Acetylation of procainamide in the rat

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Procainamide (PA) seems to be polymorphically acetylated in man. It has been shown to follow a bimodal distribution similar to that of isoniazid, sulphadimidine and dapsone (Gibson et al 1975; Giardina et al 1977; Reidenberg et al 1975).

Reports on the acetylation of PA in the rat have been published recently (Schneck et al 1978a,b). Working with only male rats, these authors concluded that, unlike in man, the acetylation of PA was monomorphic in this species. In our earlier studies we observed sex-determined differences in the acetylation of sulphadimidine (Zidek & Janku 1976, 1979 in press). Also, treatment of male rats by complete Freund's adjuvant was found to greatly influence the percentage of acetylated sulphadimidine excreted in the urine (Zidek et al 1977).

In this study we reinvestigated monomorphic acetylation of PA in the rat as reported by Schneck et al (1978a,b) also using female rats, and examined the potential effect of different doses of PA and Freund's adjuvant on the degree of PA acetylation in the same rat.

A genetically heterogenous sample of 10–12 weeks old random-bred albino rats of the Wistar stock (VELAZ, Prague) was used. Procainamide (Spofa) was given intravenously at 1, 5, 10 or 40 mg kg^{-1}, or orally 10 or 40 mg kg^{-1}. Urine was collected in glass metabolism cages for 4 h after the drug. Blood samples were obtained by decapitation 5 min after injection of the drug.

Unchanged and acetylated PA were determined spectrophotometrically by a modified Bratton & Marshall (1939) method.

Experiment 1: Investigation of PA acetylation in either sex, using different doses of PA. The mean percentages of *N*-acetylprocainamide (NAPA) excreted in the urine are shown in Table 1. There was no statistically significant differences between the male and female in both i.v. and orally treated animals ($F_{(1,28)} = 0{\cdot}05$, $P > 0{\cdot}05$, and $F_{(1,13)} = 0{\cdot}42$, $P > 0{\cdot}05$, respectively). Only the dependence on the administered dose was statistically significant, the NAPA % was lower both in the highest i.v. and oral dose used ($F_{(1,28)} = 4{\cdot}45$, $P < 0{\cdot}05$, and $F_{(1,13)} = 7{\cdot}7$, $P < 0{\cdot}05$, respectively).

Table 1. Percentage of *N*-acetylprocainamide in the urine 4 h after the administration of procainamide.

	Female rats		Male rats	
Route	n	mean	n	mean
i.v.				
1 mg kg^{-1}	4	36·6 ± 8·9*	4	39·0 ± 11·6
5 mg kg^{-1}	5	49·3 ± 7·6	5	44·1 ± 10·4
10 mg kg^{-1}	4	45·2 ± 12·6	4	37·8 ± 8·7
40 mg kg^{-1}	4	25·1 ± 7·8	5	35·3 ± 15·3
Oral				
10 mg kg^{-1}	4	52·7 ± 12·0	4	51·6 ± 11·5
40 mg kg^{-1}	4	45·0 ± 12·0	5	43·9 ± 14·8

* 5% limits of confidence.

Five min after i.v. injection of 10 mg kg^{-1} of PA, mean blood concentration amounted to 11·4 ± 3·4 μg ml^{-1} in females, and 9·43 ± 3·4 μg ml^{-1} in males, the difference being not statistically significant ($t_{(6)} = 1{\cdot}29$, $P > 0{\cdot}10$). The NAPA % in the blood displayed near identical levels (38·1 ± 14·9) in females had (42·8 ± 26·9) in males ($t_{(6)} = 0{\cdot}13$, $P > 0{\cdot}50$).

A distribution histogram of the NAPA % (Fig. 1) was constructed on the basis of the data obtained from the sexes after 1, 5 and 10 mg kg^{-1} i.v. of PA as no significant difference among them was found ($F_{1,21} = 1{\cdot}97$, $P > 0{\cdot}05$). It can be seen from this figure that the NAPA % follows a unimodal distribution curve.

Experiment 2: Investigation of the effect of Freund's adjuvant on the NAPA % in the urine. Three weeks after application of 0·1 ml adjuvant s.c., the rats received 10 mg kg^{-1} i.v. of PA. The NAPA % determined in the urine of 10 control and 10 adjuvant-treated male rats were 52·7 ± 6·2 and 47·0 ± 5·3, respectively. The difference was not statistically significant ($t_{(18)} = 0{\cdot}62$, $P > 0{\cdot}05$).

