creasing amplitude of the b-wave (strong veratrinization) isolating the slow-decaying negative potential which might be referred to as the PIII component. Difference between effective doses of weak and strong veratrinization in the retina is small[6,7], as in other tissue[1]. In figure 1, almost no effect was observed in appearance by veratridine administration (weak veratrinization). However, by administration of 2×10^{-2} M sodium aspartate (which is usually enough to abolish the PII component and to isolate the PIII component[8]), PIII as well as PII disappeared. In figure 2, the PIII component was isolated at first by administration of 2×10^{-2} M sodium aspartate. Sodium aspartate by itself is a very safe chemical as sodium salt, and PIII, isolated by sodium aspartate of this level of concentration, is always very stable[8]. To this retina, veratridine of 6×10^{-5} M was administrated. Then, PIII was markedly reduced in amplitude and disappeared in 10–15 min. On the recording of 18 min, a moderate positive wave of 600–700 msec peak latency was observed. An important finding in these experiments was that generation of PIII component as well as the PII component of ERGs was severely damaged by simultaneous presence of veratridine and sodium aspartate in perfusate. Hanitzsch[8] studied effects of sodium aspartate upon the rabbit retina and analyzed PIII into 3 subcomponents, a) an aspartate-insensitive distal PIII, b) an aspartate-sensitive PIII, and c) an aspartate-insensitive slow PIII. PIII isolated in this study might be referred to a) or c), or a mixture of both subcomponents of Hanitzsch[8]. Further analysis is impossible in this study employing superficial electrodes, but it might be said that veratridine effects (weak and strong veratrinization) on the PII and aspartate-insensitive PIII components of perfused rabbit retinas were modified by presence of sodium aspartate, or in other words, that effects of sodium aspartate were modified by the presence of veratridine.

6 Y. Honda, Acta Soc. ophthal. jap. *81*, 135 (1977).
7 Y. Honda, Acta Soc. ophthal. jap. *81*, 139 (1977).
8 T. Furukawa and I. Hanawa, Jap. J. Physiol. *5*, 289 (1955).
9 R. Hanitzsch, Vision Res. *13*, 2093 (1973).

Sex factors and plasma levels of oxytetracycline (OTC) in rats[1]

Darinka Dekanić, Mirjana Kupinić[2], Tea Maljković and D. Kello[3]

Institute for Medical Research and Occupational Health, Moše Pijade 158, Y-41000 Zagreb (Yugoslavia),
20 October 1976

Summary. Sex related differences in plasma OTC concentrations were found in rats 4–24 h after a single i.p. application of 100 and 50 mg/kg OTC.

Reports on bone retention of tetracyclines in rats indicate that age and sex significantly influence the deposition of these antibiotics in the skeleton[4–6]. The differences were either not specially commented upon[5] or the authors tried to interpret them as an indicator of different bone growth[4]. It was also assumed that they could be due to other changes in the metabolism of antibiotics in the body caused by age or sex[6]. In the present paper the influence of sex factors on plasma levels of OTC was investigated as a possible explanation of different OTC retention in the bone, and as a factor which might be relevant for assessing the general efficiency of the OTC treatment.

Methods and results. The experimental animals, 12-month-old male and female albino rats (body weights 425 ± 18 g and 254 ± 13 g, respectively) and 12-month-old ovariectomized animals (body weight 280 ± 8 g; ovaries removed at the age of 4 months) were injected i.p. with 100 mg/kg OTC (Geomycin, Pliva, Zagreb). 2 lower doses of OTC, 10 and 50 mg/kg were injected in the same way to male and female rats of similar age (12–13 months old) and body weights (434 ± 7, 256 ± 5 g). Blood samples were taken 1, 4, 8, 24 and 48 h after OTC application from the orbital venous plexus and plasma was separated by centrifugation at 5000 rev/min (3000 × g) for 10 min. The concentration of the antibiotic was assayed on agar plates against Sarcina Lutea. It can be seen on table 1 that 1 h after administration of 100 mg/kg OTC plasma levels of OTC were practically the same in all groups of animals. After 4 h, the values for males and ovariectomized females

