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L-Deprenyl Inhibits Tumor Growth, Reduces Serum Prolactin, and Suppresses Brain Monoamine Metabolism in Rats with Carcinogen-Induced Mammary Tumors

Srinivasan ThyagaRajan and S. Kaleem Quadri

Neuroendocrine Research Laboratory, Kansas State University, Manhattan, KS

Previously, we have reported that L-deprenyl decreased the incidence of mammary tumors and pituitary tumors in old acyclic rats. The objective of the present study was to investigate the effects of L-deprenyl, a monoamine oxidase-B (MAO-B) inhibitor, treatment on the development and growth of tumors and on the metabolism of catecholamines and indoleamine in the medial basal hypothalamus (MBH) and the striatum (ST) of rats bearing 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors. Female Sprague-Dawley rats with DMBA-induced mammary tumors were injected (sc) daily with 0.25 mg or 5.0 mg of deprenyl/kg BW or the vehicle (saline; control) for 12 wk. Tumor diameter, tumor number, body weight, and feed intake were measured every week of the treatment period. Serum PRL and the concentrations of catecholamines, indoleamine, and their metabolites were measured by RIA and HPLC, respectively. Treatment with 5.0 mg deprenyl decreased the tumor diameter, tumor number, and serum prolactin (PRL) level. Although the body weight increased in all three groups, the body weight gain in the 5.0 mg group was smaller than that in the control and 0.25 mg groups. Deprenyl treatment had no effect on feed intake. The concentrations of dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were decreased in the MBH and the ST, and the concentration of 5-hydroxyindoleacetic acid (5-HIAA) was decreased in the MBH of deprenyl-treated rats. Treatment with 5.0 mg deprenyl enhanced the concentrations of norepinephrine (NE) and serotonin (5-HT) in the MBH and in the ST, and the concentration of dopamine (DA) in the MBH. These results suggest that the suppression of the development and growth of DMBA-induced mammary tumors by chronic deprenyl treatment may be mediated through alterations in the synthesis and metabolism of catecholamines and indoleamine in the MBH and inhibition of PRL secretion.

Key Words: Medial basal hypothalamus, catecholamines, indoleamines, prolactin, breast cancer.

Introduction

L-Deprenyl, an irreversible monoamine oxidase-B (MAO-B) inhibitor, is used in the treatment of Parkinson's disease and Alzheimer's disease *(1,2)*. Treatment of old male rats with deprenyl has been known to extend lifespan, increase sexual activity, and correct age-related behavioral deficits *(3–5)*. It is believed that the beneficial effects of deprenyl are facilitated through an increase in dopamine (DA) release in the striatum and by preventing the re-uptake of DA into neurons *(6)*. Several studies have described that the loss of reproductive function associated with aging is due to a decrease in catecholaminergic activity in the hypothalamus *(7–11)*. Along with the loss of reproductive function, the development and growth of mammary tumors is common in old female rats *(7,12)*. These tumors are primarily dependent on PRL and estrogen for their development and growth *(12)*. The age-related decline in the hypothalamic dopaminergic activity is known to increase PRL secretion that promotes the development and growth of mammary tumors *(7)*. Treatment with drugs such as L-dopa and pargyline has been reported to inhibit the growth of mammary tumors by increasing dopaminergic activity and decreasing PRL secretion *(13,14)*. Underfeeding is also known to suppress the growth of mammary tumors by lowering PRL secretion through an enhancement in hypothalamic dopaminergic neurotransmission *(15,16)*. We have reported that deprenyl altered the synthesis and metabolism of catecholamines and indoleamines in the hypothalamus of old female rats, and inhibited PRL secretion in young and old female rats *(17,18)*. The present study was conducted to investigate the effects of deprenyl

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Author to whom all correspondence and reprint requests should be addressed: S. ThyagaRajan, Ph. D., Center for Neuroimmunology, Loma Linda University School of Medicine, 11021 Campus Street, Loma Linda, CA 92350. Email: sthyagarajan@som.llu.edu

