Myocardial (left ventricle) concentrations (μmol/g wet weight) of ATP, ADP, ATP + ADP, creatine (Cr), creatine phosphate (CrP) and Cr + CrP

Spezies	n	ATP	ADP	ATP + ADP	ATP/ADP
Mini-pigs	6	4.51 ± 0.34	0.94 ± 0.20	5.44 ± 0.35	5.10 ± 1.22
Dogs	8	6.15 ± 0.67	0.85 ± 0.16	7.02 ± 0.81	7.61 ± 1.14
p		< 0.0005	> 0.15	< 0.0005	< 0.0025
Spezies	n	CrP	Cr	CrP + Cr	CrP/Cr
Mini-pigs	6	10.70 ± 1.17	10.84 ± 1.59	21.57 ± 1.90	1.03 ± 0.23
Dogs	8	14.09 ± 1.74	11.52 ± 2.67	25.68 ± 2.72	1.37 ± 0.51
p		< 0.0025	> 0.25	< 0.005	< 0.05

Data from 6 mini-pigs (23 biopsies) and 8 dogs (23 biopsies). The mean values of each ventricle were used for the statistical analysis with an unpaired t-test[24]. Values in the table are $\bar{x} \pm s_{\bar{x}}$.

ATP[12], CrP[13], ADP[14] and Cr[15] were determined according to published methods. All enzymes, coenzymes and substrates were from Boehringer and sons.

Results and discussion. The results obtained in 6 mini-pigs (23 biopsies) and 8 dogs (23 biopsies) are compiled in the Table. The concentrations in the dog heart agree well with results published by others under comparable conditions[5–9,16,17]. High levels of CrP[5–7] are correlated with a low oxygen consumption of the heart[6,7]. With the exception of ADP and Cr all values differ significantly in the two species. Species differences and possible analytical errors have been repeatedly reviewed[4,9,17–22]. We do not know if the different coefficients (ATP/ADP and CrP/Cr) are due to the anaesthesia. An average value of 6.24 for ATP/ADP is commonly found in dogs under aerobic conditions[9]. However, NÄGLE et al.[23] and KÜBLER[7] did not find a change in total creatine (CrP + Cr) during ischemia and anoxemia lasting 1 h. According to SPIECKERMANN[9], the sum of the adenine nucleotides is identical in pentobarbital and halothan anaestheisa and the concentrations of ATP are equal in pentrane and pentobarbital anaesthesia. We believe therefore that, assuming identical coefficients of ATP/ADP and of CrP/Cr in both species, all metabolites have a lower concentration in the mini-pig.

Using a t-test to analyse differences of paired samples[24], the concentrations of all metabolites in the most distal (apex) biopsies were compared with those of the most proximal ones. No significant differences could be found at a confidence level of $P < 0.05$. A random distribution of ATP, CrP and lactate in left ventricles of dogs under aerobic conditions has been reported by BRAASCH et al.[6,25].

Zusammenfassung. Die Gewebskonzentrationen an ATP, ADP, ATP + ADP, Kreatinphosphat, Kreatin und Kreatinphosphat + Kreatin sind unter vergleichbaren Bedingungen im linken Ventrikel von Mini-pig-Herzen kleiner als im Hundeherzen. Die Unterschiede in den Koeffizienten (ATP/ADP und Kreatinphosphat/Kreatin) dürfen narkosebedingt sein. Sämtliche Messgrössen sind nicht mit dem Entnahmeort der Biopsien (apikal, basal) korreliert.

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Effect of Lithium on the Blood and Intestinal Serotonin Contents of Rats

Lithium salts are widely used as a specific remedy for manic states[1]. Recently they have been reported to accelerate the synthesis rate of serotonin in the brain[2,3]. Early side effects commonly associated with lithium treatment are a variety of gastro-intestinal discomforts, such as nausea, vomiting, diarrhea and stomach pain[4]. It seemed possible that these symptoms were associated with disturbance of serotonin metabolism in the blood and

alimentary tract, so we examined the levels of serotonin in the blood and intestine after lithium treatment.