Table 1. OTC concentrations in plasma (μg/ml) after a single i.p. injection of 100 mg/kg*

		Time after dose (h) 1	4	8	24
Female rats					
A) controls		48.9±1.0	46.0±1.4	20.0±2.0	2.7±0.1
B) ovariectomized		49.2±0.6	81.1±4.7	33.5±5.0	3.7±0.3
Male rats					
C) controls		47.1±3.3	76.0±5.4	48.5±3.9	4.0±0.6
	A:C	$p>0.1$	$p<0.001$	$p<0.001$	$p<0.05$
	A:B	$p>0.1$	$p<0.001$	$p<0.02$	$p<0.001$
	B:C	$p>0.1$	$p>0.1$	$p<0.02$	$p>0.1$

*Each figure represents the mean of 8 animals ± SE.

Table 2. OTC concentrations in plasma (μg/ml) after a single i.p. injection*

Dose mg/kg	Sex		Time after dose (h) 1	4	8
50	A) female		22.0±1.8	10.5±1.5	0.5±0.01
	B) male		19.0±1.2	8.9±1.3	3.5±0.3
10	C) female		4.1±0.2	1.3±0.1	
	D) male		3.8±0.4	1.4±0.2	
		A:B	$p>0.1$	$p>0.1$	$p<0.001$
		C:D	$p>0.1$	$p>0.1$	

*Each figure represents the mean of 8–12 animals ± SE.

were significantly higher than for female controls. After 8 h, the values were significantly different for all groups of animals; the highest were observed in males, lower in ovariectomized females and the lowest in control females. After 24 h the OTC plasma levels in all groups of animals decreased below 6 µg/ml, but in males and ovariectomized females they were still significantly higher than in control females. After 48 h, OTC values in the plasma were not measurable. When doses of 10 and 50 mg/kg OTC were injected, the antibiotic could not be detected in plasma 8 and 24 h after the application respectively. It is evident from table 2 that with the dose of 10 mg/kg the concentrations of the antibiotic 1 and 4 h after the application did not vary significantly with the sex of the animal. With the dose of 50 mg/kg, the plasma levels in male and female rats differed significantly only in the later time interval, i.e. 8 h after injection of the antibiotic.

Discussion. Studying the influence of sex factors on fatty liver induced by tetracycline, Brenn et al.[7] found no significant differences in the serum levels of antibiotic between male and female rats 3 h after an i.p. application (50–100 mg/kg). However, according to our results, at this early interval sex differences are not likely to be noticeable since they seem to appear at a later stage. The mechanism by which observed differences in plasma levels of OTC occur is uncertain. The metabolic transformation and the volume of distribution seem unlikely to be operative in this case, but the latter possibility cannot be completely excluded in ovariectomized females which have an increased amount of fatty tissue[8]. However, our results indicate that the increased retention of OTC in the bones of male rats observed earlier[4,6] is not necessarily due to differences in the bone turnover but could also be a result of increased OTC level in the plasma. Ovariectomized animals have higher plasma levels than controls. They nearly approach those of male rats indicating that a lack of ovarian sex hormones is partly responsible for the observed effect.

However, it should be kept in mind that the observed sex differences in the plasma levels of OTC might also be of clinical importance, when the antibiotic is administered parenterally in higher doses according to body weight. Further studies are needed to clarify the role of sex factors in OTC metabolism, especially in its elimination, which seems to be of primary importance for explanation of presented data.

1 Acknowledgments. The authors thank Prof. K. Kostial for critical comments and suggestions in the preparation of the manuscript. – This work was partly supported by a research grant from the US Department of Agriculture and the 'Pliva', Pharmaceutical Works, Zagreb.

