increase actually observed (60%) agrees fairly well with the theoretically expected change. The reduction of the substrate inhibition observed on figure 1 is also expected from the Debye-Hückel theory which predicts an increase in the value of the substrate inhibition constants[12]. The true substrate inhibition constants, however, cannot be measured, because the mechanism of the substrate inhibition is unknown (NADH) or not very clear (oxaloacetate). Consequently, in this case, no comparison between theory and experiment can be made.

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Reduction in dietary vitamin E prevents onset of hypertension in developing spontaneously hypertensive rats[1]

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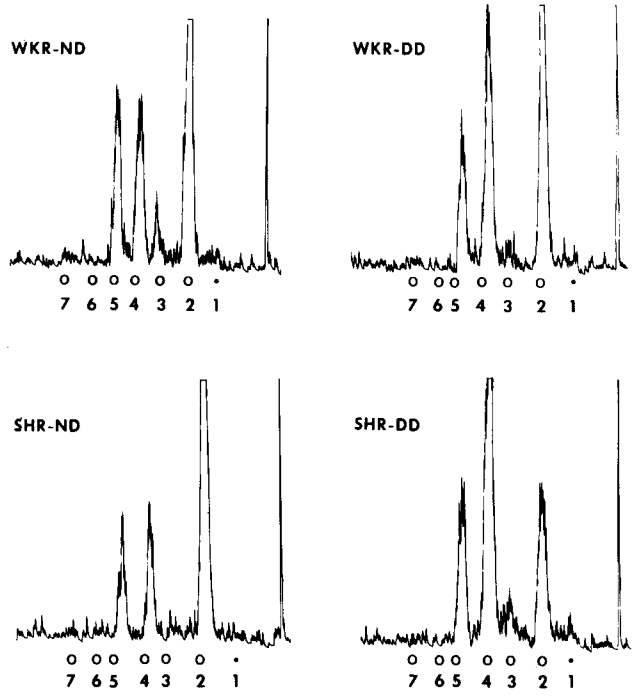
Summary. Reduction in dietary vitamin E intake in developing spontaneously hypertensive rats abolished the onset of hypertension which is normally evident by 3 months of age.

The spontaneously hypertensive rat is a popular model for the study of human essential hypertension. Because the rats are not hypertensive at birth they provide a convenient model for studies on the etiology of hypertension since they can be studied in various stages of hypertension, i.e., pre, early, and established stage.

In previous studies we demonstrated an age-dependant increase in renal prostaglandin catabolism in the normal rat which reaches a peak at 19 days postnatally (60-fold relative to the adult) thereafter quickly dropping to adult levels by day 40. Prostaglandin biosynthetic activity did not change[2]. The potential importance of this prostaglandin catabolic activity profile was quickly realized when a similar study was carried out in the developing spontaneously hypertensive rat. While renal prostaglandin catabolism in these rats was normal at birth, it quickly reached levels that were 2–2.5-fold deficient over normal by 19 days postnatally which preceded elevations in systemic blood pressure[3]. These experiments suggested a possible correlation between deficient prostaglandin catabolism during a 'critical' postnatal stage in renal development and the subsequent onset in elevated blood pressure in the spontaneously hypertensive rat.

In our attempts to alter prostaglandin catabolism in the normal and the spontaneously hypertensive rat, we tested variations in dietary intake in vitamin E which as an antioxidant could participate in prostaglandin biosynthetic or catabolic pathways. As large amounts of this vitamin are known to inhibit prostaglandin biosynthesis[4, 5], we set out to investigate the effect of a reduction in its dietary intake.

Materials and methods. Pregnant rats (Wistar, Aoki-Okamoto spontaneously hypertensive and Kyoto normotensives) were purchased from Taconic Farms, Germantown, New York. Directly upon giving birth, litters were divided into 4 groups (2 litters/group) and placed on diets containing normal content of vitamin E (132 IU/kg - Purina) or deficient in vitamin E (12 IU/kg - Teklad). At 21 days, rats were divided and placed 2 in each cage and maintained on



Radiothin layer profiles showing enhanced prostaglandin catabolism in renal cortical homogenates from hypertensive rats (SHR) maintained on a vitamin E deficient (12 IU/kg) diet (DD). Also shown for comparison are parallel incubations of homogenates of renal cortex from normotensive rats (WKR) fed normal diet (ND, vitamin E = 132 IU/kg) and DD and SHRs fed ND. The assay was performed using 0.5 ml homogenate (1/10 w/v) in 0.05 M KH_2PO_4-NaOH buffer (pH 7.4), in 2 tubes containing 9 β-$^3H_1$-$PGF_{1\alpha}$ (NEN, 200,000 cpm) and either 1 or 5 µg $PGF_{1\alpha}$ (Upjohn Co. Kalamazoo) and NAD^+ (4 mM, Sigma). After 10 min at 37 °C incubations were terminated with 5 vol. ethanol. The scans refer to experiments using 1 µg substrate $PGF_{1\alpha}$.

the respective diets with normal access to tap water. Each month, systolic blood pressure was monitored by the tail cuff method using a Narco electrosphygmomanometer. At 3-4 months of age, renal prostaglandin biosynthesis and catabolism was assayed by the radiotracer technique already published[2].

