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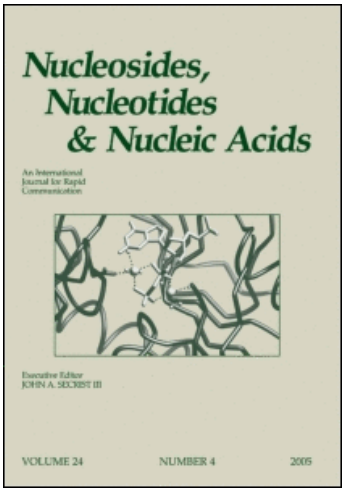

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M. Milavec-krizman[a]; H. Wagner[a]; A. Kralj[a]; J. P. Evenou[a]; F. Gadient[a]
[a] Preclinical Research, Sandoz Pharma Ltd., Basle, CH

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CARDIOVASCULAR EFFECTS OF ADENOSINE DERIVATIVES IN CONSCIOUS NORMOTENSIVE RATS

Milavec-Krizman, M.*, Wagner, H., Kralj, A., Evenou, J.P. and Gadient F.
Preclinical Research, Sandoz Pharma Ltd., CH 4002 Basle

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Abstract

All adenosine receptor agonists, regardless of their A_1/A_2 selectivity ratio, dose dependently reduced blood pressure (MAP) whereas their effects on heart rate (HR) and plasma renin activity (PRA) depended on their receptor subtype selectivity. Thus an adenosine receptor agonist with an optimal A_1- and A_2- receptor selectivity (no increase in HR and PRA) and which does not penetrate the brain, might be a useful antihypertensive drug.

Introduction

Adenosine, a naturally occurring purine nucleoside, induces a wide variety of pharmacological actions including vasodilation, decrease in the rate and force of cardiac contraction, inhibition of the release of neurotransmitters and renin, inhibition of lipolysis and of platelet aggregation (1). Adenosine exerts its pharmacological effects through interaction with A_1- and A_2- adenosine receptors which are differentially coupled to adenylate cyclase: activation of the A_1-receptor inhibits the enzyme, whereas A_2-receptor stimulation induces an increase in enzyme activity. However, adenosine receptors are also coupled to other effector systems such as potassium (2) and slow calcium channels (3).

Adenosine and its derivatives decreased blood pressure in rats (4), dogs (5) and cynomolgus monkeys (6). In the last few years, adenosine has often been used as a hypotensive agent in patients undergoing intracranial vascular or aortic aneurysm surgery (7,8) or removal of pheochromocytoma (9). It was of interest to investigate the cardiovascular effects of adenosine receptor agonists with different selectivities for A_1- and A_2-adenosine receptors in the rats.

Method

Male Wistar Ivanovas (WSA) rats, weighing ~ 350g were used. An indwelling catheter was inserted in the aorta