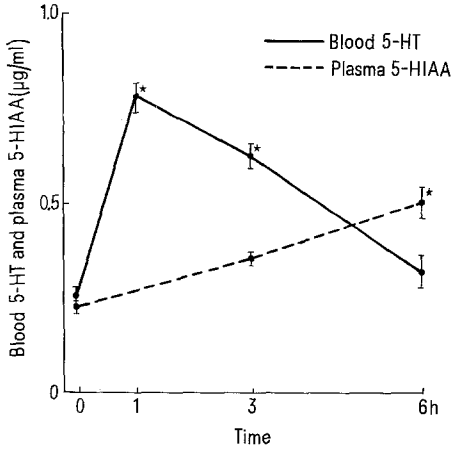
Materials and methods. Male Sprague-Dawley rats, weighing 220–250 g were used. Food was withheld for 18 h before experiments. Lithium was administered per os as an isotonic solution of lithium chloride, prepared by dissolving lithium carbonate in an equivalent amount of hydrochloric acid. Animals were given a dose of 5 meq of lithium/kg body wt. and were sacrificed 1, 3, and 6 h later. Control rats were treated with the same volume of saline. Animals were decapitated between 13.00 h and 15.00 h and 5-HT in the blood, stomach, duodenum and jejunum was assayed fluorometrically by the method of BOGDANSKI et al.[5]. Plasma 5-HIAA was assayed by the method of UDENFRIEND et al.[6]. Symptoms after lithium administration were evaluated in animals receiving normal food.

Results. The Figure shows the concentrations of blood 5-HT and plasma 5-HIAA after lithium administration. The blood 5-HT level 1 h after lithium treatment was 3 times the control level, and it returned to the control level 6 h after lithium treatment. The plasma 5-HIAA level increased gradually reaching 220% of the control level 6 h after lithium treatment. Stomach 5-HT content did not change significantly after lithium treatment (Table). However, the duodenum and jejunum 5-HT contents decreased significantly by 23% and 17%, respectively, after 1 h, and 39% and 45%, respectively, after 6 h. Within 1 h after lithium administration, the animals receiving food showed increased defecation of slight diarrhea.

Effects of lithium administration on the contents of 5-HT in the stomach, duodenum and jejunum in rats

	Control	Hours after lithium treatment	
		1	6
Stomach	2.56 ± 0.11	2.51 ± 0.48	2.55 ± 0.11
Duodenum	6.65 ± 0.12	5.08 ± 0.10[a]	4.05 ± 0.30[b]
Jejunum	4.13 ± 0.09	3.44 ± 0.12[a]	2.29 ± 0.29[b]

Values are μg 5-HT/g tissue (wet wt.) and are means ± S.E. of those in 4 to 5 experiments. [a] Significantly different from control level ($P < 0.01$). [b] Significantly different from control level ($P < 0.001$).



Effect of lithium administration on the levels of blood 5-HT and plasma 5-HIAA in rats. The blood 5-HT level at zero time was 0.25 ± 0.02 μg/ml. The plasma 5-HIAA level was 0.22 ± 0.01 μg/ml. Points and vertical bars show means ± S.E. of values in 5 animals. * Significantly different from control level ($P < 0.01$).

Discussion. WOOLEY et al.[7] reported that on continuous treatment with 5-HT, injected as 5-hydroxytryptophan, mice developed severe diarrhea. These workers showed that the diarrhea induced by 5-HTP could be completely prevented by prior treatment of the animals with potent anti-5-HT compounds. HAVERBACH and DAVIDSON[8] also observed enhanced intestinal motility in human subjects on treatment with 5-HTP, and its inhibition by 2-bromo-D-lysergic acid diethylamide (BoL-148). So, diarrhea in these cases seems to be a direct result of an abnormally high level of circulating 5-HT.

In this work we observed that lithium administration induced pronounced increase in the blood 5-HT level (Figure), and a significant decrease in the duodenum and jejunum 5-HT contents (Table). These results suggest that lithium ion acts on the storage site of 5-HT in the intestine, causing its release into the blood. Therefore, it seems likely that diarrhea induced by lithium is due to a transient elevation of the level of circulating 5-HT, due to its release from the intestine.

In support of this idea, there is some evidence that gastro-intestinal discomforts may be induced by high amounts of circulating 5-HT. For example, cases with the dumping syndrome[9] show epigastric discomfort, nausea, vomiting, abdominal bloating and cramp, and hyperperistalsis with diarrhea. It has been reported[10] that these symptoms are due to release of duodenum 5-HT and elevation of blood 5-HT. Thus it is concluded that the early side effects of lithium therapy depend, at least in part, on elevation of the level of circulating 5-HT.

Zusammenfassung. Nachweis, dass der Blutspiegel des Serotonins bei Ratten 1 h nach oraler Gabe von 5 mEq/kg Lithium anstieg, während der Serotonin-Gehalt im Jejunum und Duodenum abnahm.

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