	Anzahl Ratten	Ohne Vorbehandlung mit MEG	Nach Vorbehandlung mit 200 mg/kg MEG
Mittlerer Blutdruck in mm Hg	18	114,7 ± 2,9[a]	129,6 ± 3,9

Vasopressin (pro kg Körpergewicht)	Anzahl Versuche	Pressorische Reaktion auf Vasopressin (mm Hg)	Pressorische Reaktion auf Vasopressin (mm Hg)	P nach t-Test
5 mIE	8	7,5 ± 0,8	15,4 ± 1,6	< 0,001
10 mIE	8	13,8 ± 1,6	26,6 ± 1,2	< 0,001
20 mIE	15	21,8 ± 0,9	47,8 ± 3,6	< 0,001
30 mIE	2	23,3 ± 4,4	58,3 ± 4,4	< 0,002
50 mIE	2	27,7 ± 1,5	62,7 ± 3,7	< 0,001

[a] Mittlere Abweichung des Mittelwertes.

Summary. 2-mercaptoethylguanidin enhances the blood pressure responses to small doses of vasopressine in the rat. This potentiation is statistically significant. The increase of the vasopressine reaction after 2-mercaptoethylguanidin is not due to an indirect effect of vasopressine on the cardiovascular system.

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Comparative Pathology after Intrathecal Endotoxin in the Rabbit, Dog and Monkey

Intravenous administration of gram negative bacterial endotoxins into mammals results in a syndrome which resembles septic shock in man. Since much smaller doses of intrathecal[1,2] or intracarotid[3] endotoxin are required for shock and death, several investigators have suggested that endotoxin acts primarily on the central nervous system (CNS)[1–4]. However, an increased sensitivity to endotoxin via the cerebrospinal route does not necessarily indicate that its systemic action is mediated via the CNS.

Zweifach[5] has emphasized that mammalian species differ in their responses to intravenous endotoxin and that a common mode of action for endotoxin in a variety of species has not been found. If endotoxin transmits its effects via the CNS, the pathological changes should resemble those following systemic administration and the changes should be specific to the species. This study investigates the pathological changes induced by CNS and intravenous endotoxin in 3 species of animals.

Methods. E. coli endotoxin was prepared from strain 0111:4B organisms by the method of MacLean and Weil[6]. This insoluble material prevented the systemic absorption of endotoxin from the cerebrospinal fluid spaces[7,8]. Its activity was retained in saline suspension in a concentration of 17 mg/ml while stored in sterile vials at −20 °C. The intracisternal LD_{80} dose was then introduced into the cisterna magna of dogs and monkeys anesthetized with i.v. sodium pentobarbital (30 mg/kg). During cisternal injection, rabbits were manually restrained. Controls were given cisternal injections of saline and blood. Complete autopsies were performed as soon after death as possible in the CNS endotoxin treated animals that died 12–24 h after injection. Since none of the control animals died, these animals were killed 72 h after the experiment with large i.v. injections of sodium pentobarbital. All organs were weighed, examined grossly, and the tissues fixed in buffered formalin. Paraffin embedded sections were cut at 5 μ and were stained with hematoxylin and eosin. Nervous tissue was stained with luxol fast blue-hematoxylin-eosin.

Results. In Table I a comparison is made of the amounts of intrathecal LD_{80} and i.v. LD_{80} administered to adult mongrel dogs, rhesus monkeys, and albino New Zealand rabbits. Intracisternal endotoxin was far more toxic.

Pathological changes following endotoxin were similar in all 3 species. None of the sections revealed the presence of intramedullary or intracortical nuclear lesions. Minimal acute meningeal reaction was observed at the site of needle puncture.

The most striking abnormality at autopsy was massive hemorrhagic pulmonary edema. Table II lists the mean lung/heart weight ratio in the 3 species for controls and animals with CNS endotoxin. Grossly the pleural surfaces of the lungs were congested and mottled, and blood and edema fluid could easily be expressed on section. Microscopic examination revealed intra-alveolar and interstitial hemorrhage and edema.

The pericardial sac frequently contained small amounts of serosanguinous fluid. The epicardial surface of the heart contained punctate hemorrhages. The left atrium was usually dilated. Subendocardial hemorrhages were present in both ventricles, especially the right. Valvular lesions and focal myocardial necrosis were found only in dog hearts. None of the animals developed myocardial zonal lesions, which are usually found in systemic endotoxin shock[9].

In all animals the livers appeared severely congested without the development of lobular necrosis, and the kidneys were hyperemic at the cortico-medullary junction. Microscopically, congestion of glomerular capillaries was present, but there was no evidence of fibrin thrombi. Hemorrhages were found at the cortico-medullary junction of the adrenal with a few areas of necrosis scattered throughout the adrenal cortex in all 3 species.

The mucosa in the gastrointestinal tract of all species was hyperemic, and a few areas were superficially ulcer-

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ated. Only a few streaks of blood were found in the lumen. The intestinal mucosa was intact except for scattered areas of erosion.

