Different effects of aspirin on blood pressure of spontaneously hypertensive rats (SHR) with high and spontaneously low levels of blood pressure

¹Michael Schirner & Christel Taube

Institute of Pharmacology and Toxicology, Martin-Luther-University of Halle, Magdeburger Str. 4, 0-4020 Halle, Germany

Spontaneously hypertensive rats (SHR) of the Okamoto strain with blood pressure above 161 mmHg and SHR with blood pressure levels of less than 160 mmHg were treated with oral doses of aspirin (100 mg kg⁻¹) for three days. Whereas the blood pressure of SHR with blood pressure above 161 mmHg was decreased by aspirin, the blood pressure of SHR below 160 mmHg was increased by aspirin. The extent and direction of blood pressure change by aspirin was strongly correlated with the blood pressure of SHR before treatment ($r = -0.88$). The effect of aspirin supports an important role for endogenous prostanoids in the regulation of blood pressure of SHR.

Keywords: SHR; blood pressure; aspirin; prostanoids

Introduction Essential hypertension involves a number of cardiac and peripheral alterations (Folkow *et al.*, 1973), although its clear aetiology is still unknown. Despite the blood pressure effects of prostanoids and their analogues administered to animals with experimental hypertension, the potential role of endogenous prostanoids formed by platelets, blood vessels or other tissues in the establishment or maintenance of hypertension has often been questioned (Stier & Itskovitz, 1988). It has been demonstrated that in spontaneously hypertensive rats (SHR) the availability of the prostanoid precursor arachidonic acid is increased by an enhanced phospholipase A₂ activity as compared to normotensive rats (Kawaguchi *et al.*, 1987). As the capacity of cyclo-oxygenase to generate the unstable prostaglandin H₂ (PGH₂)/PGG₂ seems not to be a limiting factor, the critical step might therefore be the formation of vasoactive prostanoids such as PGI₂, PGE, PGF_{2α} and thromboxane A₂ (TxA₂) or the sensitivity of the blood pressure regulatory system to these prostanoids (Taube & Schirner, 1992). Up to now, there has been no convincing experimental evidence that endogenous vasodilator prostanoids may decrease the hypertensive stage. Most recently, the failure to develop hypertension in adult offspring of SHR with hypertensive levels was observed (Sim & Singh, 1987). Using the cyclo-oxygenase inhibitor, aspirin, which may reduce the biosynthesis of prostanoids, the present study focused on the potential involvement of prostanoids in the normotension of adult offspring of SHR.

Methods Male, 4–6 month old SHR of the Okamoto strain (Institute of Pharmacology and Toxicology, University of Halle, Germany) were allocated to one of the three groups according to their blood pressure before treatment: (i) above 161 mmHg ($n = 13$); (ii) 141–160 mmHg ($n = 5$); (iii) below 140 mmHg ($n = 7$). As in other reports, we observed in 10–15% of the offspring of SHR, blood pressure levels of less than 160 mmHg. The blood pressure was determined by the tail cuff methods for three days running before the start of treatment. Blood pressure was recorded while the rats were resting quietly in a chamber at 35°C. Aspirin (acetylsalicylic acid; Berlin-Chemie AG, Berlin, Germany) was

Figure 1 (a) Effect of aspirin (100 mg kg⁻¹) on the mean systolic blood pressure of SHR with different levels of blood pressure before start to treatment. Each point represents the mean $\pm$ s.e.mean. *Indicates significant difference ($P < 0.05$). (b) Regression analysis between the change of blood pressure by aspirin (day 3 – day 0) in individual SHR and their blood pressure before treatment (day 0); $n = 25$, $r = -0.88$, $P < 0.01$.

¹ Author for correspondence at present address: Experimental Oncology, Schering AG, Müllerstraße 170–178, W-1000 Berlin 65, Germany.

given in single oral doses of 100 mg kg^{-1} for three days. Control animals received saline. The blood pressure was measured 1 h before treatment.

Statistical analysis was performed by the Friedman test.

Results Figure 1a demonstrates the antihypertensive effect of aspirin in SHR in which blood pressure was above 161 mmHg. The maximal blood pressure decrease was observed at day 2 (from 187 mmHg to 165 mmHg). At day 3, a slight return to higher blood pressure was found. In contrast, aspirin led to an increase in blood pressure in SHR with control blood pressure below 160 mmHg. SHR in which blood pressure was 147 mmHg before the start of treatment developed a significantly higher blood pressure following aspirin treatment (165 mmHg). The increase in blood pressure was more pronounced in SHR with a blood pressure of 125 mmHg before start of treatment. Aspirin treatment for three days led to an increase of 31 mmHg. No alteration in blood pressure was observed in the controls (Figure 1a).

Figure 1b shows the result of a regression analysis between the blood pressure before the start of treatment with aspirin (day 0) and the extent of blood pressure change induced by aspirin (day 3 – day 0) for each individual SHR. The analysis demonstrates a strong correlation ($r = -0.88$) between these two parameters.

There was no difference in formation of 6-keto-PGF_{1 α} or TxB₂ in pieces of the aortae from the three blood pressure groups with or without aspirin treatment (data not shown).

Discussion The decrease in blood pressure in experimental models of hypertension following administration of vasodilator prostanoids and their analogues suggests a role for vasodilator prostanoids in the regulation of hypertension (Moncada, 1982). Despite this experimental evidence, there are some doubts about the importance of endogenous pros-

tanoids in the maintenance and regulation of hypertension. In order to clarify this, cyclo-oxygenase inhibitors have been widely investigated in models of hypertension. Aspirin has been shown to decrease the blood pressure of SHR, suggesting a role for vasoconstrictor prostanoids (TxA₂; PGF_{2 α}) in the maintenance of hypertension (Tuttle *et al.*, 1988). The present investigation also demonstrates an antihypertensive effect of aspirin, which further supports a critical role of vasoconstrictor prostanoids in the hypertensive stage. In contrast, aspirin treatment has no significant effect on the blood pressure of normotensive Wistar-Kyoto rats (Tuttle *et al.*, 1988). More interestingly, 10–15% of offspring of SHR do not develop hypertension. Apart from an increased sensitivity of arterial vessels to vasoconstrictor stimuli, such as histamine and noradrenaline (Sim & Singh, 1987), there is no further explanation for this normotension. The present investigation demonstrates a marked increase in blood pressure induced by aspirin in SHR which were approximately normotensive before the start of treatment. Furthermore, the extent of the increase in blood pressure depended upon the blood pressure before administration of aspirin. As cyclo-oxygenase inhibition by aspirin in SHR with approximately normotensive blood pressure induced an increase to a hypertension, a contribution of vasodilator prostanoids to the failure to develop spontaneous hypertension might be expected. Since no differences in the formation of prostacyclin or TxA₂ in pieces of the aortae from the three blood pressure groups were seen, further investigations have to determine additional prostanoids as well as prostanoid biosynthesis in other organs. In conclusion, the results of the present investigation provide strong evidence for a critical role of vasodilator as well as vasoconstrictor prostanoids in experimental hypertension.

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