Short Communication

CIMETIDINE AMPLIFIES THE ANTI-NEOPLASTIC EFFECT OF TRICHINELLA SPIRALIS IN MICE

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Mast-cell mediators, including histamine, exert a variety of pharmacological effects, which can be explained by assuming two kinds of receptors, designated H1 and H2 (Rocklin et al., 1979). H2 receptors have been shown on e.g. T lymphocytes, their function being suppressed by histamine.

In two recent papers (Osband et al., 1981; Gifford et al., 1981) cimetidine, an H2-receptor antagonist, was shown to possess anti-neoplastic properties in mice. In the experimental tumour models used, the specific immunity, based on the presence of cytotoxic T cells, was probably enhanced by the pharmacological blocking effect of cimetidine on H2-receptor-bearing suppressor cells.

Experimental infections with the parasitic nematode Trichinella spiralis exert an immunomodulating activity on responses to unrelated antigens, including pathogens and tumour cells. The immunomodulation was reported to be connected to the intestinal phase (Ljungström & Huldt, 1977).

Furthermore, the intestinal phase (i.e. the adult worm) is accompanied by a marked intestinal mastocytosis (Ruitenberen & Elgersma, 1976). It has been suggested that mast-cell proliferation, IgE-triggered mediator release (including histamine) and the ensuing hypersensitivity reaction might play a role in the regulation of malignancies (Lynch et al., 1978).

Consequently, we tested the possibility of the involvement of histamine in the anti-neoplastic effect of T. spiralis on the growth of a murine fibrosarcoma using an H2-receptor antagonist (cimetidine) and an H2-receptor agonist (tolazoline).

The mice used were conventional inbred female BALB/c, 7–9 weeks of age, obtained from the Central Institute for the Breeding of Animals, TNO, Zeist, The Netherlands. The tumour was a fibrosarcoma originally induced by 3-methylcholanthrene in the same inbred strain. The tumour was non-immunogenic and non-metastasizing (Ruitenberen et al., 1978). The T. spiralis strain was maintained in our Institute (Ruitenberen et al., 1977). Tolazoline hydrochloride was obtained from Brocacef Ltd, Maarssen, The Netherlands. Cimetidine (Tagemnet®) was obtained from Smith, Kline and French, Rijswijk, The Netherlands.

Groups of 8–10 mice were orally infected with 200 T. spiralis larvae each, 8 days before s.c. inoculation in the hind foot pad of 5 × 10^5 tumour cells in 0.05 ml (Day 0). Cimetidine (50 mg/kg) or tolazoline HCl 0.5 mg/kg were administered i.p. at Days −8, −6, −4, −2, and 0. Dilutions were prepared in saline. Tumour growth was measured twice weekly. The number of larvae and the intervals to tumour inoculation were selected on the basis of preliminary experiments in which a reproducible regression was observed using this schedule (unpublished data).

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Pre-infection with 200 *T. spiralis* larvae caused tumour-growth retardation detectable as early as 5 days after tumour-cell inoculation (Figure).

Cimetidine caused an additional tumour-growth retardation visible from Day 5 onwards until the end of the experiment (Day 19). Tolazoline did not influence the *Trichinella*-induced tumour-growth retardation. Both drugs alone had no effect on tumour growth.

The actual mechanism of the immunomodulation caused by *Trichinella* is unknown, but is connected with the intestinal phase (Ljungström & Huld, 1977). During this period also an anti-neoplastic effect is observed. The intestinal phase is accompanied by an increase in intestinal mast cells (Ruitenber & Elgersma, 1976). There is no published evidence that pharmacologically active mediators, including histamine, are released during the intestinal phase of *Trichinella* in the mouse. However, since the H2-receptor antagonist, cimetidine, increased the *Trichinella*-induced tumour regression, but had no effect on uninfected animals, a possible relationship can be suggested. It is conceivable that the anti-tumour effect of *Trichinella* might be modulated by parasite-induced suppressor T cells, known to possess H2-receptors (Rocklin et al., 1979), whose effect is blocked by the H2-receptor antagonist cimetidine, which increases the anti-neoplastic effect. Cimetidine alone exerted no anti-tumour effect. This is probably due to the lack of suppressor T-cell induction by the tumour itself.

Although not studied in detail, cimetidine did not seem to exert any effect on either worm expulsion or number of
intestinal mast cells (data not presented). Therefore, the cimetidine effect is probably due to its action on the \( \text{H}_2 \)-receptors on the target cells, and not to a possibly decreased histamine release by diminished stimulation of histamine-containing cells.

We conclude that \( \text{H}_2 \)-receptor-bearing cells partially suppress the anti-neoplastic effect of *Trichinella*. In contrast to the data presented by Osband *et al.* (1981) and Gifford *et al.* (1981) cimetidine had no direct anti-neoplastic effect in our tumour model but amplified the parasite-induced anti-tumour effect. These observations further support the potential of cimetidine in regulating immune responses, including its role in cancer immunotherapy.

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