Discussion. Lethal doses of i.v. endotoxin produced different effects in the 3 species[5,10]. In the dog massive hemorrhagic necrosis of the gastrointestinal tract, central lobular necrosis of the liver, congestion of the kidney, minimal edema of the lungs, and occasional areas of myocardial necrosis with zonal lesions occurred[9,10]. The rabbit demonstrated minimal gastrointestinal lesions, thrombosis of the hepatic vessels with necrosis, myocardial hemorrhages and necrosis, and massive hemorrhagic pulmonary edema[10]. The monkey responded with less pulmonary pathology than the rabbit and less gastrointestinal pathology than the dog and displayed no hepatic congestion[10]. In the present experiments, the pathologic changes induced in all 3 species by intrathecal endotoxin were essentially the same; massive hemorrhagic pulmonary edema, subendocardial hemorrhage and congestion of the splanchnic bed, liver, kidneys, and adrenals. These results indicate that the mechanism of death following CNS endotoxin is similar in the 3 species studied. Since intrathecal endotoxin does not induce changes which resemble those seen following i.v. endotoxin, it is unlikely that endotoxin administered i.v. acts primarily on the central nervous system.

Table I. LD_{80} *E. coli* endotoxin by i.v. and intracisternal routes

Species	Intravenous	Intracisternal
Dog	11.0 mg/kg	5.1 mg/kg
Rabbit	27.6 mgm/kg	3.5 mg/kg
Monkey	91.9 mgm/kgm	30.0 mgm/kgm

Table II. Lung/heart weight ratio (mean $\pm$ S.E.)

Species	Control	$\bar{p}$ Intracisternal endotoxin
Dog	1.23 ± 0.04	2.70 ± 0.33
Rabbit	1.74 ± 0.18	3.34 ± 0.26
Monkey	1.64 ± 0.09	2.83 ± 0.41

Zusammenfassung. Pathologische Veränderungen bei Kaninchen, Hunden und Affen nach intrazysternaler Verabreichung von Bakterienendotoxinen sind einander sehr ähnlich, während sie nach i.v. Injektion bei allen 3 Tiergruppen auffallend verschieden sind. Dies führt zur Annahme, dass die Wirkung des Endotoxins zur Hauptsache offenbar nicht über das Zentralnervensystem geht.

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The Effect of Some Anticholinesterase Agents and of Hemicholinium on the Amount of Substance P in Rabbit Brain and Gut

It has been reported that physostigmin decreased the content of substance P (SP) in gut and in brain of rabbit[1,2]. In order to elucidate the action of other anticholinesterase agents on the SP content in the abovementioned organs of the rabbit, we studied the effect of phospholine iodide and of paraoxon. Phospholine iodide, an anticholinesterase agent which does not penetrate the blood-brain barrier[3], and paraoxon, an anticholinesterase agent, which penetrates the barrier[4], were used to clarify more precisely the influence of these agents on the SP content in brain and in gut. We administered, also, hemicholinium No. 3 (HC-3) in order to inhibit cholinacetylase activity[5] and measured thereafter the concentration of SP in rabbit's small intestine and in brain.

Rabbits of both sexes were used weighing from 2–3 kg. The extracts were made from the whole of the small intestine and from the brain, cerebellum being left out. The brain and small intestine were ground and boiled in acidified distilled water. After precipitation with ammonium sulfate, SP was adsorbed on aluminium oxide and eluted with distilled water as described by PERNOW[6] and EULER[7]. Bioassay was performed on the isolated guinea-pig ileum bathed in tyrode solution which, also, contained atropine, promethazine and D-lysergic acid diethylamide. A preparation of SP (manufactured by Hoffmann-La Roche, Basle, Switzerland) containing 75 U/mg was used as a standard. The recovery was checked and the mean recoveries were of the order of 78%.

Drugs used were: phospholine iodide (dietoxyphosphoryltiocholine iodide), paraoxon (diethylparanitrophenil) and hemicholinium No. 3 (HC-3). All drugs were injected s.c. once a day. Phospholine iodide was administered for 4 days, 25 µ/kg on the first day and 12.5 µ/kg on the other 3 days. Paraoxon was administered for 2 days, 150 µ/kg on the first day and 75 µ/kg on the second day. HC-3 was injected once in dose of 2.5 mg/kg. With such a big (toxic) dose we got more uniform results than with smaller (0.5 mg/kg and 0.25 mg/kg) doses. About 1 h after 2.5 mg/kg of HC-3 the animals died with symptoms of asphyxia.

The results are shown in the Table. Phospholine iodide and paraoxon lowered the SP content in the rabbit small intestine. HC-3, on the other hand, increased the SP content in the small intestine (from 2.53 ± 0.2 U/g in control experiments to 5.70 ± 0.7 U/g). Phospholine iodide did not change the SP content in the brain, while paraoxon and HC-3 lowered it.

The present experiments are in accordance with previously reported results that physostigmine decreases the

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