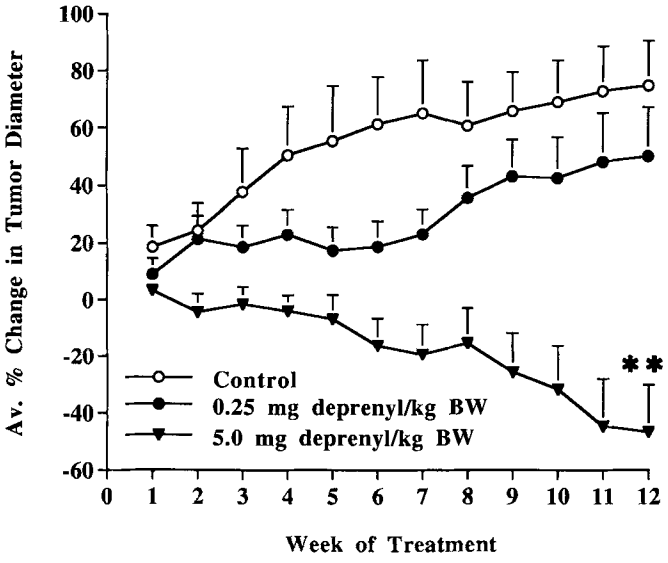

Fig. 1. Effects of deprenyl treatment on the average tumor diameter in rats with DMBA-induced mammary tumors. Tumor-bearing rats were injected sc daily with saline, 0.25 mg, or 5.0 mg/kg BW of deprenyl during the 12-wk treatment period. **Significantly ($p < 0.05$) different from the control and 0.25 mg groups.

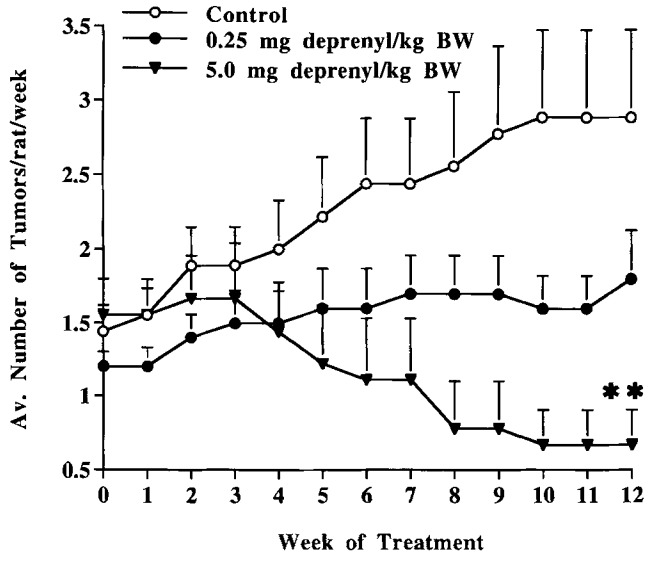

Fig. 2. Effects of deprenyl treatment on the number of tumors/rat/week in rats with DMBA-induced mammary tumors. **Significantly ($p < 0.05$) different from the control and 0.25 mg groups.

on the growth of DMBA-induced mammary tumors, PRL secretion, feed intake, and body weight. The concentrations of catecholamines, indoleamines, and their metabolites in the MBH and the ST were also measured.

Results

Tumor Diameter

Tumor growth during the 12-wk treatment period is shown in Fig. 1. Tumor size continued to grow progressively during the treatment period in the control group. During the 12-wk treatment period, the tumor diameter increased by 75.1 ± 15% (Mean ± SE) in the control group but only by 50.5 ± 16% in the 0.25 mg group. In contrast, treatment with 5.0 mg of deprenyl significantly ($p < 0.05$) decreased the tumor size by 46.7 ± 16% at the end of the treatment period. All nine rats in the control group had a consistent increase in tumor diameter but only five of nine rats in 0.25 mg group showed a similar increase in tumor diameter. In contrast, the tumor diameter decreased in four rats, remained unaltered in four rats, and increased in only one rat in the 5.0 mg group.

Tumor Number

In the control group, the average number of tumors per rat increased from 1.4 ± 0.2 to 2.8 ± 0.5 during the treatment period (Fig. 2). In rats that were treated with 0.25 mg of deprenyl, there was a modest increase in the tumor number, from 1.2 ± 0.1 at the beginning of treatment to 1.8 ± 0.3 at the end of the treatment period. In contrast to the control and low dose groups, there was a significant ($p < 0.005$) reduction in the tumor number in the rats treated with 5.0 mg of deprenyl, from 1.5 ± 0.2 at the beginning of treatment to 0.6 ± 0.2 at the end of the treatment period.

