1971) and female (Harrison, Ambrus & Ambrus, 1952; Sever & Caldwell, 1974) rats become tolerant to the hyperthermic action of amphetamine on prolonged dosage, so that there are apparently no sex differences in the tolerance mechanisms. Furthermore, there is no significant difference between the hyperthermic response to amphetamine in the two sexes, as shown in this work. Table 1 shows that both male and female rats convert the pretreating drugs in part to *p*-hydroxynorephedrine and this suggests that the production of this metabolite is not related to the tolerance to amphetamine hyperthermia seen in the rat since the sex difference in protection is not paralleled by a deficiency in the tolerance mechanism.

On the data available at present, a plausible explanation of the sex difference observed here is not possible. There may be sex differences in the pharmacokinetics and metabolism of the pretreating drugs, as has been shown with *p*-hydroxyamphetamine, whose metabolism is more extensive in the male than the female (P. S. Sever, J. Caldwell & L. G. Dring unpublished data).

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The influence of atrial temperature on the *in vitro* selectivity of isoprenaline for atria and of orciprenaline for trachea

Many studies on selective β-adrenoceptor agonists utilize isoprenaline as a reference drug and its potency is given an arbitrary value, for example of 100, on the various tissues. In previous *in vitro* studies from this laboratory isoprenaline has been found to be selective for atria, i.e. its potency on guinea-pig atria was significantly greater than that on tracheal chains (O'Donnell, 1970, 1972; O'Donnell & Wanstall, 1974). The experimental conditions for these two preparations differed in one respect, namely the atrial preparations were maintained at 30° whereas the tracheal preparations were at 37°. Other workers have previously described an increased sensitivity of isolated heart preparations to sympathomimetic amines if the temperature was decreased (Trendelenburg, 1968; Oppermann, Ryan & Haavik, 1969). The aims of the present study were to establish whether a similar temperature-dependent supersensitivity could account for the apparent selectivity for atria of isoprenaline noted above and to examine retrospectively whether the lower atrial temperature might also have influenced the selctivity for trachea observed for compounds related to isoprenaline and orciprenaline (O'Donnell & Wanstall, 1974). Thus isoprenaline and

orciprenaline have been investigated on tracheal and atrial preparations maintained at the same temperature (37°) and the results compared with those obtained from experiments where atria were maintained at 30° and tracheae at 37°. Tracheae were not examined at 30° because preparations do not gain spontaneous tone at this temperature.

Cumulative log dose-response lines were obtained on guinea-pig isolated tracheal chain and atrial (rate) preparations as described previously (O'Donnell & Wanstall, 1974). The mean value of the negative log molar concentration required to produce 50% of the maximum response to isoprenaline (mean negative log EC50) was obtained for:

1. *Isoprenaline* (*a*) on trachea at 37° and atria at 30° (preparations from 5 animals). In 1 of the 5 experiments a further dose-response line was carried out on atria after raising the temperature to 37°. (*b*) on trachea at 37° and atria at 37° (preparations from 5 animals). In 1 of the 5 experiments a further dose-response line was carried out on atria after lowering the temperature to 30°.
2. *Orciprenaline* in trachea at 37° and atria at 30° or 37° (preparations from 5 animals). In these 5 experiments two dose-response lines were obtained on each atria, one at each temperature. The bath temperature used first was randomized.

The results are summarized in Table 1. Both isoprenaline and orciprenaline tended to be more potent on atria at 30° than at 37° The difference in potency was significant for isoprenaline (2·2 fold; $0{\cdot}01 > P > 0{\cdot}001$) but only 1·5 fold for orciprenaline. In experiments where concentration-response lines were obtained on the same atrial preparation at both temperatures, differences in potency, of the same order of magnitude as above, were observed whichever temperature was studied first.