Results. While spontaneously hypertensive rats developed the usual sustained elevations in blood pressure when maintained on a normal diet containing 132 IU/kg of vitamin E, blood pressures were normal in those rats fed a diet deficient in this vitamin (12 IU/kg). The table shows blood pressure data for each of the groups at 3 and 4 months of age. Measurements of renal cortical prostaglandin catabolism during 3 separate studies on age-matched rats from each group show a highly significant elevation (2-3-fold) in enzyme activity only in the spontaneously hypertensive group fed the vitamin E deficient diet. A typical experiment is shown in the figure where the renal catabolic activity is compared between each of the 4 groups of rats fed a normal and a vitamin E deficient diet. Values observed for 15-hydroxyprostaglandin dehydrogenase catabolic enzyme were (mean ± SEM): normotensive, normal diet = 919 ± 75, deficient diet 922 ± 39; hyptertensive, normal diet 562 ± 18, deficient diet 1309 ± 220 ng product/10 min at 37 °C. Prostaglandin biosynthesis was not affected by the vitamin E deficient diet in either group.

These findings reveal that 1. expression of the hypertensive trait might be related to dietary factors, 2. reduction in dietary vitamin E intake appears to control the expression of this disease, 3. renal prostaglandin catabolism is enhanced in the experimental diet. Experiments are under way to determine if the observed reduction in blood pressures of the 'hypertensive' rats is permanent or will revert to the normally high levels when these rats are placed back on the normal (high vitamin E) diet.

Systolic blood pressures of normotensive (WKR) and hypertensive (SHR) rats maintained since birth on normal diet (ND, vitamin E = 132 IU/kg) and vitamin E deficient diet (DD, vitamin E = 12 IU/kg)

	Blood pressure (mm Hg ± SEM)	
	3 months	4 months
WKR		
ND	146 ± 3	146 ± 3
DD	129 ± 3	136 ± 3
SHR		
ND	173 ± 4	190 ± 2
DD	122 ± 4	127 ± 2

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The importance of the terminal hemi-acetal group for the ionophoric properties of nigericin

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Summary. Opening of the terminal hemi-acetal in dihydronigericin drastically reduces the ionophoric properties of nigericin and dehydroxymethylnigericin with 6 intact heterocycles. This is shown by 2 complementary methods, first with a liquid membrane electrode system, secondly by testing their ionophoric activities in rat liver mitochondria.

Carboxylic ionophores of the nigericin group are a large and growing class of antibiotics[2]. Solid state studies by X-ray diffraction showed that these polyethers adopt a pseudocyclic conformation with a head-to-tail hydrogen bond system, thus forming a cavity in which an unhydrated alkali cation can be complexed[3]. The resulting neutral complex has a strongly lipophilic outer envelope with a hydrophilic pole formed by the carboxylic group[4]. These amphiphilic characteristics can account for the well established ability of these molecules to transport cations through membranes[4].

In the course of our investigations concerning the complexing cavity formation, we studied nigericin[5] (**I**) (isolated from the strain NRRL B 1865) and 2 derivatives, dihydronigericin (**II**), and dehydroxymethylnigericin (**III**) first prepared by Chamberlin[6]. We tested their cation transporting abilities by 2 complementary methods.

1. The selectivity scales for alkali cations were measured with a liquid membrane electrode containing the ionophore as sensor in the membrane. EMF-values obtained are plotted against the reciprocal Goldschmidt ionic radius (figure 1). We have thus a measure of cationic affinities, relative to potassium, for the 3 compounds. For nigericin (**I**) we observed the order $K^+ > Rb^+ > Na^+$, Cs^+, Li^+ with a clear preference for K^+ and slighthy less for Rb^+, in good agreement with previous results[7]. The opening of the hemi-acetal F by $NaBH_4$ in **II** even though creating 2 hydroxyl groups, resulted in a derivative which had lost almost the whole discriminating power of the natural molecule. Furthermore, treatment of **II** by $NaIO_4$ induced the formation of **III** with a reconstituted hemi-acetal F′. The selectivity curve of a carboxylic ionophore was again obtained, in which the complexing ability of the ligand was just slightly lowered compared with that of nigericin.

2. We tested the ionophoric activities of the compounds in rat liver mitochondria. The experiments were carried out as follows: the mitochondria were first loaded with K^+ glutamate in the presence of valinomycin. Then, 90 sec after, K^+ and glutamate effluxes were monitored in the presence of **I** ~ **III** by 2 different methods. The kinetics obtained are plotted in figure 2. The addition of **I** and **III** induced a release of 120 natoms K^+/mg protein/30 sec (figure 2A), with no measurable difference between the 2 structures. Dihydronigericin (**II**) had no effect at this concentration. Figure 2B shows glutamate movements, measured under the same conditions as for K^+. Valinomycin induced uptake of 26 nmoles/mg protein/90 sec of (^{3}H)-glutamate; the addition of **I** and **III** resulted in an equivalent release of the