Serum PRL

Changes in serum PRL concentrations are shown in Fig. 3. In the control group, the serum PRL concentration was 4.8 ± 1.0 ng/mL. Serum PRL concentration was 3.4 ± 1.0 ng/mL in the 0.25 mg group, but decreased significantly ($p < 0.05$) to 2.3 ± 0.4 ng/mL in the 5.0 mg group.

Neurotransmitters

The concentrations of DA metabolites, dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), in the MBH and ST are shown in Fig. 4. The concentrations

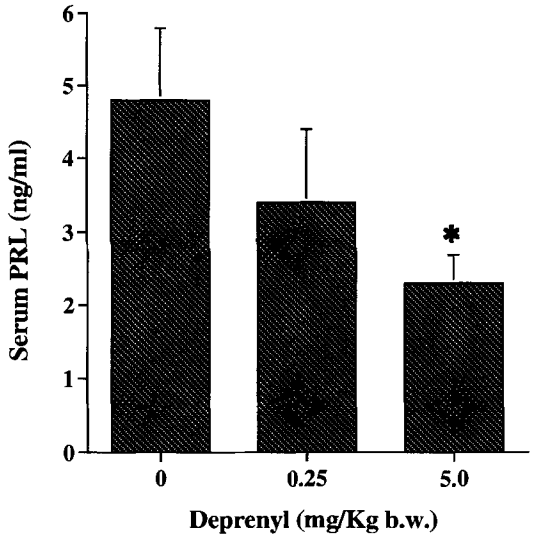

Fig. 3. Effects of deprenyl treatment on the serum prolactin concentrations in rats with DMBA-induced mammary tumors. *Significantly ($p < 0.05$) different from the control group.