Irrespective of the atrial temperature, isoprenaline always showed selectivity for atria and orciprenaline selectivity for trachea. However, increasing the atrial temperature to 37° significantly decreased the selectivity of isoprenaline for atria

Table 1. *Effect of changing atrial temperature from 30° to 37° on potency and β-adrenoceptor selectivity of isoprenaline and orciprenaline.* In all experiments the trachea was maintained at 37°. Number of experiments is in parentheses.

Isoprenaline	Mean neg. log EC 50 ± s.e. atria	Mean neg. log EC 50 ± s.e. trachea	Selectivity for atria (difference in log units ± s.e. difference)
Atria at 30°	8·62 ± 0·08 (5)	8·12 ± 0·03 (5)	0·50*** ± 0·09
Atria at 37°	8·27 ± 0·02 (5)	8·04 ± 0·09 (5)	0·23* ± 0·09
Supersensitivity of atria at 30° (difference in log units ± s.e. difference)	0·35** ± 0·08		
Orciprenaline			**Selectivity for trachea (difference in log units ± s.e. difference)**
Atria at 30°	6·56 ± 0·06 (5)	7·03 ± 0·06 (5)	0·47*** ± 0·08
Atria at 37°	6·37 ± 0·07 (5)		0·66*** ± 0·09
Supersensitivity of atria at 30° (difference in log units ± s.e. difference)	0·19 ± 0·09		

* significant difference ($0{\cdot}05 > P > 0{\cdot}01$).

** ,, ,, ($0{\cdot}01 > P > 0{\cdot}001$).

*** highly significant difference ($P < 0{\cdot}001$).

($0{\cdot}01 > P > 0{\cdot}001$) whereas it significantly increased the selectivity of orciprenaline for trachea ($0{\cdot}05 > P > 0{\cdot}01$).

This observation that guinea-pig atria were supersensitive to isoprenaline at 30° compared with 37° was qualitatively similar to, although quantitatively less than, that of Woppel & Trendelenburg (1973) whose experiments were on atria at 27° and 37°. Even though the atrial potency of isoprenaline was reduced if experiments were carried out at 37°, isoprenaline was still selective for atria. This suggests that the selectivity of isoprenaline for atria previously reported by us in experiments where atria were at 30° (O'Donnell & Wanstall, 1974) was not solely due to the temperature difference between atrial and tracheal preparations. Nevertheless the use of a temperature of 30° for the atrial experiments exaggerated the selectivity of isoprenaline for atria because atria are supersensitive to isoprenaline at the lower temperature.

The reasons for this temperature-dependent supersensitivity remain unclear. It has been claimed that, in guinea-pig and mouse hearts, a major cause is an impairment of catechol-*O*-methyl transferase (COMT) activity at the lower temperature (Opperman, Ryan & Haavik, 1972; Munoz-Ramirez, Haavik & Ryan, 1973). We found, as did Woppel & Trendelenburg (1973), that orciprenaline, like isoprenaline, was consistently more potent if atrial experiments were carried out at a temperature lower than 37° although in our experiments the difference was not statistically significant. Woppel & Trendelenburg (1973) concluded that, since orciprenaline is not attacked by COMT, a temperature-induced reduction in atrial COMT activity could not explain the supersensitivity to sympathomimetic amines. However, if the extents of the supersentivity to orciprenaline and isoprenaline are compared, it is found that lowering atrial temperature has a greater effect on isoprenaline than on orciprenaline. This observation suggests that changes in COMT activity could play a minor role at least in the supersensitivity.

Because the sensitivity of atria to orciprenaline was low when atria were at 37°, the selectivity of orciprenaline for trachea was greater in these experiments than in experiments where atria were at 30°. It is therefore concluded that, in our previous experiments designed to examine the selectivity for trachea of sympathomimetic amines related to isoprenaline and orciprenaline, the conditions used, i.e. trachea at 37°, atria at 30°, would tend to cause underestimation of the selectivity for trachea if all the compounds examined behave like isoprenaline and orciprenaline and are more potent on atria at 30° than 37°.

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