We wish to thank Boehringer for a donation of [^{3}H]clonidine.

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Note added in proof: During the preparation of the manuscript U'Prichard, Greenberg and Snyder published an increase in B_{max} of [^{3}H]WB 4101 but not of [^{3}H]clonidine in the whole brain of SHR. (Nervous System and Hypertension, P. Meyer and H. Schmidt, ed., Wiley Flammarion, Paris, 1979, pp. 31–48).

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Effects of chronic heat exposure on drug metabolism in the rat

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Chronic exposure of rats to high ambient temperature may cause a variety of pathophysiological changes such as lowering basal metabolism (Chaffee & Roberts 1971) and diminution of liver weight (Ray et al 1968). Little is known, however, about the possible effects of chronic heat exposure on the disposition of drugs in animals or man. A few studies have shown increased drug toxicity following heat exposure (Hovevy-Sion & Kaplanski 1979; Keplinger et al 1959). A possible cause for the increased toxicity, may be the reduced rate of drug metabolism. We have found that in vitro hepatic *N*-demethylation of *p*-chloro-*N*-methylaniline and aniline hydroxylase activities in chronically heat exposed rats are substantially reduced (Kaplanski & Ben-Zvi 1980). The present study was therefore undertaken to investigate the rate of oxidative drug metabolism in vivo in chronically heat exposed rats.

Materials and methods. Male Charles River rats, 8 weeks old, were housed two per cage for at least 30 days in one of two rooms: a control room kept at 22±2 °C and 40% relative humidity and a hot room kept at 35± 2 °C and 20–30% R.H. Both rooms were illuminated from 5 a.m. until 7 p.m. Rat chow and water were freely available.

Hexobarbitone (Sigma, St. Louis, Missouri, U.S.A.) was dissolved by dropwise addition of 1M NaOH and injected intraperitoneally at a dose of 100 mg kg^{-1} (20 mg ml^{-1}). On day 31 of heat exposure, sleeping time was recorded as the time during which the righting reflex was absent.

[^{14}C] Antipyrine (50 Ci mmol^{-1}, The Radiochemical Centre Amersham, U.K.) was diluted with antipyrine (BDH Chemicals Ltd, Poole, U.K.) and injected intraperitoneally at a dose of 15 mg kg^{-1} (12·53 Ci mmol^{-1}) on days 32 and 34 of heat exposure. Samples of blood were withdrawn from the tail of each rat under light ether anaesthesia. Antipyrine blood concentration was determined after extraction according to Bakke et al (1974). Antipyrine half-life time ($t_{\frac{1}{2}}$) was estimated from least squares regression analysis of the log blood concentration of antipyrine versus time in the elimination phase. Apparent volume of distribution (aVd) was calculated according to Aarbakke et al (1978), assuming complete absorption of antipyrine after an intraperitoneal injection. Metabolic clearance rate (MCR) was calculated according to the formula

$$MCR = \frac{aVd \times \ln 2}{t_{\frac{1}{2}}} \quad .. \quad .. \quad .. \quad (1)$$

Rectal temperatures were recorded just before injection of hexobarbitone or antipyrine in the respective experiments.

All drugs were injected between 8 and 10 a.m. to avoid possible variation related to circadian rhythm. Statistical evaluation of the data was carried out using the Students *t*-test.

Results. Table 1 shows that the biological half-life time of antipyrine was almost doubled in heat exposed rats

* Correspondence.

Table 1. Rectal temperature and pharmacokinetic parameters of antipyrine (Results are presented as mean ± s.e.m.)

Group of rats	Rectal temp. (°C)	$t_{\frac{1}{2}}$ (h)	Apparent volume of distrib. (litres kg^{-1})	Metabolic clearance (ml kg^{-1} min^{-1})
Heat exposed (n = 10)	39·1 ± 0·2*	3·41 ± 0·29*	1·35 ± 0·07**	4·93 ± 0·53*
Control	37·5 ± 0·2	1·78 ± 0·14	1·58 ± 0·07	11·45 ± 0·97

* $P<0·01$ Heat exposed versus control rats.
** $P<0·05$ Heat exposed versus control rats.

($P<0·01$) while the apparent volume of distribution was significantly decreased by more than 15%. The metabolic clearance rate, as calculated from equation (1) was also significantly reduced in the heat exposed rats by more than 55%.

Exposure of rats to high ambient temperature, resulted in an increase of 1·6 °C in rectal temperature (RT). The elevated rectal temperature was observed as early as 1 h after exposure, and remained so throughout the entire period of exposure.

Hexobarbitone sleeping time in the heat exposed rats was 37·1 ± 2·5 min, significantly longer than that of control group (15·9 ± 1·4 min, $P<0·01$).

Discussion. Antipyrine serves as a model for heptatic drug metabolism (Bakke et al 1974; Vesell & Page 1969). It is metabolized by oxidative pathways followed by conjugation (Aarbakke 1978), so that the rate of its disappearance from the blood reflects metabolic oxidative rate. Thus, our observations (Table 1) indicate a decreased metabolic rate of antipyrine.

Hexobarbitone sleeping time depends on many factors (Vesell 1968). A major determinant is blood concentration of the drug (Gut & Becker 1975). Metabolic oxidation reduces blood concentration and diminishes the hypnotic activity. The twofold longer hexobarbitone sleeping time found in chronically heat exposed rats suggests lower rate of metabolic oxidation of antipyrine.

Our finding of a reduced metabolic oxidation rate of antipyrine, correlates well with the impaired in vitro hepatic *N*-demethylase and aniline hydroxylase activities of Kaplanski & Ben-Zvi (1980). Since the liver is the main organ responsible for drug detoxification, the impaired detoxication of drugs both in vivo and in vitro in chronically heat exposed rats may be due to either diminished liver activity or reduction of liver mass or both.

The effects of hyperthermia on drug metabolism reported in the literature differ depending on the model studied. Most of these investigations were carried out during acute hyperthermia. Data in man in whom fever was induced by etiocholanolone are variable and depend on the drug investigated (Song et al 1972; Blaschke et al 1973; Elin et al 1975). In rats, in which hyperthermia was caused by the intraventricular injection of prostaglandin E, the metabolic clearance rate of antipyrine did not change although changes in half-life time and apparent volume of distribution were observed (Aarbakke et al 1978). In our investigations (Ben-Zvi & Kaplanski unpublished data), hyperthermia caused by acute exposure to high environmental temperature, did not result in any changes in drug metabolism both in vivo and in vitro. It seems that the longer duration of hyperthermia allows the development of pathophysiological changes such as reduction of liver mass and metabolic activities.

Other contributing factors may be differences in the blood distribution to the various organs, especially the liver (Bradley 1949; Rowell et al 1970), or endocrine changes related to stress (Chung & Brown 1976). We have observed that in chronically heat exposed rats, plasma concentrations of corticosterone are not elevated (Kaplanski & Ben-Zvi 1980). Therefore, it is unlikely that stress plays a major role under present experimental conditions.

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