Absorption of intraduodenally administered ^{203}Pb in rats

Group	No. of rats	Dose of Pb^{2+} (μg per rat)	Stool + GIT content	Absorption(%)
1. Acceptors	9	10.6	63.1 ± 4.2	36.9 ± 4.2
2. Bile duct non-cannulated	4	10.6	64.4 ± 5.6	35.6 ± 5.6
3. Bile duct cannulated	4	10.6	81.2 ± 2.5	18.8 ± 2.5

Group 1: Acceptors: Biliary excreted ^{203}Pb (from donors) was administered intraduodenally. Group 2: $^{203}PbCl_2$ was administered intraduodenally. Bile duct non-cannulated. Group 3: $^{203}PbCl_2$ was administered intraduodenally. Bile duct cannulated. The results are expressed as a percentage of the intraduodenally dose (means and 95% confidence limits of means). GIT = gastrointestinal tract.

was immediately administered to acceptors (9 rats) through a cannula into the duodenum[6]. From acceptors the bile was collected for 24 h. 2. group: 4 rats without bile duct cannulated were given intraduodenally $^{203}PbCl_2$ every 2 h. 3. group: 4 rats with bile duct cannulated were given intraduodenally $^{203}PbCl_2$ every 2 h. The dose of lead received by the rats in the 2nd and 3rd group in the course of 24 h was equal to that received by acceptors in donor's bile within the same time interval (10.6 μg of Pb^{2+} per rat).

Determination of percentage of absorption and measurement of samples were performed in the same way as described formerly[6]. Each animal received about 8 μCi of ^{203}Pb. Carrier-free ^{203}Pb was kindly supplied by the Gustaf Werner Institute, University of Uppsala, Sweden.

Results and discussion. The average cummulative biliary excretion of ^{203}Pb in donors was 8.5% of the administered dose during 24 h. In acceptors (group 1) and in the rats from group 3 excretion via bile during 24 h was 1.6 ± 0.4% resp. 0.9 ± 0.4% of the intraduodenally administered dose of ^{203}Pb.

The Table shows the values of ^{203}Pb absorption in separate groups of rats. The results clearly indicate that percentage of absorption in acceptors as well as rats from group 2 (bile duct non-cannulated) is similar (36.9 and 35.6% resp.). The percentage of absorption in the group 3 (bile duct cannulated) is significantly lower –18.8% ($p<0.05$). It is therefore obvious that absorption of ^{203}Pb administered into the duodenum decreases in rats with cannulated bile ducts. On the other hand, there are no differences between absorption of biliary excreted ^{203}Pb and of ^{203}Pb administered into duodenum in rats without cannulation of the bile duct. Presence of bile seems to increase absorption of ^{203}Pb from the gastrointestinal tract. Lead probably forms a complex (or complexes) with some of bile components, most probably proteins[3,7], perhaps via a non-enzymatic way.

Comparison with results of the study of EHC of ^{52}Mn[6] shows that the percentage of absorption of lead excreted via bile is similar to values found in manganese. In case of lead, much lower biliary excretion in comparison with manganese means, however, much smaller importance of EHC in the total turnover of lead in the organism of the rat.

Summary. The author studied absorption of ^{203}Pb after administering intraduodenally ^{203}Pb eliminated with bile. The results obtained were compared with absorption of ^{203}Pb administered into the duodenum as $^{203}PbCl_2$ in rats forming 2 groups, one with bile ducts cannulated, the other intact. It was found that bile played an important role in absorption of Pb from the gastrointestinal tract. Absorption of Pb^{203} is significantly reduced if the bile is drained off by means of a canula.

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Effects of Temperature on the Responses to Noradrenaline, Isoprenaline and Histamine on Isolated Rabbit Mesenteric Artery

In experiments on isolated organs, the responses to β-sympathomimetic drugs were found to be highly sensitive against alteration of temperature, decrease of extracellular H^+ concentration and against metabolic inhibitors. From these observations, it is concluded that the effects of β-adrenoceptor stimulant drugs depend on the metabolic state of an organ[1,2]. Moreover, using α- and β-sympathomimetic drugs as relaxants on the rabbit ileum temperature elevation reveals a clear cut separation of adrenoceptors into the temperature sensitive β- and the insensitive α-adrenoceptors[3].

In order to prove whether this holds true also on the mesenteric artery of the rabbit, the effects of temperature elevation either on the affinity or on the intrinsic activity of α- and β-sympathomimetic drugs were investigated. It was further of interest to study the effects of histamine under similar experimental conditions.

