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Opiate Antagonists Can Inhibit Mammary Tumor Growth in Rats[1] (40479)

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The endogenous opioid peptides (enkephalins and endorphins), as well as morphine and related drugs, are best known for their analgesic and behavioral effects (1, 2). Morphine (3) and the endogenous opioid peptides (4–7) also can increase pituitary prolactin and growth hormone secretion, and reduce gonadotropin and thyrotropin secretion (4). Naloxone and naltrexone are competitors for specific binding sites of morphinomimetic drugs in the brain, and hence can counteract the actions of morphinomimetic drugs on hormone secretion (4–7). Recently, it was reported that naloxone or naltrexone given alone to rats can decrease prolactin and growth hormone (GH) secretion (4–7), and that naloxone can increase secretion of gonadotropins (4), suggesting that the endogenous opioid peptides participate in control of anterior pituitary hormone function. Since development and growth of mammary tumors in rats are dependent on prolactin and ovarian steroids (8, 9), and also may be influenced by GH (8), we considered it of interest to determine whether naloxone and naltrexone could alter mammary tumor growth in rats.

Materials and methods. Multiple mammary adenocarcinomas were induced in 55- to 60-day old virgin female Sprague-Dawley rats by a single intravenous (iv) injection of 5 mg 7,12-dimethylbenz(a)-anthracene (DMBA) (Upjohn Co., Kalamazoo, MI) (10) in the first two experiments, and by iv injections of 5 mg *N*-nitrososomethyl-urea (NMU)/100 body wt at 3 monthly intervals (11) in the third experiment. After the cancers reached about 2 cm in average diameter in the first experiment the rats were injected s.c. with 0.2 mg naloxone/kg body wt 3 times daily, in the second experiment with 1.0 mg naltrexone/kg body wt twice daily, and in the third experiment with 2.0 mg naltrexone/kg body wt twice daily. Control animals were injected with equal volumes of physiological saline. Individual tumors were measured at 5- to 7-day intervals for width and length with vernier calipers, and the sum of the two diameters was tabulated for each tumor per rat. Mammary tumor growth is represented as % change in average tumor diameter as compared with the initial measurement, and also as compared with growth of tumors in control rats injected with physiological saline. Serum prolactin was measured by radioimmunoassay (12) in the third experiment on the final day of treatment from blood samples collected in the morning 1/2 hr after the final injection of naltrexone.

Tumor measurements and hormone levels were analyzed statistically by analysis of variance (ANOVA). The level of significance chosen was $P < 0.05$. The number of animals used in each experiment and statistical significance are given in the legends.

Results. It can be seen that injections of naloxone 3 times daily completely suppressed growth of DMBA-induced mammary cancers, but did not induce regression of tumors (Fig. 1a). Tumor diameters were significantly different at the 2nd week of treatment. Twice daily injections of 1.0 mg naltrexone/kg body wt similarly inhibited DMBA-induced tumor growth without producing regression (Fig. 1b). Tumors were significantly ($P < 0.05$) inhibited by day 18 of treatment. Twice daily injections of 2.0 mg naltrexone/kg body wt also significantly ($P < 0.05$) suppressed NMU-induced tumor growth by day 13, and upon withdrawal of naltrexone after 18 days of treatment, there was resumption of tumor growth (Fig. 1c). Serum prolactin values on the 18th day of the third experiment were

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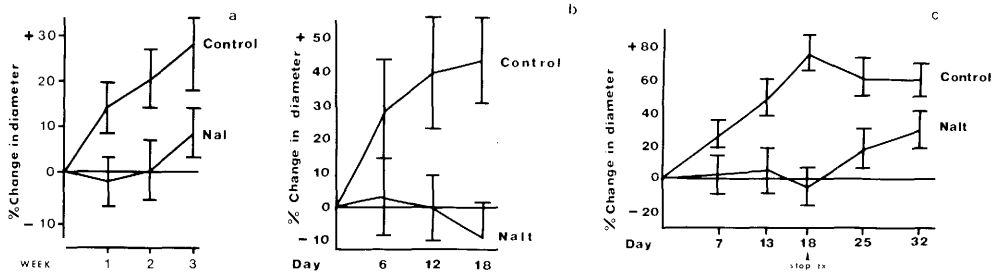

FIG. 1a. Growth of DMBA-induced mammary cancers in eight control and eight naloxone (NAL) injected rats during a 3-week period. Each line represents the mean percent change in diameter of 30 and 31 tumors in the control and naloxone treated groups, respectively. Differences at week 2 are significant ($P < 0.05$). Bars represent standard error of the mean. b. Growth of DMBA-induced mammary cancers in seven control rats and seven rats injected with 1.0 mg/kg naltrexone (NALT) twice daily. Each line represents the mean percent change in diameter of 27 and 30 tumors in the control and naltrexone treated groups, respectively. Differences at day 18 are significant ($P < 0.05$). c. Growth of NMU-induced mammary cancers in eight control rats and eight rats injected with 2.0 mg/kg naltrexone (NALT) twice daily during and after termination (stop TX) of NALT treatment on the 18th day. Each line represents the mean percent change in diameter of 23 and 25 tumors in the control and naltrexone treated groups, respectively. Differences at days 13 and 18 are significant ($P < 0.05$).

approximately 50% lower in the naltrexone-treated than in the control group.

Discussion. These observations demonstrate that naloxone and naltrexone, both antagonists of endogenous opioid peptides, can significantly inhibit growth of carcinogen-induced mammary cancers in rats without causing regression of these cancers. This is in contrast to the effects of prolactin release-inhibiting drugs such as *L*-dopa and ergots (8, 9) which not only prevent growth but also induce regression or even disappearance of mammary cancers. The lesser effectiveness of naloxone and naltrexone may be due to the particular doses used, to their relatively short duration of action (13), or to increased secretion of gonadotropins (4) with a resultant rise in ovarian hormone production. The observation in the third experiment that tumor growth resumed after cessation of treatment with naltrexone suggests that the endogenous opioid peptides may stimulate mammary tumor growth, via their ability to promote prolactin and GH secretion. These results raise the interesting possibility that the endogenous opiate peptides may contribute to growth of spontaneous mammary tumors in aging rats. Whether endogenous opioid peptides can influence growth of breast cancer in human subjects remains to be studied.

Summary. Female rats with carcinogen-induced mammary adenocarcinomas were injected 2–3 times daily with naloxone or naltrexone, specific antagonists of endogenous opioid peptides. Both drugs completely prevented mammary tumor growth without inducing regression of the cancers, effects believed to be due to reduced prolactin and perhaps GH secretion. These results suggest a possible role for endogenous opioid peptides in rat mammary tumor growth.

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