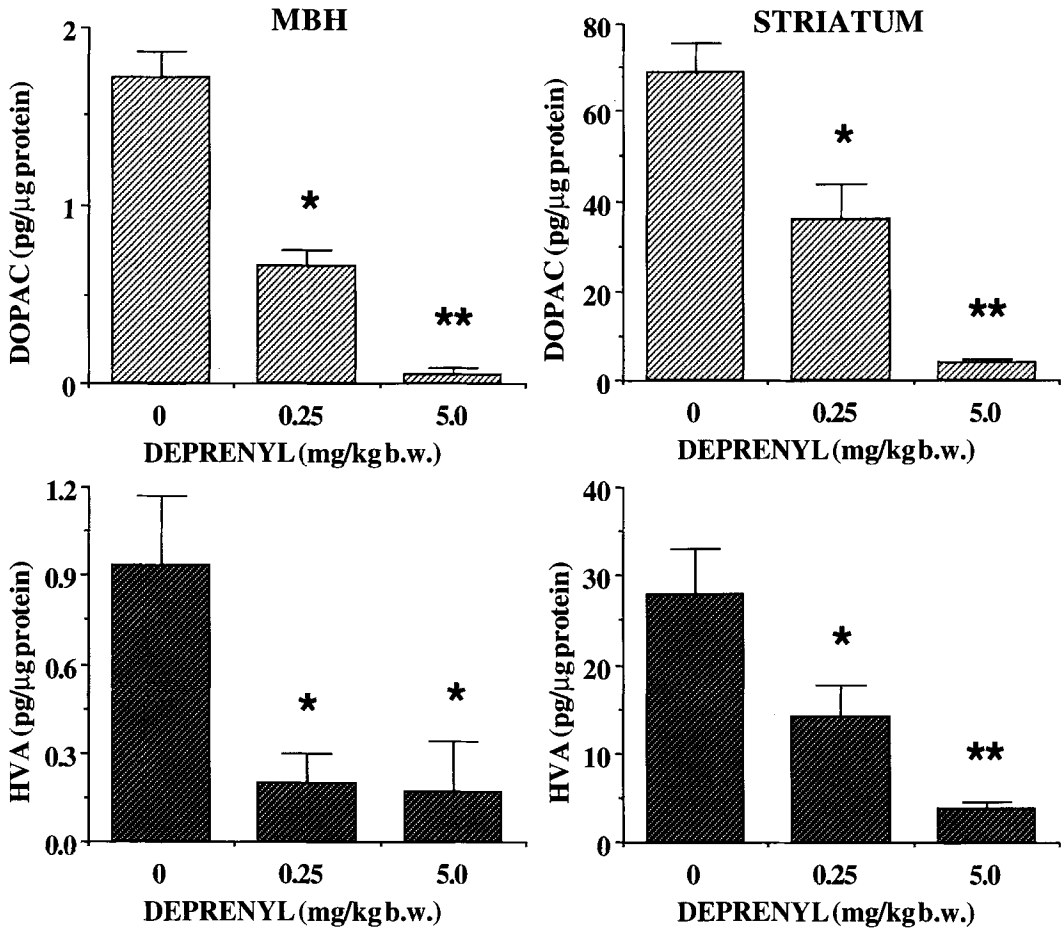

Fig. 4. Effects of deprenyl treatment on the concentrations of DOPAC and HVA in the MBH and the ST of rats with DMBA-induced mammary tumors. *Significantly ($p < 0.05$) different from the control group. **Significantly ($p < 0.05$) different from the control and 0.25 mg groups.

of DOPAC and HVA in the MBH and ST were lower in the 5.0 mg group and in the 0.25 mg group than that in the control group

The effects of deprenyl treatment on the concentrations of DA and NE are shown in Fig. 5. The hypothalamic dopamine (DA) concentration was higher in the 5.0 mg group than that in the control group and the 0.25 mg group. The concentration of DA was not altered in the ST by deprenyl treatment. The concentration of NE in the MBH was higher in the 5.0 mg group than that in the control group and the 0.25 mg group. In the ST, the concentration of NE was higher in the 5.0 mg group and the 0.25 mg group than that in the control group.

5-Hydroxyindoleacetic acid (5-HIAA) concentration in the MBH was lower in the 5.0 group and in the 0.25 mg group than that in the control group (Fig. 6; top). There were no significant differences in the concentration of 5-HIAA in the ST due to deprenyl treatment. The concentration of 5-HT in the MBH was higher in the 5.0 mg group than that in the control group and the 0.25 mg group (Fig. 6; bottom). In the ST, the 5-HT concentration was higher in the 5.0 mg group and in the 0.25 mg group than that in the control group.

Body Weight and Feed Intake

The average body weight of the control and deprenyl-treated rats is shown in Fig. 7. In the control and 0.25 mg deprenyl groups, there was a consistent increase in body weight by the end of the treatment period. In contrast to the control and the 0.25 mg groups, there was a moderate increase in the body weight of animals treated with 5.0 mg deprenyl.

The average feed intake per rat is shown in Fig. 8. There was no significant difference in feed intake between control and deprenyl-treated rats during the 12-wk treatment period.

Discussion

These results demonstrate that deprenyl treatment suppresses the development and growth of DMBA-induced mammary tumors and the effects on tumor growth and tumor number were matched by an increase in the synthesis of DA in the MBH, which in turn is known to decrease PRL secretion.

Treatment with 5.0 mg deprenyl resulted in suppression of tumor growth with corresponding reduction in PRL

