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# **NO-synthase inhibitors induce a transient contraction of guinea pig ileum by a substance P dependent "non-neurokinin" receptor mechanism**

Rafael Garcia Villar, Christelle Dupuis, Jean Fioramonti, Lionel Bueno

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Milan, Italy - June 16-19, 1995

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WILL PRESENT THE PAPER:  
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**NO-SYNTASE INHIBITORS INDUCE A TRANSIENT CONTRACTION OF GUINEA PIG ILEUM BY A SUBSTANCE P-DEPENDENT "NON-NEUROKININ" RECEPTOR MECHANISM**  
**R. Garcia-Villar, C. Dupuis, J. Fioramonti & L. Buéno.**  
INRA, Department of Pharmacology, BP.3, 31931, Toulouse, France.

Both substance P (SP) and nitric oxide (NO) are described respectively as activatory and inhibitory transmitters of the non-adrenergic non-cholinergic (NANC) control of gut motility. In a previous work we demonstrated that a NO-synthase (NOS) was specifically activated by SP in guinea pig ileum, but the neurokinin (NK) receptor subtype (NK1, -2, -3) involved in this activation was not precised. The present study was aimed at identifying these receptors.

**Methods:** Longitudinal strips of guinea pig ileum (8 x 2 mm) were superfused in vitro (Krebs, 37°C, 2 ml/min) with tachykinin agonists (0.1 to 10 µM; SP, GR 73,632 [NK1], GR 64,349 [NK2], senktide [NK3]), and antagonists (1µM; CP 99,941 [NK1], SR 48,968 [NK2]), SR 142,801 [NK3], as well as KCl (60 mM). NO-related agents used were L-NAME, L-NMMA, aminoguanidine (AG), L-arginine (L-ARG), D-arginine (D-ARG), sodium nitroprusside (SN) and methemoglobin (MH). Isometric contractions were recorded and quantified.

**Results:** SP and NK-receptor agonists (0.1-10 µM) produced concentration-dependent contractions of ileum strips. NOS inhibitors L-NAME, L-NMMA and AG (1 µM), superfused before any contractile agent, failed to affect muscle strip contractility. In contrast, when superfused 10 min after SP (0.1µM), they induced a transient contraction (40-70 s) of high amplitude (78±11% compared to KCl 60 mM, n=30). This contractile response was not obtained in strips stimulated by any NK-agonist (up to 10 µM), or KCl (60 mM), instead of SP. Furthermore, NK-antagonists (1 µM) did not prevent the contraction induced by NOS-inhibitors (1 µM) after SP. This response was prevented by L-ARG but not by D-ARG (1 µM), but also by both the NO donor SN (1µM) and the NO scavenger MH (10 µg/ml).

**Conclusion:** Substance P, through a mechanism which does not involve "classical" NK1-, NK2- or NK3-receptors, enables NOS inhibitors to contract the guinea pig ileum in vitro. This is likely to be achieved by blockade of SP-induced NO production, unveiling an underlying contractile state whose origin is unknown.

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Milan, April 10, 1995

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## EXPRESS MAIL

Ref.: Your submitted abstract  
"NO-SYNTHASE INHIBITORS INDUCE A TRANSIENT CONTRACTION OF GUINEA..."

Dear Dr. GARCIA-VILLAR,

on behalf of the Scientific Program Committee we are pleased to inform you that your contributed paper has been accepted for POSTER presentation.

# 249

Your poster has been scheduled on **Saturday, June 17, 1995** in the session "**GASTROINTESTINAL PHARMACOLOGY: MOTILITY**".

Each poster session will have a duration of **one day**.

For your better information please refer to the enclosed instructions sheet.

We wish to remind you that no paper can be presented without having paid the corresponding fee; therefore, if you have not paid your **registration fee** yet, please do so immediately.

In case you could not attend the Congress please notify us promptly.

With our best regards.

Yours sincerely,

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