Our results show that there is no sex dimorphism or polymorphic acetylation of PA in rats. This confirms the findings of Schneck et al (1978a,b) who used only male rats. The present results are divergent from our previous findings, showing sex-dependent differences in the acetylation of sulphadimidine in rats of the same strain as used in the present study (Zídek & Janku 1976). Comparison of our previous and present results indicate that different types of *N*-acetyltransferase are

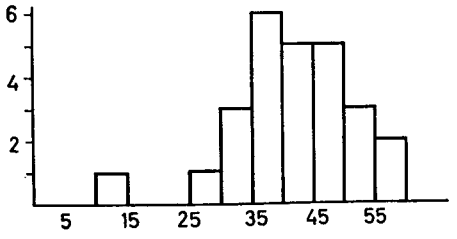

FIG. 1. Frequency of acetylator phenotype in rats after i.v. injection of procainamide. The 4 h urine excretion of *N*-acetylprocainamide (ordinate: NAPA %). Abscissa: number of animals.

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most probably involved in the transformation of sulphadimidine and PA in random-bred albino rats of the Wistar stock. That adjuvant treatment did not affect PA acetylation compared with a increase of acetylated sulphadimidine in adjuvant-treated male rats (Zídek et al 1977) is indicative of different metabolic patterns of PA and sulphadimidine. Different doses of PA (1, 5, 10 mg kg^{-1}) failed to affect the percentage of NAPA in the urine. Only the higher dose (40 mg kg^{-1}) was accompanied by a decrease of NAPA % in the urine. This observation agrees with the findings of Olson et al (1978) who found this effect with sulphadimidine in man.

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Responses of guinea-pig lung parenchymal strips to prostaglandins and some selected autacoids

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Guinea-pig isolated tracheobronchial smooth muscle preparations have extensively been used in the immunopharmacological studies and for screening bronchodilators and anti-allergic drugs (Chand & Eyre 1978). In 1976, Lulich et al introduced the use of lung parenchymal strips for the pharmacological evaluation of the peripheral airways (bronchiolar-alveolar ducts and alveoli). The immunological release of histamine, prostaglandins, kinins and several other chemical mediators of anaphylaxis in the lung of man and animals has frequently been reported (Piper 1977). The study of the actions of the naturally occurring autacoids (histamine, prostaglandins etc . . .) on the airway smooth muscles is important for the better understanding of the pathophysiological mechanisms in the development of lung diseases. This report describes the effects of some selected pharmacological mediators of anaphylaxis on isolated lung parenchymal strips (peripheral airways) of guinea-pig.

Twenty-seven guinea-pigs of either sex, 450 to 700 g, were killed by cervical dislocation. Lungs were immediately removed and placed in cold oxygenated Krebs-Henseleit solution (Chand & DeRoth 1979). Lung strips of about 20 × 3 × 2 mm were prepared following the method of Lulich et al (1976). The lung strips were mounted in isolated tissue baths containing Krebs-Henseleit solution bubbled with 5% CO_2 in O_2, maintained at 37 °C. Tissues were allowed to equilibrate for at least 1 h under a resting load of 1·5 g. Cumulative dose-response curves to agonists were recorded at 60 min intervals using isotonic transducer and pen recorder. Appropriate controls for the solvent (ethanol for prostaglandins) were simultaneously carried out. Single dose-response curves to bradykinin were recorded. The relaxant responses to PGE_1 or PGE_2 were recorded on lung strips which were maximally contracted to $PGF_{2\alpha}$ (5×10^{-5}M). Drug concentrations are expressed as molar (M) bath concentrations.

The strips exhibited concentration-dependent contractions to bradykinin (BK), histamine, carbachol or $PGF_{2\alpha}$ (Figs 1, 3) with EC50 values of 4, 5, 7 and 10 μM for $PGF_{2\alpha}$, histamine, carbachol and bradykinin respectively. Therefore, the order of the relative potencies of these spasmogenic agents on GPLS was $PGF_{2\alpha}$ > histamine > carbachol > 5-HT. The latter produced only 20% of maximum response to histamine (Fig. 1).

Lung strips which were maximally contracted to $PGF_{2\alpha}$ (5×10^{-5}M) responded to PGE_1 and PGE_2 with relaxations in concentration dependent manner (Fig. 2). PGE_1 was about 2 to 5 times more effective than PGE_2 in relaxing the $PGF_{2\alpha}$-contracted lung strips (Fig. 2). Typical responses of the guinea-pig lung strip to histamine, carbachol and $PGF_{2\alpha}$ are shown in Fig. 3. Adrenaline (10^{-7} to 5×10^{-3}M) (Fig. 3) and noradrenaline (10^{-6} to 10^{-4}M) also relaxed lung strips which were pre-contracted to $PGF_{2\alpha}$, carbachol or histamine.

Guinea-pig lung parenchyma possesses large quantities of alveolar duct smooth muscle (Miller 1921) and may also contain contractile interstitial cells in the pulmonary alveolar septa (Kapanci et al 1974). The relaxation of the lung parenchymal strips to large doses of adrenaline and noradrenaline in guinea-pig (this study) and cat (Lulich et al 1976) is taken as a strong

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