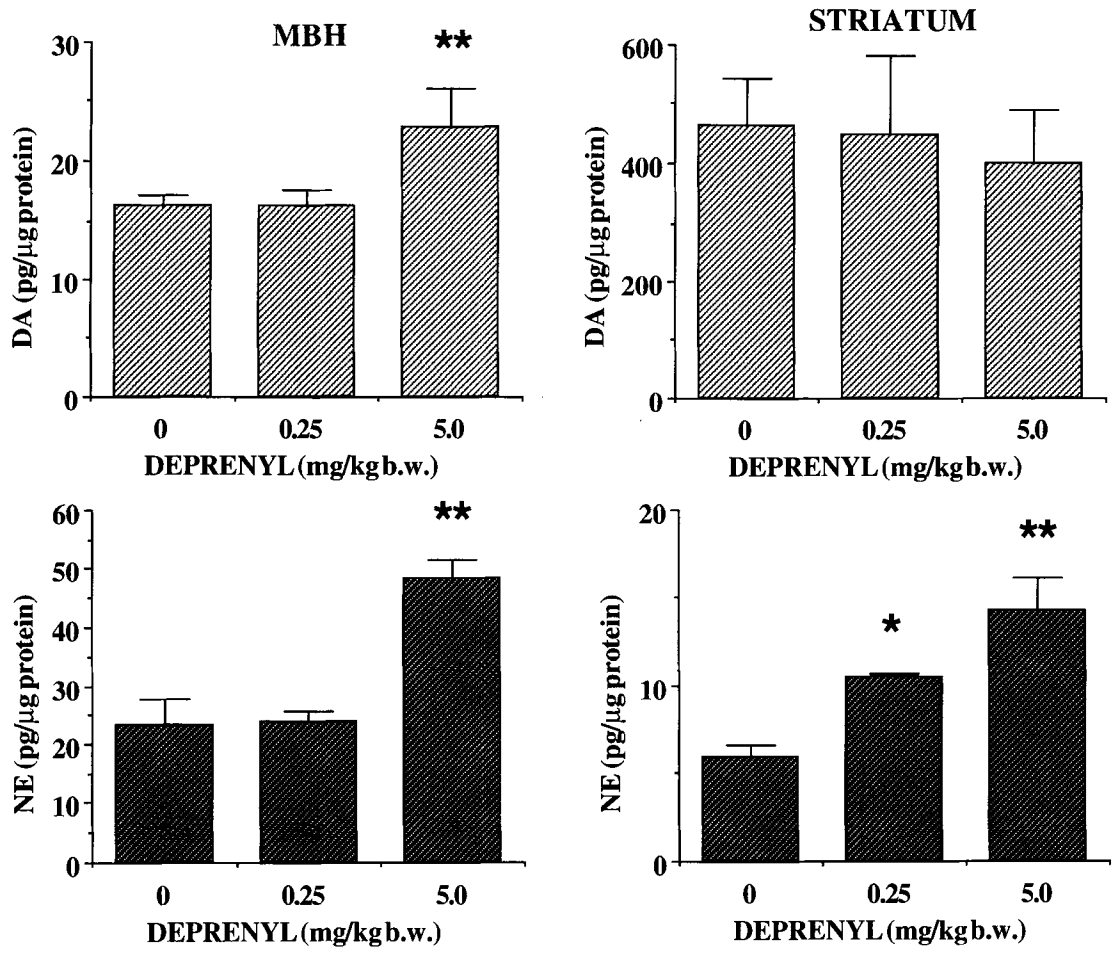

Fig. 5. Effects of deprenyl treatment on the concentrations of DA and NE in the MBH and the ST of rats with DMBA-induced mammary tumors. *Significantly ($p < 0.05$) different from the control group. **Significantly ($p < 0.05$) different from the control and 0.25 mg groups.

secretion. Both spontaneous and DMBA-induced mammary tumors are dependent on PRL for their development and growth *(7,12)*. Any procedures that increase PRL secretion such as lesions in the median eminence, pituitary grafts in the kidney capsule, chronic treatment with reserpine, and treatment with haloperidol and LSD resulted in promotion of mammary tumorigenesis *(7,12,14,19)*. Alternatively, any procedures that decreased PRL secretion such as administration of L-dopa and pargyline, hypophysectomy, ovariectomy, and adrenalectomy inhibited development and growth of mammary tumors *(7,12–14,19)*. A single dose of deprenyl significantly reduced PRL secretion in female rats within hours after administration of deprenyl *(18)*. Long-term treatment of old female rats with deprenyl inhibited PRL secretion accompanied by lower incidence of spontaneous mammary and pituitary tumors *(17)*. The present study provides further evidence for the inhibitory effect of deprenyl on PRL secretion and also on the development and growth of chemically induced mammary tumors. A significant decline in tumor growth was observed in 5.0 mg deprenyl-treated rats despite a small reduction of 47% in serum PRL level suggesting that tumor regression may be influenced by the amount of PRL receptors in the tumor and variation in the secretory patterns of PRL *(12,19)*. Treatment with deprenyl not only affected the growth of mammary tumors but also the development of tumors during the treatment period. Compared to over a 90% increase in the number of tumors in the control rats, treatment with the low dose of deprenyl produced only a 58% increase in the tumor number while treatment with the high dose of deprenyl reduced the number of tumors by 43% at the end of the treatment period.

