Potentiation of Norepinephrine and Adenosine in the Renal Circulation by 2,6-Bis (diethanolamino)-4,8-dipiperidino-pyrimido (5,4-d) pyrimidine (Dipyridamole®) Treatment (Preliminary Report)

Keigo Yasuda, Susumu Satoh, Norio Taira and Koroku Hashimoto

Department of Pharmacology (Prof. K. Hashimoto), Tohoku University School of Medicine, Sendai

It was demonstrated in both in vivo and in vitro experiments on the renal circulation that dipyridamole produced the potentiation of vascular responses not only to adenosine but also to norepinephrine. The potentiation of these responses was observed when concentrations of dipyridamole were relatively low. As the concentration of dipyridamole was elevated, the potentiation was rather decreased and finally abolished. Furthermore, in in vitro experiments, higher concentrations of dipyridamole blocked the action of norepinephrine. These results cast doubt on the mode of dipyridamole action, which has been interpreted as inhibition of deamination of adenosine.

Since dipyridamole was introduced as an effective coronary vasodilator into the clinical use, a considerable amount of information has been accumulated on the mode of action of this compound. Among them, a significant potentiation of the vasodilator effect of adenosine and of the reactive hyperemia by dipyridamole treatment was proved in the coronary circulation and such effect was accepted as an important clue to the explanation of essential action of this drug, because adenosine is understood as the vasoactive metabolite of adenine nucleotides in the cardiac tissue. This is strongly supported by the biochemical studies in the ischemic heart.

Later, adenosine and AMP were proved to cause vasoconstriction in the renal artery in contrast to the vasodilator effect of other adenine nucleotides such as ATP and ADP. Furthermore, the vasoconstriction by adenosine as well as the postocclusive vasoconstriction specially observed in the renal artery was enhanced by dipyridamole pretreatment. These results may suggest a certain physiological role of adenosine in the renal circulation. The biochemical study, however, showed that AMP was deaminated to IMP in the renal tissue. Recently the present authors observed in both in vivo and in vitro experiments that dipyridamole enhanced the vasoconstrictory responses of the renal artery not only to adenosine but also to norepinephrine. In this paper the results obtained are briefly described.
METHODS

The left kidney of a dog, anesthetized by i.v. 30 mg/kg of sodium pentobarbital, was perfused with own blood led from both femoral arteries by a Sigma-motor pump. The perfusion pressure was adjusted at 100 mmHg and the change in perfusion pressure was recorded. For the in vitro experiments, the kidney was removed from the dog anesthetized with sodium pentobarbital, and then the renal artery was excised as far as its branches of about 1 mm in diameter. Larger branches above this size were ligated, unless these were removed without injury. The excised renal artery was perfused at a constant rate with Krebs bicarbonate solution aerated with 95% O₂ and 5% CO₂. Experiments were done at 37°C.† In both experiments dipyridamole was continuously infused at rates of 0.05 to 0.1 ml/min into the artery with an infusion pump. The volume of injection of norepinephrine or adenosine solution was 0.1 ml in a period of 10 seconds, and its effects were compared between before and during dipyridamole infusion.

RESULTS

Fig. 1 shows the response of the renal circulation to adenosine and norepinephrine which was differently modified according to different concentrations of dipyridamole. Norepinephrine and also adenosine produced vasoconstriction in the renal artery. The effects of norepinephrine as well as adenosine were potentiated by infusion of dipyridamole, and the grade of potentiation was almost the same with norepinephrine and adenosine. When the concentration of dipyridamole in perfused blood was elevated from very low level (about 0.05 μg/ml) to a relatively high one (3 μg/ml), the grade of potentiation to both drugs became maximum at a concentration of about 0.2 μg/ml. Above this level the potentiation became less in inverse proportion to increased concentration of dipyridamole, and at last no potentiation was observed at a level of from 0.4 to 1.0 μg/ml. Even if the concentration of dipyridamole was further increased, the response either to norepinephrine or to adenosine never became further depressed.

Fig. 2 shows an in vitro experiment on an isolated renal artery perfused with Krebs bicarbonate solution. The excised and perfused renal artery did not

Fig. 1. The responses produced by norepinephrine (NE) and adenosine (ADE) were potentiated at a low concentration of dipyridamole (0.24 μg/ml) but the potentiated responses were reduced near to the control level at a comparatively high concentration (0.4 μg/ml). S.B.P., systemic blood pressure; P.P., perfusion pressure; and P.F., perfusion flow.
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In the in vitro perfusion experiment, the response of the renal artery to norepinephrine was enhanced at a low concentration of dipyridamole (0.5 \( \mu \)g/ml), but blocked at a high one (2.8 \( \mu \)g/ml). P.P., perfusion pressure; and P.F., perfusion flow.

respond to adenosine. Then the effect of dipyridamole on the response to norepinephrine was studied. The response was potentiated at a lower concentration of dipyridamole but blocked at a higher one.

Assuming that norepinephrine and adenosine have pharmacologically different modes of action, such enhancement of responses to both naturally occurring substances in the same grade produced by infusion of dipyridamole was not believed to be a fortuitous coincidence. Thus the present authors think the conventional hypotheses unlikely, which have been proposed by many workers on the mode of action of dipyridamole in the potentiation of the effect of adenosine.4-10 In fact, the present authors observed that the responses to nerve stimulation, tyramine, 5-HT and angiotensine were also potentiated in the renal circulation by the infusion of dipyridamole. The present authors are developing their researches with the working hypothesis that dipyridamole would have some effect on the ionic movement necessary for the contraction of the renal vascular smooth muscle.

The details of the experiments will be reported elsewhere.

References


2) Miura, M., Tominaga, S. & Hashimoto, K. Potentiation of reactive hyperemia in the coronary and femoral circulation by the selective use of 2,6-bis (diethanolamino)-4,8,di-piperidino-pyrimido (5,4-d) pyrimidine. *Arzneimittel-Forsch.*, 1967, 17, 976-979.


