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Stamler

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(54) **METHODS FOR PRODUCING NITROSATED HEMOGLOBINS AND THERAPEUTIC USES THEREFOR**

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(58) **Field of Search** 514/6, 832; 530/385, 530/824

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(57) **ABSTRACT**

S-nitrosothiols (RSNOs) can donate the NO group to the β93 cysteine residues of hemoglobin (Hb) without inactivating the heme. S-nitrosylation of Hb is under the allosteric control of oxygen and the oxidation state of heme. NO group release from S-nitrosohemoglobin (SNO-Hb) is further facilitated by intracellular low molecular weight thiols, forming RSNOs which can be exported from the erythrocyte to regulate blood pressure and platelet activation. SNO-Hb can be formed by reaction of Hb with S-nitrosothiol. This procedure avoids oxidation of the heme. Other methods can be used which are not specific only for thiol groups, but which nitrosate Hb more extensively, and may produce polynitrosated metHb as a product or intermediate product of the method. SNO-Hb in its various forms and combinations thereof (oxy, deoxy, met; specifically S-nitrosylated, or nitrosated or nitrated to various extents) can be administered to an animal or human where it is desired to oxygenate, to scavenge free radicals, or to release NO^{30} groups to tissues. Thiols and/or NO donating agents can also be administered to enhance the transfer of NO^{+} groups. Examples of conditions to be treated by SNO-Hbs or other nitrosated or nitrated forms of Hb include ischemic injury, hypertension, angina, reperfusion injury and inflammation, and disorders characterized by thrombosis.

9 Claims, 17 Drawing Sheets