D) It is conceivable that the close relation between hypothalamic and cardiac NE during stress could be relevant for the clinical management of some situations, including acute myocardial infarction.

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Sodium excretion after bilateral adrenalectomy in rats with experimental cirrhosis

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Summary. Bilateral adrenalectomy (ADX) or a sham procedure was performed in cirrhotic and control rats. After ADX, controls increased their sodium excretion with respect to the basal values but cirrhotics did not. When sodium-loaded, the ADX cirrhotic rats retained a significant amount of the load. These data do not support a primary role of aldosterone in the impaired sodium handling by cirrhotic rats.

An increase of aldosterone plasma levels has been claimed to have a primary role in water and salt retention by the kidney in chronic hepatic disease[2,3] and other situations which generate oedema and ascites[4]. Marson[5] observed natriuresis after bilateral adrenalectomy (ADX) in a patient with hepatic cirrhosis who had not responded to habitual therapeutics. Disappearance of oedema and improvement of sodium excretion were also observed[6,7]. To explore the problem, sodium excretion was followed after bilateral ADX on rats in which chronic experimental cirrhosis had been produced. The study was carried out in male Wistar rats. Experimental cirrhosis was induced in a group of 17 rats weighing about 150 g by a combinated treatment of sodium phenobarbital (Luminal®, Bayer) given orally and Carbon tetrachloride by inhalation, according to the schedule reported by Lopez-Novoa et al.[8,9]. All the animals had, at the time of the experiment, histologically proven cirrhosis and showed a variable amount of ascites. Their weight averaged 249±3 g (SEM). 16 rats drinking sodium phenobarbital chronically were used as controls to obviate the possible effects of the Luminal administration on sodium handling. The control rats did not show any histological alteration in the liver and their weight was not different from that of cirrhotic rats (254±3 g, $p > 0.01$).

All the animals were placed into individual metabolic cages with free access to drink and a fixed amount of standard rat food in powdered form (total sodium content 0.605±0.091 mEq; 5 determinations). The animals remained in the metabolic cages for 5 days. On the 6th day, after light ether anesthesia, a bilateral ADX was performed in 11 cirrhotic and 10 control rats, by dorsal incision. 6 cirrhotic and 6 control rats were subjected to the same procedure but adrenalectomy was not performed. Strict care was taken to prevent loss of ascitic fluid. The animals were again placed into the metabolic cages for 3 days. Afterwards, the drink was substituted by 30 ml of a sodium chloride solution,

Sodium excretion after adrenalectomy (ADX) and Na load

		Cumulative Na excretion		Cumulative Na balance		Percentage of the Na load excreted
		Prior ADX	After ADX	Prior ADX	After ADX	
Control, ADX	$\bar{x}$	1.78	3.71[c]	+0.02	−1.90[c]	84.9
(n=10)	SEM	0.11	0.35	0.06	0.16	3.2
Control, sham	$\bar{x}$	1.76	1.67[a]	+0.04	+0.12	86.2
(n=6)	SEM	0.10	0.19	0.09	0.09	4.3
Cirrhosis, ADX	$\bar{x}$	1.24[a]	1.56[a]	+0.56[a]	+0.23[a]	64.3[a]
(n=11)	SEM	0.07	0.17	0.06	0.13	4.8
Cirrhosis, sham	$\bar{x}$	1.26[a]	1.32[a]	+0.54[a]	+0.48[a]	41.4[a b]
(n=6)	SEM	0.17	0.14	0.15	0.13	4.4

All the data are expressed as mEq in 3-day periods. [a] $p < 0.05$ with regard to the group control-ADX; [b] $p < 0.05$ with regard to the group cirrhosis-ADX; [c] $p < 0.05$ with regard to the period previous to ADX.

140 mEq/l (total daily amount: 4.2 mEq) containing 2% sucrose. This solution was administered 2 more days, later the phenobarbital solution was reinstituted.

Every day the animals were weighed and the drink and food intake measured. Clean urine was collected under mineral oil in graduated cylinders. Sodium was measured by flame photometry. All the animals consumed all the amount of food and drink (when limited) administered, therefore, daily sodium intake was the same for all the animals.

