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# Detection of drugs with peripheral vascular effects similar to those of nicotinic acid

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Guinea-pigs anaesthetized with urethane respond with a marked rise in skin temperature due to dilation of the cutaneous vessels after the administration of nicotinic acid. Recording the ear temperature of these animals can therefore be used as a simple and sensitive method for the detection of drugs with peripheral vascular effects similar to those produced by nicotinic acid.

Flushing of the skin due to dilation of the cutaneous vessels (Bean & Spies, 1940) especially in the brachiocephalic region is frequently experienced in man after the administration of nicotinic acid. This phenomenon is associated with a rise in skin temperature and is difficult to reproduce in animals. It has not been observed in mice, rats, rabbits, ground squirrels, sheep and dogs, even after large doses (Altschul, 1964a). However, it has been reported that nicotinic acid (Chevillard, Giono & Laury, 1958) and β-pyridylcarbinol (Fromherz & Spiegelberg, 1948) elicit flushing of the guinea-pig ear. This led us to develop a method for detecting drugs with vascular effects similar to those of nicotinic acid.

## EXPERIMENTAL

Male guinea-pigs weighing 250–300 g were anaesthetized by the intraperitoneal injection of 1500 mg/kg of urethane (6 ml/kg of a 25% w/v solution).

A chromium-nickel-constantan thermo-couple (type RM6, Ellab instruments, Copenhagen, Denmark) was placed with its thermo-junction on the skin of the ear. The temperature was recorded on a six channel strip chart recorder (type Z8, Ellab instruments, Copenhagen, Denmark). The accuracy of the recordings was ±0·1°.

The compounds were injected intraperitoneally (8 ml/kg). Substances, sparingly soluble in water, were suspended in 0·9% saline containing 2% methylcellulose. The pH and tonicity of the solutions were adjusted to physiological levels by adding NaCl, NaOH or HCl. The experiments were made at a room temperature of 22–23°.

## RESULTS

The ear temperature of 100 unanaesthetized guinea-pigs was 33·2 ± 1·5° (mean ± s.e.) and was markedly affected by the handling of the animals. However, the temperature of guinea-pigs anaesthetized with urethane did not vary more than ±0·1° during a period of 10 min shortly after the onset of anaesthesia. The temperature during the 10 min pre-drug period as obtained on 100 animals was 28·8 ± 1·0° (mean ± s.e.). Under similar conditions anaesthesia induced by sodium pentobarbitone (35 mg/kg, i.p.) gave variations of several degrees.

In 15 control animals the intraperitoneal administration of 8·0 ml/kg of a 0·9% NaCl solution gave a small and gradual decrease in ear temperature in all animals which amounted to 0·3 ± 0·2° (mean ± s.e.) 60 min after the injection. The

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corresponding value after the injection of a solution containing 2% methylcellulose was 0·3 ± 0·3° (mean ± s.e., n = 15). An increase in ear temperature of at least 0·3° above the pre-drug value was therefore defined as a significant effect.

Nicotinic acid in doses between 5–150 mg/kg gave a significant increase in ear temperature (Table 1). In most cases the temperature began to rise within 2 min after the injection and reached its peak value after 3 to 8 min, returning to pre-drug values usually within 10–20 min after the onset of the rise. No significant correlation of the maximum rise in skin temperature and the dose given was observed.

Table 1. *The effect of a single intraperitoneal injection of nicotinic acid on the ear skin temperature of guinea-pigs anaesthetized with urethane. An increase in temperature of* 0·3° *was considered significant*

| Nicotinic acid dose in mg/kg | Number of responders / Number of animals injected | Maximum rise in ear temperature in ° C (mean ± s.e.) |
|---|---|---|
| 1·5 | 2/10 | 0·4 ± 1·2 |
| 5 | 6/10 | 1·4 ± 1·1 |
| 15 | 7/15 | 1·7 ± 0·8 |
| 30 | 13/15 | 1·3 ± 0·8 |
| 50 | 12/16 | 2·2 ± 1·2 |
| 100 | 14/15 | 2·2 ± 1·1 |
| 150 | 21/29 | 1·8 ± 1·0 |

## DISCUSSION

The reason for the different responses of various peripheral vascular beds (Altschul, 1964) in man to nicotinic acid is not clear. The large differences in the vascular reactivity towards this drug between various species is also unexplained. The unresponsiveness of laboratory animals has prevented the development of simple methods for detecting drugs with vascular effects similar to those of nicotinic acid.

Measurements of fore-paw temperature in conscious mice is used as a screening method for detecting drugs with peripheral vasodilatory properties (Richter, 1964; Campbell & Richter, 1967). In our hands this method fails to detect nicotinic acid in doses up to 500 mg/kg intraperitoneally. The present method seems to fulfil the requirement of a simple, sensitive screening procedure for this purpose. The number of animals which reacted increased with dose (Table 1). However, no correlation was found between the magnitude of the rise in ear skin temperature and the dose (Table 1). This is similar to the situation in man where no clear relation has been found between the vascular effects and the dose of nicotinic acid (Altschul, 1964b).

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## REFERENCES

ALTSCHUL, R. (1964a). *Niacin in Vascular Disorders and Hyperlipemia*, p. 51, Springfield: Thomas.

ALTSCHUL, R. (1964b). *Ibid.*, p. 157.

BEAN, W. B. & SPIES, T. D. (1940). *Am. Heart J.*, **20**, 62–76.

CAMPBELL, E. S. & RICHTER, W. (1967). *Acta pharmac. tox.*, **25**, 345–363.

CHEVILLARD, L., GIONO, L. & LAURY, M.-CL. (1958). *C.r. Séanc. Soc. Biol.*, **152**, 1074–1077.

FROMHERZ, K. & SPIEGELBERG, H. (1948). *Helv. physiol. Acta*, **6**, 42–54.

RICHTER, W. (1964). *Acta pharmac. tox.*, **21**, 91–104.