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TITLE: Agonist and Antagonist Pharmacology of the Antinociceptive Effect of Spinally Administered α_2 Agonists

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To examine the pharmacology of the spinal α receptor which modulates thermal nociceptive transmission (52.5°C hot plate; HP)[1], the dose dependent antagonism of the antinociceptive effects of three spinally administered α_2 preferring agonists (dexmedetomidine: DMET, clonidine: CLON and ST-91) by four competitive adrenergic antagonists (atipamezole, idazoxan, yohimbine and prazosin)[2,3] with varying α_2 preferring profiles was examined. In rats with chronic lumbar intrathecal catheters, the three agonists produced a dose dependent increase of the HP latency with the ED50 and the dose which was just maximally effective(JME) being DMET (3.4 µg; 10 µg); CLON (27 µg; 100 µg) and ST-91 (4.9 µg; 20 µg). After determining the time of peak antagonist effect, studies were run in which the JME dose of each agonist was given in conjunction with one of several doses of the several antagonists. The ID50 for the several antagonists against each of the three agonists was: yohimbine: DMET (126µg)=CLON (70µg) =ST-91(72µg); atipamezole: DMET (4.1µg)=CLON (5.1µg) <ST-91 (>100µg); prazosin: ST-91 (38µg) << DMET (>6000µg)=CLON (>6000µg); idazoxan: DMET (2.5 µg)<CLON (29 µg)<ST-91 (>1000µg)(see Fig 1). The common potency of yohimbine confirms that in the spinal doses employed, all three agents act as α_2 agonists. The differential rank ordering of antagonist potency for atipamezole, idazoxan and prazosin suggests that in the spinal cord, ST-91 acts upon an α_2 receptor which is distinct from that acted upon by DMET and CLON. Given the minimum effect of spinal α_1 agonists[1], the effects of prazosin against ST-91 suggest the probable role of an α_2 "non-A" subclass of receptors[3].

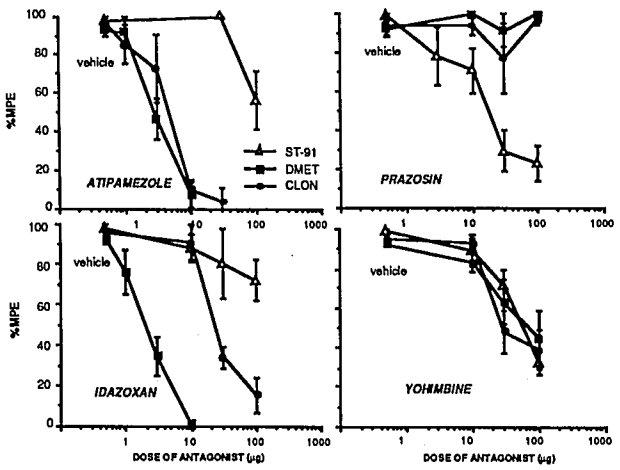

Fig 1. Antagonist dose response curves for intrathecal atipamezole, prazosin, idazoxan and yohimbine assessed with hot plate test against intrathecal DMET, ST-91 and CLON. Each dot represents the mean ± SEM of 4 - 6 rats.

This work was supported in part by NISDA02110 (TLY) and Koshigaya Hospital, Dokkyo University, School of Medicine (YT).

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A631

TITLE: **Effects of capsaicin, potassium and histamine on the endotracheal pressure changes and neuropeptides release from guinea-pig lung in vitro**

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Introduction The entire airway, including lung is densely innervated by primary sensory afferents, containing calcitonin gene-related peptide(CGRP) and neurokinin A(NKA)[1]. These peptides have been found to have potent biological effects, e.g. vasodilatation, plasma extravasation and bronchial constriction[1]. In the present study, an isolated guinea-pig lung model was developed, in which airway pressure changes and release of CGRP and NKA during endotracheal perfusion with capsaicin(Cap), potassium(K^+) and histamine (His) were studied.

Method Guinea-pigs (300±50g) were anesthetized with Nembutal 60mg/kg i.p.. Both lungs with trachea (1.5 cm above carina) were dissected out and placed into a temperature controlled chamber (37°C). The lungs were constantly perfused by the trachea with Krebs solution(5%CO_2 in O_2, 37°C) at a perfusion rate of 2ml/min. This infusion results in continuous outflow from the lung surface without rupture of the visceral pleura. Perfusates were collected at 2.5 min intervals in tubes containing 0.1ml acetic acid. They were frozen, lyophilized and subjected to radioimmunoassay for measuring CGRP and NKA. The pressure in the trachea (Ptr) was monitored via a T-tube connection, utilizing a pressure transducer.

Result Cap(10^{-8}, 10^{-7}, 10^{-6}M) induced a concentration-dependent increase in Ptr and simultaneous increases on CGRP and NKA levels in the perfusates(see Table). There was a correlation between release of NKA and Ptr increase during Cap application (r=0.51, p<0.001). Cap at 10^{-6}M demonstrated a significant tachyphylaxis. Thus, following a second subsequent exposure to the same concentration of Cap, both responses (Ptr and peptides release) were absent. The magnitude of tachyphylaxis was concentration-dependent. Application of 10^{-6}M Cap after previous exposure to 10^{-8}M Cap evoked similar amount release of CGRP and NKA, and the increase in Ptr remained the same. K^+120mM increased Ptr as well as NKA and CGRP release. However, His 10^{-6}M increased only Ptr, but displayed no reliable effect on peptides release.

	Ptr (cmH2O)	CGRP (fmol/ml/g)	NKA (fmol/ml/g)
Basal	58±8	0.20±0.04	0.32±0.06
Cap 10^{-8}M	130±11	1.00±0.15	0.57±0.12
Cap 10^{-7}M	152±25	1.28±0.46	1.33±0.47
Cap 10^{-6}M	179±32	4.04±0.71	3.49±1.26
K^+120mM	128±8	5.63±0.94	1.64±0.18
His 10^{-6}M	153±27	0.31±0.17	0.92±0.25

(n=4-5)

Conclusion Cap and K^+ evoked Ptr increase, possibly due to the release by these agents of neuropeptides e.g. NKA, which is known as a potent bronchial constrictor. Evoked CGRP release may contribute to other function changes, e.g. vasodilatation, during the stimulation of primary afferents. The effect of histamine on Ptr, in contrast, appears independent of the neuropeptide release.

(This work is supported by Tobacco-related disease research program of University of California.)

Reference
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