2 Institute for the Control of Drugs, Moše Pijade 160, Y–41000 Zagreb, Yugoslavia.

3 Mailing address: Dr. Dinko Kello.

4 D. A. Buyske, H. M. Eisner and R. G. Kelly, J. Pharmac. exp. Ther. *130*, 150 (1960).

5 K. I. Hawkins, Analyt. Biochem. *45*, 128 (1972).

6 D. Dekanić, PhD Thesis, University of Zagreb, 1975.

7 K. J. Breen, S. Schenker, M. Heimberg, Gastroenterology *69*, 714 (1975).

8 V. Korenchevsky and K. Hall, J. Endocr. *4*, 103 (1945).

Uptake of noradrenaline in high altitude native's heart

J. R. Rapin, J. Coudert, L. Drouet, J. Durand and Y. Cohen

Department of Pharmacology and Physiology, University Paris XI, Rue J. B. Clément, F–92290 Chatenay Malabry (France), 22 November 1976

Summary. Uptake of ^{3}H-noradrenaline by the heart was studied with sections of isolated atria obtained from high or lowlanders. In native highlanders, affinity for ^{3}H-noradrenaline by human atria is more significant than in lowlanders. Furthermore, the Michaelis Menten constant is lower in high altitude native's heart.

People born and residing permanently above 3500 m have a different circulatory pattern from lowlanders. Pulmonary hypertension and right ventricular hypertrophy were described previously[1]. More recently, reduction in regional blood flow and in cardiac output were reported[2–5]. Decrease in local blood supply was accompanied by an increase oxygen arteriovenous difference in such a way that local oxygen consumption was maintained. However, there is an exception: reduction in coronary blood flow was not compensated by a parallel decrease of oxygen content in the blood of the coronary sinus, so that oxygen consumption related to heart weight was reduced in high altitude residents[6].

These results may be related to changes in the noradrenergic nervous system. Studies carried out on rats artifically maintained in conditions of high altitude have demonstrated that the level of cardiac noradrenaline decreased during the period of acclimatization[7–9] and subsequently returned to its normal rate, probably following decreased use of the transmitter. This was parallel to a slight decrease of the turn-over found in hypobaric hypoxia[10], which may be due either to modifications of biosynthesis or to changes in the inactivation of noradrenaline. This paper reports the differences in noradrenaline uptake main route of inactivation of the transmitter, studied on sections of human atria collected at high altitude or low altitude in Andean or European populations.

1 A. Rotta, A. Canepa, A. Hurtado, T. Velasquez and R. Chavez, J. appl. Physiol. *9*, 328 (1956).

2 Y. Bidart, L. Drouet and J. Durand, J. Physiol. *70*, 333 (1975).

3 J. Durand and J. P. Martineaud, Ciba Found. Symposium on High Altitude Physiology 1971, p. 159.

4 J. Durand, J. P. Marc-Vergnes, J. Coudert, M. C. Blayo and J. J. Pocidalo. XXVI int. Congr. Physiol. Sci. Krogh Centenary Symposium, Srinagar, 12–16 October 1974.

5 M. Zelter, J. Mensch-Dechene, G. Antezana, J. Coudert and A. Lockart, IX ann. Meet Eur. Soc. clin. Invest., Rotterdam, 24–26 April 1975.

6 P. R. Moret, Ciba Found. Symposium on High Altitude Physiology 1971, p. 131.

7 J. N. Davis and A. Carlsson, J. Neurochem. *21*, 783 (1973).

8 D. A. Hurwitz, S. M. Robinson and I. Barofsky, Psychopharmacologia (Berl.) *19*, 26 (1971).

9 M. Stupfel, J. Roffi, C. r. Soc. Biol. *155*, 237 (1961).

10 M. Prioux-Guyonneau, J. Durand, J. R. Rapin and Y. Cohen, Experientia *32*, 1024 (1976).