Helically strips of the mesenteric artery of the rabbit were prepared for isometric recordings. They were suspended under a tension of 2 g in a 50 ml bath containing Krebs-Henseleit solution bubbled with 95% O_2 and 5% CO_2. The strips were allowed to equilibrate for 60 min prior to application of the drugs at 25° and at 42°C,

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Maximal responses and pD_2-values of noradrenaline and histamine on the mesenteric artery of the rabbit.

	25 °C		42 °C	
	Control	Prindolol (100 n*M*)	Control	Prindolol (100 n*M*)
Noradrenaline				
Maximal responses (mg)	2096.4 ± 461.0 (9)	2040.1 ± 300.0 (9)	2939.9 ± 656.0 (10)	2857.6 ± 520.3 (10)
pD_2-values	6.54 ± 0.13 (9)	6.72 ± 0.08 (9)	6.42 ± 0.07 (10)	6.40 ± 0.08 (10)
Histamine				
Maximal responses (mg)	2950.0 ± 244.5 (9)	–	4565.3 ± 438.8[a] (7)	–
pD_2-values	5.29 ± 0.11 (9)	–	4.87 ± 0.11[a] (9)	–

Given are means ± SE, number of experiments in brackets. [a] $p < 0.02$ compared with 25 °C.

respectively. Noradrenaline (0.01–50 μM) and histamine (0.5–100 μM) elicited increasing contractile responses with cumulative administration of increasing doses and exerted maximal responses which were in all cases higher for histamine than for noradrenaline (Table). The elevation of temperature from 25° up to 42 °C did not significantly alter the maximal response for noradrenaline. Also the pD_2-value (negative logarithm of that molar concentration causing a half maximal effect) at 25° did not differ from that at 42 °C. On the other hand, the elevation of temperature enhanced significantly the maximal effect induced by histamine. At the same time, the pD_2-value for this amine at 42 °C decreased significantly. The β-adrenoceptor stimulant isoprenaline in concentrations up to 0.1 mM did not elicit any relaxing effect on strips from the mesenteric artery contracted by 10 μM histamine. In the presence of the β-adrenolytic drug prindolol (100 nM), the maximal contractile response to noradrenaline was not altered at all, either at 25° or at 42 °C (Table). If β-adrenoceptors were present in the mesenteric artery of the rabbit, it would be anticipated that their blockade would increase the contractile response to noradrenaline. Likewise the pD_2-value for noradrenaline after prindolol should be elevated by excluding the inhibitory effect of β-adrenoceptor stimulation. In fact, prindolol yielded no alteration of the pD_2-value for noradrenaline (Table). These observations imply that in the mesenteric artery of the rabbit β-adrenoceptors are lacking.

The results presented are consistent with observations on the rat aorta which describe the peak contractile responses to several drugs to be enhanced by elevation of temperature[4]. Histamine was found to have a higher ceiling effect than noradrenaline at both temperatures investigated. In addition, it was demonstrated that the pD_2-value of histamine decreased with increasing temperature, whereas that of noradrenaline remained unaffected. Although the effects of histamine on vascular smooth muscle are closely related to the adenyl cyclase system, whereas that of α-sympathomimetic drugs is not[5], it is still rather unsettled whether the receptor itself or the metabolic events following the stimulation of the receptor were affected by temperature. A comparison with the effects of catecholamines on β-adrenoceptors on this organ is impossible since the results presented demonstrate the absence of β-adrenoceptors on the mesenteric artery of the rabbit. Also the pulmonary artery of the guinea-pig does not contain β-adrenoceptors[6,7].

Summary. On the rabbit mesenteric artery, the elevation of temperature from 25° up to 42° diminished the affinity of histamine, whereas that of noradrenaline to the α-adrenoceptors remained unchanged. The presence of β-adrenoceptors could not be demonstrated.

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Bufuralol, a New β-Adrenoceptor Blocking Agent

The continuing search for drugs which will block β-adrenoceptors has led to the observation that compounds with an N-substituted ethanolamine or oxypropanolamine moiety attached to a heterocyclic or aryl nucleus can produce the desired pharmacological effect[1].

Consideration of the structural relationship between phenoxypropanolamines and oxygen-heterocyclic ethanolamines directed attention to a series of benzofuran-2-ethanolamines **1**. Structure-activity studies indicated that maximum β-adrenoceptor blocking potency was achieved with 7-alkyl or 7-alkenyl substituents, and with small branched alkyl substituents on the amino function. This led to the choice of 1-(7-ethylbenzofuran-2-yl)-2-*tert*-butylamino-1-hydroxyethane **2**, Ro 03-4787, bufuralol, for extended pharmacological, and eventually clinical, evaluation.

Bufuralol has been prepared by the following route. Treatment of 5-bromo-3-ethylsalicylaldehyde **3** in ethanolic sodium hydroxide solution with chloroacetone

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