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# Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility

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The effect of diethylcarbamazine pretreatment on uterine contractility was investigated in both pregnant and non-pregnant rats. The pretreatment potentiated the uterine responses to oxytocin and acetylcholine, and enhanced the spontaneous uterine contraction of rats in oestrus or 17–20 days pregnant. This enhanced contraction was antagonized both in-vivo and in-vitro by indomethacin, suggesting the involvement of prostaglandins.

Diethylcarbamazine citrate (DECC) is a potent anti-filarial drug in dog and man (Rollo 1965) and has been used with varying results in the treatment of bronchial asthma (Mallen 1965; Benner & Loweel 1970; Srinivas & Antani 1971; Koivikko 1973; Sly & Matzen 1974).

DECC contracts various smooth muscles (Harned et al 1948; Venkata & Biswas 1971; Abaitey & Parratt 1977) and can induce a release of histamine (Deline et al 1973) but is also known to inhibit the antigen-induced release of both histamine and slow-reacting substances of anaphylaxis (Orange & Austen 1968; Orange et al 1970; Ishizaka et al 1971). DECC is contra-indicated in pregnancy, and has an abortifacient action (Venkata & Biswas 1971) which is the subject of the report.

## *Materials and Methods*

Virgin Wistar rats, 170–200 g, of known stages of oestrus cycle (Yochim & McCarthy 1964), and rats 200–230 g at known stages of pregnancy (Vane & Williams 1973) were used. Some were pretreated intraperitoneally, for five days, with DECC (10 mg $kg^{-1}$); on the fifth day some were also pretreated with indomethacin intraperitoneally (10 mg $kg^{-1}$). On the sixth day the rats were killed with a blow to the head and each uterine horn after being mounted in a 10 ml organ bath containing de Jalon solution (mM: NaCl 154, KCl 5·6, glucose 2·8, $NaHCO_3$ 5·95, $CaCl_2$ 0·2) at 32 °C bubbled with air, was connected to an isotonic transducer (Ugo Basile). After equilibration for 30 min under a resting load of 1 g the spontaneous or agonist-induced contractions were registered with a pen-recorder.

The drugs used were: diethylcarbamazine citrate (Burroughs Wellcome); acetylcholine salt, oxytocin and indomethacin (Sigma).

## *Results*

DECC (1–100 μg $ml^{-1}$) failed to elicit any contraction or relaxation of uteri from non-pregnant controls irrespective of the stage of oestrus cycle. Uteri from DECC-pretreated rats 17–20 days pregnant, and rats in oestrus, showed enhanced spontaneous contractions, and pre-treatment with indomethacin (10 mg $kg^{-1}$) reduced or prevented the contractions (Fig. 1). Uteri from pretreated rats in earlier stages of pregnancy did not show any difference from their controls. Sets of five rats were used for each experiment.

Uteri from rats 17–20 days pregnant showed enhanced spontaneous contractions when challenged with DECC (1 μg $ml^{-1}$); these were concentration-dependently inhibited by pre-incubation with indomethacin (Fig. 2).

Uteri from pretreated rats in oestrus showed a potentiated response to oxytocin or acetylcholine (Fig. 3).

## *Discussion*

Prostaglandins have been suggested to play a part in the expulsion of the uterine contents at parturition because

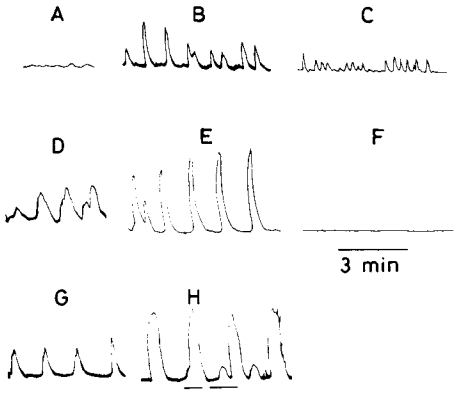


FIG. 1. The effect of DECC on the spontaneous contractions of isolated uterus from: A. Non-pregnant rat (in oestrus). B. Non-pregnant rat (in oestrus) pretreated with DECC (10 mg $kg^{-1}$). C. Non-pregnant rat (in oestrus) pretreated with DECC (10 mg $kg^{-1}$) and indomethacin (10 mg $kg^{-1}$). D. 17–20 days pregnant rat. E. 17–20 days pregnant rat pretreated with DECC. F. 17–20 days pregnant rat pretreated with DECC and indomethacin. G. 17–20 days pregnant rat. H. 17–20 days pregnant rat, in the presence of DECC (1 μg $ml^{-1}$).

The details of the experiment are the text. The horizontal bar represents a time interval of 3 min and each tracing is representative of a group of five.

* Correspondence.