The increase in sodium excretion after bilateral ADX or sham procedure and the handling of sodium load are shown in the table. The following deduction can be made: bilateral ADX on normal rats produced, in the 3 days after surgical procedures, a significant increase in sodium excretion (more than twice the basal values). This increase was not observed in the cirrhotic animals.

Cirrhotic ADX rats were able to eliminate during 3-day period 64% of a 2-day 8.4 mEq sodium overload, an amount significantly greater than in the sham-operated cirrhotic rats, but significantly less than the excretion percentage of ADX or sham-operated control rats.

Adrenalectomy in the rat strain used does not abolish the aldosterone production but induces a transient aldosterone depletion. The lack of natriuretic response after ADX in cirrhotic rats supports the hypothesis that factors others than aldosterone play a primary role in sodium and water retention by the kidney of cirrhotic rats. However this observation must be regarded with caution because of the possibility of an increase in the half-life of aldosterone in the liver-damaged animals. When sodium-loaded, the ADX cirrhotic rats excreted more sodium than sham-operated animals, but did not reach the sodium excretion of control animals.

From the above experiment, it can be deduced that aldosterone does not play a primary role in the water and sodium retention in this model of experimental liver cirrhosis in the rat, although it might contribute to increase the distal tubular reabsorption of an already decreased sodium load.

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Prolonged action of drugs in rats with flavonoid-deficiency

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Summary. In flavonoid-deficient Wistar-rats, the action of caffeine, harmine, hexobarbital, morphine and pentobarbital is enhanced. In contrast, the thiopental sleeping time is shortened. These observations may indicate impaired drug metabolism as a consequence of the flavonoid-deficiency state.

Flavonoids are a class of compounds widely distributed in plants and all having the 2-phenylbenzo-γ-pyrone structure[1]. However, the physiological role of these substances, in plants as well as in animals, has not been totally elucidated. There are some indications that, in rats at least, flavonoids are related to vitamins[2].

In flavonoid-deficient rats, pentobarbital- and hexobarbital-induced sleeping times are prolonged. This results from impaired metabolism of barbiturates.[3].

The question arose as to whether other types of drugs, eliminated by different metabolic pathways, also have a prolonged action. Therefore, rats given a diet lacking flavonoids[4], for a period in excess of 25 weeks, were treated with caffeine, harmine, morphine or thiopental. Motor activity, tremor duration, duration of response to a pain stimulus and sleeping time were then estimated and compared with controls. In addition, hexobarbital and pentobarbital were used, since the present results deal with a different strain of rat than those described in a former publication[3].

Materials and methods. Male Wistar rats (Bäumler/Wolfratshausen, BRD) weighing approximately 240 g, were given a flavonoid-deficient diet[4] for in excess of 25 weeks. Following this treatment, 1 group of 5 rats was dosed with caffeine (50 mg/kg i.p.). Motor activity was followed 15 min after injection by counting the interruptions of a light beam from a suspended lamp falling on photosensitive cells. A 2nd group of 5 flavonoid-deficient rats was treated with harmine hydrochloride (10 mg/kg i.v.). The rats immediately went into tremor, the duration of which was followed as previously described[5]. A 3rd group of 10 rats was treated with morphine hydrochloride (5 mg/kg

Action of different drugs in flavonoid-deficient rats in comparison to controls

Drug	Control rats	Deficient rats
Caffeine	354 ±51 (5)	501 ±34 (5)
Harmine	78 ± 3 (5)	95 ± 4 (5)
Morphine 20 min	9.1± 1.3 (10)	12.6± 1.5 (10)
30 min	7.1± 1.0 (10)	10.5± 1.4 (10)
Hexobarbital	12.3± 0.7 (10)	16.7± 1.0 (10)
Pentobarbital	25.3± 2.2 (10)	37.5± 2.7 (10)
Thiopental	2.6± 0.3 (10)	1.9± 0.2 (10)

Units of measurement: Caffeine, interruptions of light beams; harmine, hexobarbital, pentobarbital and thiopental, min; morphine, sec. (n)=rats/group. For detail see Materials and methods.