IS THERE A ROLE FOR THE PINEAL GLAND IN NEOPLASTIC GROWTH?

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INTRODUCTION

Investigations on the relationship of the pineal gland to neoplastic disease have a long history. The first possible association between the pineal gland and neoplasms was made in 1929 by Georgiou who described inhibition of carcinoma cells growth in pinealectomized mice. In contrast to that early observation, many subsequent studies showed an enhancement of tumor growth following the removal of the pineal gland. Numerous recent studies have reported an effect of the pineal gland in the induction or the growth of experimentally-induced malignant tumors, though the results are often contradictory. There are also some recent investigations on the relation of melatonin to neoplastic growth in humans.

In this paper, recent data (including authors' own) on the influence of the pineal gland and melatonin on the growth and development of experimentally-induced tumors as well as an influence of the presence of neoplastic disease in humans on melatonin concentrations are reviewed and discussed.

THE PINEAL GLAND AND TUMOR GROWTH IN ANIMALS

Studies on the link between the pineal gland and tumor development did not always yield consistent results, though many of the reports pointed to oncostatic action of the pineal. However, there have also been several papers reporting that the pineal has no, or even stimulatory, effects on the growth of some tumors. Differences in the results obtained by various authors may depend on a number of reasons. In fact, precise comparison of the studies on relationship between the pineal and neoplastic growth is very difficult due to the diversity of the experimental approaches, i.e., various tumor models used, different methods of measurement of tumor growth (neoplastic cells proliferation, tumor weight, tumor volume, survival time of the tumor-bearing animals), in vivo and/or in vitro studies, differences in mode and timing of melatonin administration, various photoperiodic environment, different species, etc. In general, however, most results have pointed toward an inhibitory effect of melatonin on tumorigenesis, and an enhancement of tumor growth following pinealectomy.
Mammary carcinoma. Various models of mammary oncogenesis have been the most extensively used for studying the effects of the pineal on tumorigenesis. It applies to mammary carcinoma induced by 7,12-dimethylbenzanthracene (DMBA) or by N-methylnitrosourea (NMU), and human breast cancer cell line MCF-7. It appears from numerous studies that the pineal significantly influences mammary carcinoma growth and/or development, and melatonin has potent oncostatic effects on neoplastic growth both in vivo and in vitro (see Blask, 1984; Blask and Hill, 1986; Blask et al., 1988; also for references). It is of special interest that in vitro inhibitory action of melatonin is serum-dependent, and probably either estradiol or prolactin are the serum factors required for melatonin's inhibitory effect (Blask and Hill, 1986).

Melanoma. It has been shown that pinealectomy stimulated growth and metastatic spread of transplantable melanoma in hamsters. Tumor volume was more than fivefold greater in pinealectomized animals than in the controls, and there was a higher frequency of metastases in the absence of the pineal (Das Gupta and Terz, 1967). However, the photoperiod under which hamsters were maintained dictated the growth rate of hamster melanoma, and the effect of pinealectomy on tumor behaviour (Stanberry et al., 1983). Pinealectomy increased melanoma growth in animals held under LD 14:10 photoperiod without altering tumor latency, whereas hamsters maintained under LD 6:18 exhibited longer tumor latency, and slower tumor growth than animals held under LD 14:10, and pinealectomy produced a further increase in tumor latency and a decrease in tumor growth in the animals kept in short photoperiod. Melatonin administration prevented stimulatory effect of pinealectomy on melanoma transplants growth, though melatonin had no effect on tumor growth in intact hamsters (El-Domeri and Das Gupta, 1973, 1976; Ghosh et al., 1976). The DMBA intragastric administration in pinealectomized hamsters resulted in increased number of melanotic nodules in comparison with sham operated and intact animals; however, tumor size did not vary among the groups (Aubert et al., 1970). Orally administered melatonin significantly reduced size and weight of B-16 melanoma in BALB/c athymic mice (Narita, 1988).

Walker 256 carcinoma. Pinealectomized rats bearing transplantable Walker 256 carcinoma had shorter survival time, increased tumor diameter, larger number of metastases (Rodin, 1963), and increased mean tumor volume (Barone and Das Gupta, 1970) than did either intact or sham-operated animals. Melatonin was found to be without effect on the growth of this tumor (Bostelmann et al., 1971).

Ovarian carcinoma. Pinealectomy increased the volume of transplantable ovarian carcinoma fivefold over that in the controls (Das Gupta, 1968). Melatonin, and other structurally-similar pineal indoles were able to inhibit in vitro the growth of two ovarian tumor cell lines (Leone et al., 1988).

Lewis lung carcinoma. Melatonin decreased survival time in DBF1 mice bearing transplantable Lewis lung carcinoma; however, effects on tumor growth have not been studied (Lapin and Ebels, 1976).

Dimethylaminobenzene-induced hepatocarcinoma. Pinealectomy exhibited a modest inhibitory effect on the growth of hepatocarcinoma induced by administration of diethyloaminobenzene in rats (Lassagne et al., 1969).

Methylcholanthrene-induced fibrosarcoma. It has been shown that 10 weeks following transplantation of methylcholanthrene (MCA)-induced fibrosarcoma cells to pinealectomized, intact or sham-operated rats, the mean tumor volume in the pineal deprived animals, and the frequency of metastases to lymph nodes were twice those of the controls (Barone et al.,