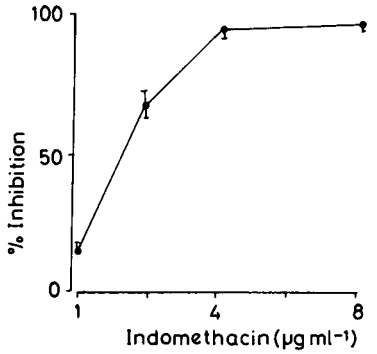


FIG. 2. Inhibition of the DECC calculated as (1 μg $ml^{-1}$)-induced contractions of isolated uterus from 17–20 days pregnant rats by pre-incubation with indomethacin for 30 min. Each value is mean ± s.e. (n = 5).

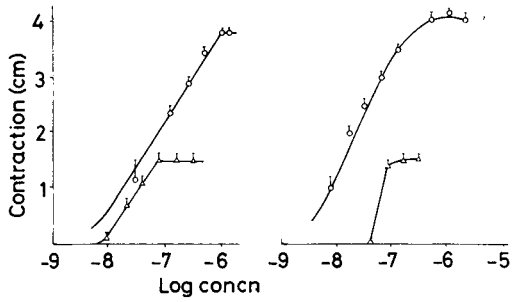


FIG. 3. Dose-response curve of isolated uteri from control rats (△), and rats pretreated with DECC (10 mg $kg^{-1}$) for five days (○), to acetylcholine and oxytocin. All rats were in oestrus. Each value is mean ± s.e. (n = 5).

of their increased concentration in human blood (Karim 1968) and amniotic fluid (Karim & Devlin 1967) during labour. This observation has been confirmed by Aiken (1972) and Chester et al (1972) who demonstrated delayed and prolonged parturition in rats after prostaglandin production had been reduced with inhibitors such as aspirin and indomethacin.

There is evidence for a basal release of prostaglandins from the uterus of pregnant rats (Vane & Williams 1973), and prostaglandins are known to potentiate responses to oxytocin in rat isolated uterus and strips of human myometrium (Pickles et al 1966; Brummer 1972). The sensitization of the isolated uterus of rats in oestrus to oxytocin or acetylcholine by DECC could be via prostaglandin synthesis.

The response of the uterus to pharmacological stimulus is greatly modulated by the hormonal status (Hawkins 1969). The effect of DECC on uterine contractility is greatest with rats 17–20 days pregnant. This uterine hypermotility induced by DECC appears to be mediated via prostaglandin synthesis and may explain the mechanism of the abortifacient action associated with DECC.

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## REFERENCES

Abaitey, A. K., Parratt, J. R. (1977) J. Pharm. Pharmacol. 29: 428–432

Aiken, J. W. (1972) Nature (London) 240: 21–25

Benner, M., Loweel, F. C. (1970) J. Allergy 46: 29–31

Brummer, H. C. (1972) J. Obstet. Gynecol. Br. Commun. 78: 305–309

Chester, R., Dukes, M., Slater, S. R., Walpole, A. L. (1972) Nature (London) 240: 37–38

Deline, T. R., Eyre, P., Wells, P. W. (1973) Arch. Int. Pharmacodyn. 205: 192–198

Harned, B. K., Cunningham, R. W., Halliday, S., Vessey, R. E., Uda, N. N., Clark, M. C., Hine, C. H., Cosgrove, R., Suba Row, I. (1948) J. Lab. Clin. Med. 33: 216–235

Hawkins, D. F. (1969) in: Evaluation of drug activities—Pharmacometrics Bacharach, L. Academic Press London, (Vol 2) 31: 666

Ishizaka, T., Ishizaka, K., Orange, R. P., Austen, K. F. (1971) J. Immunol. 106: 1267–1273

Karim, S. M. M. (1968) Br. Med. J. 4: 618–621

Karim, S. M. M., Devlin, J. (1967) J. Obstet. Gynecol. Br. Commun. 74: 230–234

Koivikko, A. (1973) Ann. Allergy. 31: 45–46

Mallen, M. S. (1965) Ibid. 23: 534–537

Orange, R. P., Austen, K. F. (1968) Proc. Soc. Exp. Biol. Med. 129: 836–841

Orange, R. P., Stechschulte, D. J., Austen, K. F. (1970) J. Immunol. 105: 1087–1095

Pickles, V. R., Hall, W. J., Clegg, P. C., Sullivan, T. J. (1966) Mem. Soc. Endocrinol. 14: 89–103

Rollo, I. M. (1965) in: Goodman, L. S., Gilman, A. (eds) The Pharmacological Basis of Therapeutics. 3rd ed. pp 1058–1089, Macmillan, New York

Sly, R. M., Matzen, K. (1974) Ann. Allergy. 33: 138–144

Srinivas, H. V., Antani, J. (1971) Ibid. 29: 418–421

Vane, J. R., Williams, K. I. (1973) Br. J. Pharmacol. 48: 629–639

Venkata Subbu, V. S., Biswas, A. R. (1971) Indian J. Med. Res. 59: 646–647

Yochim, I. M., McCarthy, J. L. (1964) in: Experimental Endocrinology. Zarrow, M. X. (ed.) pp 26–27, Academic Press, New York