGMP dependent mechanism to inhibit Ca++ release from internal stores, and thereby depress smooth muscle contraction (Schmidt, Lohmann, et al., *Biochem. Biophys. Acta*, Vol. 1178, pgs. 153–175 (1993)). In contrast to expanding data about the effects of NO in smooth muscle, relatively little is known about the role of NO or cyclic nucleotides in skeletal muscle function.

In one aspect the present invention provides a process for relaxing or inhibiting the contraction of skeletal muscle of a mammal, particularly a human, by treating the mammal with an effective amount of nitric oxide. This encompasses the use of nitric oxide species, particularly for example nitroxyl ion (NO^-), nitrosonium ion (NO^+), and uncharged nitric oxide, which can be provided by gaseous nitric oxide and/or nitric oxide adducts or providers in the treatment of disease states. Such disease states may be those which result from or are exacerbated by undesirable contractions of skeletal muscle, such as, for example, spastic muscle disease. Such nitric oxide species also may be employed in the treatment of muscle spasms.

In particular, this aspect of the invention is directed to a method for relaxing skeletal muscle by administering a therapeutically effective amount of one or more of the compounds identified herein (particularly an S-nitrosothiol compound) to an animal, particularly a human.

Compounds contemplated for use in the invention are nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer nitric oxide to a site of its activity, such as on a cell membrane, in vivo. As used here, the term "nitric oxide" encompasses uncharged nitric oxide(NO●) and charged nitric oxide species, particularly including nitrosonium ion(NO^+) and nitroxyl ion(NO^-). The nitric oxide releasing, delivering, or transferring compounds, having the structure X-NO, include any and all such compounds which provide nitric oxide to its intended site of action in a form active for their intended purpose. As used here, the term "NO adducts" encompasses any of such nitric oxide releasing, delivering or transferring compounds.

One group of such NO adducts is the S-nitrosothiols, which are compounds that include at least one —S—NO group. Such compounds include S-nitroso-polypeptides(the term "polypeptide is contemplated to include proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof), S-nitrosylated amino acids(including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof), S-nitrosated sugars, S-nitrosated oligonucleotides and derivatives thereof (preferably of at least 5, and more particularly 5–200, nucleotides), S-nitrosated hydrocarbons where the hydrocarbon can be a branched or unbranched, saturated or unsaturated aliphatic hydrocarbon, or an aromatic hydrocarbon, S-nitroso hydrocarbons having one or more substituent groups in addition to the S-nitroso group, and heterocyclic compounds. S-nitrosothiols and the methods for preparing them are described in U.S. Pat. No. 5,380,758, filed Sep. 14, 1992, Oae et al., Org. Prep. Proc. Int., 15(3):165–198 (1983); Loscalzo et al., J. Pharmacol. Exp. Ther., 249(3):726729 (1989) and Kowaluk et al., J. Pharmacol. Exp. Ther., 256: 1256–1264 (1990), all of which are incorporated in their entirety by reference.

One particularly preferred embodiment of this aspect relates to S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. For example, such compounds include the following: S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-homocysteine, S-nitroso-cysteine and S-nitroso-glutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins(where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins, heme proteins such as hemoglobin and serum albumin; and biologically active proteins, such as the immunoglobulins and the cytokines. Such nitrosylated proteins are described in PCT Published Application No. WO 93/09806, published May 27, 1993.

Further examples of suitable S-nitrosothiols include those having the structures:

$$CH_3(CH_2)_xSNO \quad \text{(i)}$$

wherein x equals 2 to 20;

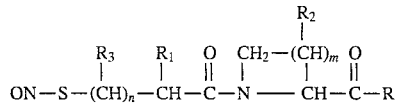
$$HS(CH_2)_xSNO \quad \text{(ii)}$$

wherein x equals 2 to 20; and

$$ONS(CH_2)_xY \quad \text{(iii)}$$

wherein x equals 2 to 20 and Y is selected from the group consisting of fluoro, C_1–C_6 alkoxy, cyano, carboxamido, C_3–C_6 cycloalkyl, aralkoxy, C_2–C_6 alkylsulfinyl, arylthio, C_1–C_6 alkylamino, C_2–C_{15} dialkylamino, hydroxy, carbamoyl, C_1–C_6 N-alkylcarbamoyl, C_2–C_{15} N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro and aryl; wherein aryl includes benzyl, naphthyl, and anthracenyl groups.

Other suitable S-nitrosothiols that are S-nitroso-angiotensin converting enzyme inhibitors (hereinafter referred to as S-nitroso-ACE inhibitors) are described in Loscalzo, U.S. Pat. No. 5,002,964 (1991) and Loscalzo et al., U.S. Pat. No. 5,025,001 (1991) both of which are incorporated in their entirety by reference. Examples of such S-nitroso-ACE inhibitors include compounds having structure (1):



(1)

wherein

R is hydroxy, NH_2, NHR^4, NR^4R^5, or C_1–C_7 alkoxy, wherein R^4 and R^5 are C_1–C_4 alkyl, or phenyl, or C_1–C_4 alkyl substituted by phenyl;

R^1 is hydrogen, C_1–C_7 alkyl, or C_1–C_7 alkyl substituted by phenyl, amino, guanidino, NHR^6, NR^6R^7, wherein R^6 and R^7 are methyl or C_1–C_4 alkanoyl;

R^2 is hydrogen, hydroxy, C_1–C_4 alkoxy, phenoxy, or C_1–C_7 alkyl;

R^3 is hydrogen, C_1–C_4 or C_1–C_7 alkyl substituted by phenyl;