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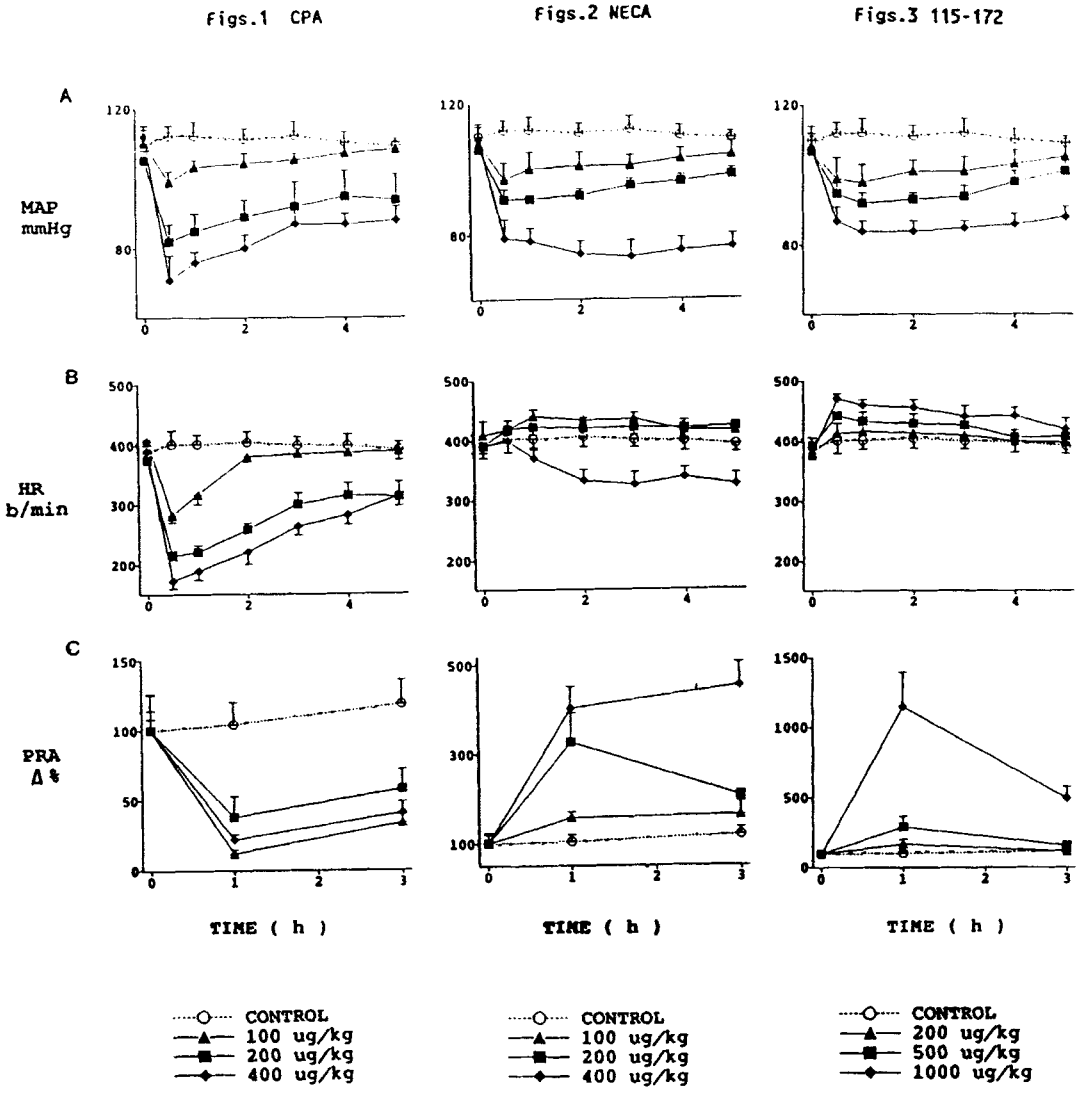

Figs. 1-3

The effects of CPA, NECA and 115-172 on MAP, HR and PRA in rats.
Results: Mean ± SEM, n=4

abdominalis via the *femoral* artery under Evipan (hexobarbital sodium; 150 mg/kg i.p.) anesthesia as described previously (10). Three to four days after surgery, the compounds were administered orally to animals fasted overnight. MAP and HR were continuously recorded. PRA (ng/ml/h) was determined before, 1h and 3h after compound administration.

Results

The highly A_1-selective agonist, N^6-cyclopentyladenosine (CPA, pKD A_1 = 9.13, pKD A_2 = 6.03, A_1 sel. = 1260 (11)) caused a dose-dependent fall in MAP and HR, the maximal response being 41% and 56% respectively, at the highest dose. However, a decrease of PRA of 90% was noted already one hour after the administration of the lowest dose (FIGS. 1 A-C).

A nonselective adenosine receptor agonist, 5'-N-ethylcarboxamido-adenosine (NECA, pKD A_1 = 8.25, pKD A_2 = 7.64, A_1 sel. = 4 (11)) , lowered MAP dose-dependently, the highest dose resulting in a 33% decrease. The effect on HR was variable, mild tachycardia at 100 μg/kg, no effect at 200 μg/kg and a delayed bradycardia (17%) at the highest dose. However, the increase in PRA was dose-dependent reaching 350% at the highest dose (FIGS. 2 A-C).

The A_2-selective agonist (12), 115-172, 2-(2-phenyl-ethylamino)- 5'-N-ethylcarboxamidoadenosine pKD A_1 = 5.21. pKD A_2 = 7.56, A_2 sel. = 220 (11), caused hypotension, tachycardia and an increase of PRA in a dose dependent manner. The maximal effects achieved by the highest dose were of 22%, 24% and 1000%, respectively (FIGS. 3 A-C).

The pharmacologically induced changes in PRA depended on the basal plasma PRA values. The higher the PRA level the better was the inhibitory effect of A_1-agonists, whereas the reverse was true for the effect of A_2-agonists.

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