

## SENSITIVITY OF NEONATAL RABBIT ILEUM TO HISTAMINE

J.H. BOTTING<sup>1</sup>

Biological and Medical Division, Sandoz Limited, Basel, Switzerland

Segments of ileum from newborn rabbits contracted in response to histamine but sensitivity declined from age 11 days. Intestine from adult animals barely contracted to histamine, even in a concentration of  $3 \times 10^{-3}$  M. Such variation with age was not observed with acetylcholine. The response to histamine was effected by mepyramine-sensitive receptors which appeared to decrease in number as the animals aged.

**Introduction** The intestine of the adult rabbit is notably insensitive to histamine compared with that of other species. During an investigation into the effects of field stimulation on the isolated intestine of neonatal rabbit, it was noticed that such preparations contracted maximally to concentrations of histamine that caused no reaction from adult rabbit intestine.

Further investigation showed that the sensitivity to histamine declined from age 11 days. Intestine from adult animals barely contracted in response to histamine even in a concentration of  $3 \times 10^{-3}$  M. Such variation with age was not observed with acetylcholine.

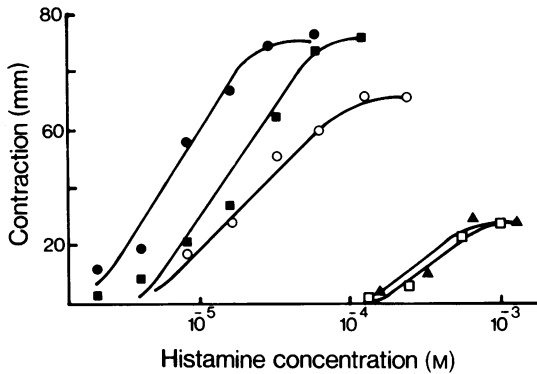
**Methods** Eighty-five preparations from 50 male and female rabbits were used. Strains used were Old English, New Zealand White, Belgian hare, Flemish giant, Swiss hare-type rabbits and a cross between Old English and New Zealand White. Segments of terminal ileum (3 cm long) were suspended in a modified Krebs fluid (Botting & Salzmann, 1974) gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub> at 34°C. Six cm lengths of ileum from neonatal animals were sometimes looped double to provide a more robust preparation. Contractions were recorded isotonicly with a frontal writing lever or transducers (load 1 gram).

Intact, finely cut or homogenized intestine from adult or neonatal animals was incubated at 37°C with solutions of histamine ( $10^{-6}$  and  $3 \times 10^{-5}$  M) in Krebs solution. Histamine content of the incubate at various times up to 2 h was estimated on isolated segments of guinea-pig ileum suspended in Krebs solution. The effects of inhibitors of imidazole-*N*-methyl transferase

(chlorpromazine, cupric chloride) and of diamine oxidase (aminoguanidine, semicarbazide, iproniazid) on the contractions produced by high concentrations of histamine were investigated on intestine from adult animals. The effects of indomethacin, hyoscine and tetrodotoxin (Sankyo Co. Ltd., Japan) on the histamine-induced contractions of neonatal ileum were investigated. The pA<sub>2</sub> value of mepyramine against histamine on neonatal ileum was estimated by the method of Lockett & Bartlett (1956).

**Results** Neonatal rabbit ileum (6-20 days) contracted in response to histamine in concentrations of  $3 \times 10^{-7}$  M to  $2.5 \times 10^{-5}$  M. This was observed with all strains of rabbit used except New Zealand Whites, which were no more sensitive than adult animals, although when New Zealand Whites were crossed with Old English the ileum of all of the progeny contracted with histamine. The sensitivity developed at about 12 days of age. Contractions produced were equivalent to those produced by acetylcholine ( $10^{-6}$  to  $10^{-5}$  M) although sometimes the maximum contraction to histamine was 20-30% greater than the maximum response induced by acetylcholine. Sensitivity to histamine declined with age, and in the adult rabbit the maximum response obtainable even with a very high concentration of histamine ( $3 \times 10^{-3}$  M) was never greater than 25% of the maximum contraction produced by acetylcholine. Figure 1 illustrates this change of histamine sensitivity with time in five litter mates of different age. Sensitivity of the ileum to acetylcholine increased slightly with the age of the animal, although the slope of the dose-response curves and height of maximum contraction were approximately the same. In neonates the responses to histamine were unaffected by hyoscine ( $4 \times 10^{-7}$  M), tetrodotoxin ( $3 \times 10^{-6}$  M) and indomethacin ( $2.8 \times 10^{-5}$  M), but were inhibited by mepyramine. A single estimate of the pA<sub>2</sub> at 2 min of mepyramine against histamine gave a value of 8.9. The small contractions produced by high concentrations of histamine applied to the ileum of adult rabbits were not affected by aminoguanidine ( $7 \times 10^{-5}$  M), semicarbazide ( $9 \times 10^{-6}$  M), iproniazid ( $1.5 \times 10^{-6}$  M) and

<sup>1</sup> Present address: Pharmacology Department, Basic Medical Sciences Group, Chelsea College, London SW3 6LX.



**Figure 1** The effect of histamine on terminal ileum of five litter-mate rabbits, age: (●) 12 days, (■) 6 days, (○) 14 days, (▲) 37 days and (□) 60 days. Each point is the mean of two contractions of a 3 cm length of tissue recorded isotonically with a load of 1 g and a magnification of 7.

chlorpromazine ( $3 \times 10^{-6}$  M). Copper chloride ( $1.7 \times 10^{-5}$  M) caused about 10% potentiation of the histamine response.

Breakdown of histamine by intact, minced or homogenized intestine was slightly more rapid with neonatal ileum than with adult ileum.

**Discussion** The sensitivity of neonatal rabbit ileum to histamine, compared to the adult, is not due to more effective catabolism in older animals, since the breakdown of histamine incubated with intestine is not greater with preparations from adult animals, and inhibition of enzymes responsible for histamine breakdown failed to potentiate histamine responses in the ileum of mature animals. Apart from these observations, if increased metabolism were the reason for the insensitivity of the intestine of adult rabbits one would expect this tissue to give dose-effect curves of similar slopes and maxima to those of neonatal tissue, when much greater concentrations of histamine were used. Neither is the action in

neonatal animals likely to be attributable to an indirect action of histamine, since it is unaffected by an inhibitor of nerve activity, an inhibitor of prostaglandin synthetase or a muscarinic receptor blocking drug. The similarity of the  $pA_2$  (8.9) with that reported by Schild (1947) for histamine against mepyramine on guinea-pig ileum (8.7) suggests that the action is effected by stimulation of  $H_1$  histamine receptors. Presumably neonatal rabbit intestine possesses large numbers of  $H_1$ -receptors, which are either lost or rendered ineffective in adult animals.

Field stimulation of ileum from neonatal rabbits, compared with similar experiments on tissue from adults indicate that the intramural nerves are not fully functional in the rabbit until about 12-20 days of age (unpublished observations). Similar observations were reported by Burn (1968) with respect to the function of adrenergic nerves. Experiments are in progress to investigate the effect which chronic denervation of adult rabbit intestine may have on histamine sensitivity.

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