95P ANTAGONISM BY PIRACETAM OF BACLOFEN ANTINOCICEPTION

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The ability of the first-orally active $GABA_B$ antagonist CGP-36742 to facilitate learning and memory processes was shown by Mondadori et al. (1992) in different tests such as mouse passive avoidance, rat social learning and rhesus monkey colour-spatial task. A potentiation of short-term memory has also been reported for the $GABA_B$ antagonist Phaclofen when this is applied directly to monkey frontal cortex (Sawaguchi et al. 1992).
Since the exact mechanism of the nootropic action of Piracetam, a cyclic derivative of GABA, is still unknown, we considered it interesting to investigate if this action, like that of CGP-36742 and Phaclofen, might depend on the antagonism of $GABA_B$ receptors. To verify this hypothesis we tried to antagonize the antinociceptive effect of the $GABA_B$ agonist Baclofen with Piracetam, since it is known that Baclofen antinociception may be prevented with the $GABA_B$ antagonist CGP-35348 (Malcangio et al.,1991).

Experiments were performed in male Swiss Webster mice (25-30 g) with two different noxious stimuli: thermal (hot-plate test termostatically set at 52.5 ± 0.1°C) and chemical (writhing test - 10 ml kg^{-1} of 0.6% acetic acid solution). The results showed that doses of Piracetam of 10 or 50 mg kg^{-1} i.p. produce, in mouse hot-plate, a significant ($p<0.001$) reduction (49.5±5.3 or 56.8±6.3% respectively) of Baclofen (4 mg/kg s.c.) antinociception 30 min after its administration. At higher doses, Piracetam was able to block Baclofen antinociception completely but at these doses it also prevented Morphine (7 mg kg^{-1} s.c.) and Clomipramine (25 mg kg^{-1} s.c.) analgesias. Piracetam alone, in the dose range of 10-50 mg kg^{-1} i.p., did not modify either pain threshold or mice normal behavior. In the mouse writhing test Piracetam, at the tested dose of 10 mg kg^{-1} i.p., reduced Baclofen (4 mg kg^{-1} s.c.) antinociception without interfering with Morphine (7 mg kg^{-1} s.c.), Clomipramine (25 mg kg^{-1} s.c.) or Ketorolac (10 mg kg^{-1} i.p.) analgesias. The antagonism of Baclofen antinociception by Piracetam in this test was 77.8±5% ($p<0.001$)

Furher experiments are now in progress to elucidate the exact mechanism of action of Piracetam. The present results however indicate an involvement of the GABAergic system in Piracetam effect.

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96P EFFECTS OF L-ARGININE ANALOGUES AND NICORANDIL ON LUMINOL-ENHANCED CHEMILUMINESCENCE GENERATED BY PMA-ACTIVATED PORCINE LEUKOCYTES

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Although chemiluminescence (CL) is widely used for the measurement of free radicals produced by leukocytes, the involvement of NO in this response has not been well characterized. The objectives of this study were to investigate the effects of L-arginine, L-arginine analogues and a NO-donor nicorandil on free radicals generated by porcine leukocytes and to examine the direct free radical scavenging activity of these substances in a cell-free system of free radicals generated by xanthine (X) plus xanthine oxidase (XO).

Leukocytes were isolated from citrated porcine venous blood and luminol-enhanced CL was measured according to the method described previously (Demiryurek et al., 1992). The effects of L-arginine analogues (1 mM) and nicorandil (1mM) were examined in the leukocyte assay either by preincubation for 20 min prior to addition of phorbol myristate acetate (PMA, 0.8 μM) or when added at the peak of the CL. In the X-XO assay, drugs were added before the stimulants. The peak chemiluminescence was measured and the effects of the drugs expressed as % change (mean ± s.e. mean) from the response to the stimulant alone.

Table 1. Drugs effects on PMA and X-XO induced CL (* $p<0.05$).

	PMA-induced CL		X-XO-induced CL
Drugs	Preincubated	Added at peak	Added before X-XO
NICORANDIL	-59 ± 8 (2)	-42 ± 0.2*(3)	-30 ± 6* (6)
L-ARGININE	-24 ± 3* (4)	-12 ± 3* (6)	-3 ± 4 (4)
D-ARGININE	-10 ± 4 (3)	-1 ± 3 (4)	-1 ± 6 (3)
L-CAN	82 ± 26*(4)	46 ± 6* (8)	-12 ± 4 (3)
L-NAME	29 ± 6* (5)	18 ± 3* (6)	-4 ± 6 (3)
L-NNA	26 ± 18 (3)	15 ± 4* (4)	-5 ± 3 (3)

The NO-donor, nicorandil, markedly inhibited CL generated by both PMA-stimulated leukocytes and X-XO (Table 1). L-, but not D-, arginine inhibited PMA-activated free radical release. These results suggest that NO is capable of inhibiting CL. L-canavanine, L-NAME, and N^{ω}-Nitro-L-arginine (L-NNA), inhibitors of the NO pathway, augmented PMA-induced CL. These effects are due to inhibition of endogenous NO which inactivates the superoxide radical. However, these NO-synthetase inhibitors had no effect on X-XO-induced CL, suggesting that these substances have no direct free radical scavenging activity.

It is concluded that contribution of the endogenous NO in leukocyte free radical release can be detected by CL and NO release may play an important role in the measurement of luminol-enhanced CL by interacting with superoxide radical.

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