Title (en)

REGULATION OF NITRIC OXIDE SYNTHASE ACTIVITY

Title (de)

REGULIERUNG DER STICKSTOFFMONOXID-SYNTHASE AKTIVITÄT

Title (fr)

REGULATION DE L'ACTIVITE DE LA MONOXYDE D'AZOTE-SYNTHASE

Publication

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Application

EP 99957226 A 19991105

Priority

- AU 9900968 W 19991105
- AU PP697698 A 19981106

Abstract (en)

[origin: WO0028076A1] This invention relates to the regulation of the activity of the enzyme nitric oxide synthase, and in particular to regulation of activity of endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS and nNOS mu). According to a first aspect, the invention provides a method of identifying modulators of AMPK-mediated activation of eNOS, comprising the step of testing putative modulators for their ability to increase or decrease phosphorylation of eNOS depending on the calmodulin and calcium ion concentrations. In an alternative aspect, the invention provides a method of identifying modulators of AMPK-mediated inhibition of eNOS, comprising the step of testing a putative modulator for its ability to decrease or increase AMPK-mediated phosphorylation of eNOS in the presence of limiting calcium ions. Preferably specific phosphorylation of threonine 495 is assessed. According to a second aspect, the invention provides a method of identifying modulators that either promote or inhibit phosphorylation of nNOS and nNOS mu at Ser-1417. Compounds which activate the AMP-activated protein kinase are expected to be useful in the treatment of ischaemic heart disease by promoting both glucose and fatty acid metabolism, as well as by increasing NOS activity to improve nutrient and oxygen supply to the myocytes and to reduce mechanical activity. These compounds would also have utility in the treatment of pulmonary hypertension and in obstructive airways disease.

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C12Q 1/26; C12Q 1/48

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CPC (source: EP)

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Citation (search report)

- [A] MICHEL THOMAS ET AL: "Nitric oxide synthases: Which, where, how and why?", JOURNAL OF CLINICAL INVESTIGATION, vol. 100, no. 9, 1 November 1997 (1997-11-01), pages 2146 - 2152, XP002236722, ISSN: 0021-9738
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- [A] VENEMA RICHARD C ET AL: "Identification, characterization, and comparison of the calmodulin-binding domains of the endothelial and inducible nitric oxide synthases.", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 11, 1996, pages 6435 - 6440, XP002236724, ISSN: 0021-9258
- See references of WO 0028076A1

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