Deprenyl treatment increases dopaminergic activity in the striatum through inhibition of DA re-uptake into neurons *(6)*. This action was believed to be responsible for the increase in sexual activity and life-span in old male rats treated with deprenyl *(3,4)*. However, the hypothalamic catecholamines and indoleamines are important in the regulation of reproduction and reproductive aging *(7–11)*. Reproductive aging is not only characterized by the loss of estrous cycles and infertility but also by the development of pituitary and mammary tumors *(7)*. In a previous study, deprenyl treatment reduced the incidence of mammary and pituitary tumors and reinstated estrous cycles in old female rats by suppressing metabolism of monoamines in the MBH *(17)*. Pre- and posttreatment of DMBA-treated rats with

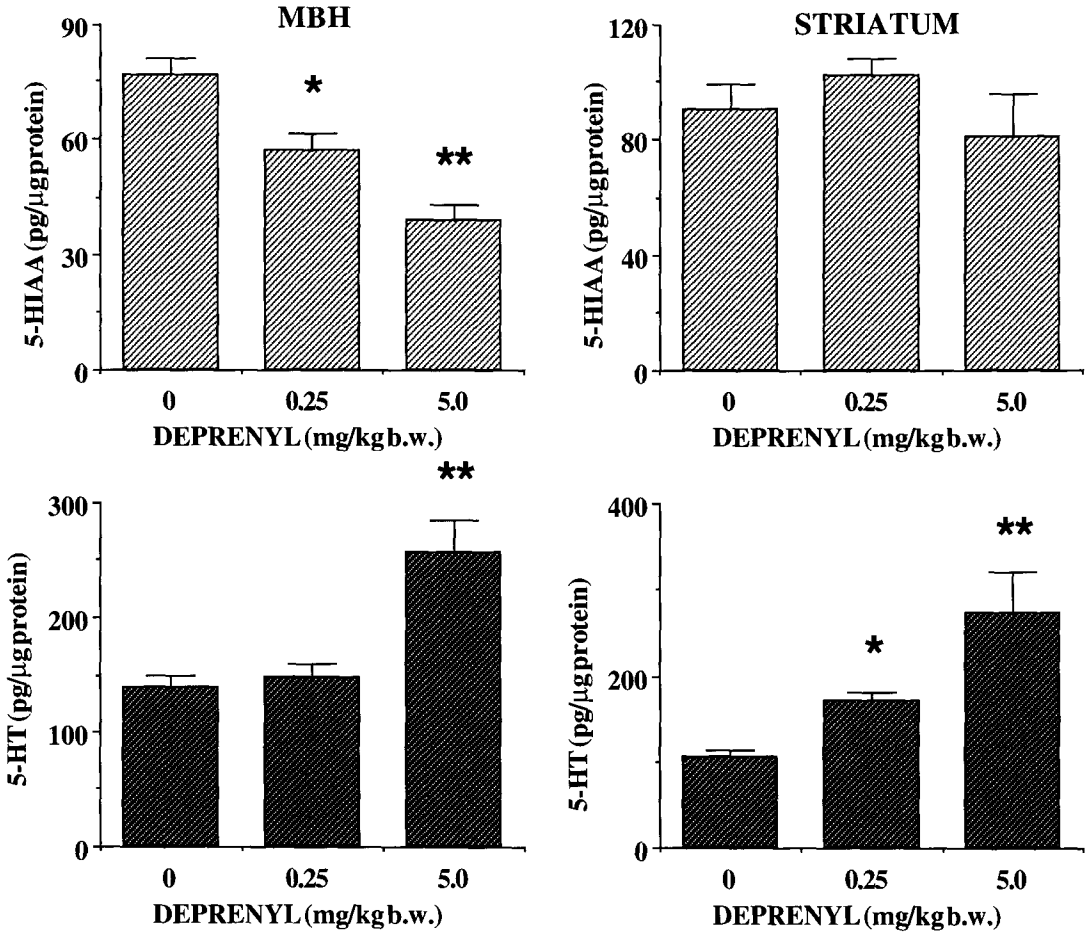

Fig. 6. Effects of deprenyl treatment on the concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and serotonin (5-HT) in the MBH and the ST of rats with DMBA-induced mammary tumors. *Significantly ($p < 0.05$) different from the control group. **Significantly ($p < 0.05$) different from the control and 0.25 mg groups.

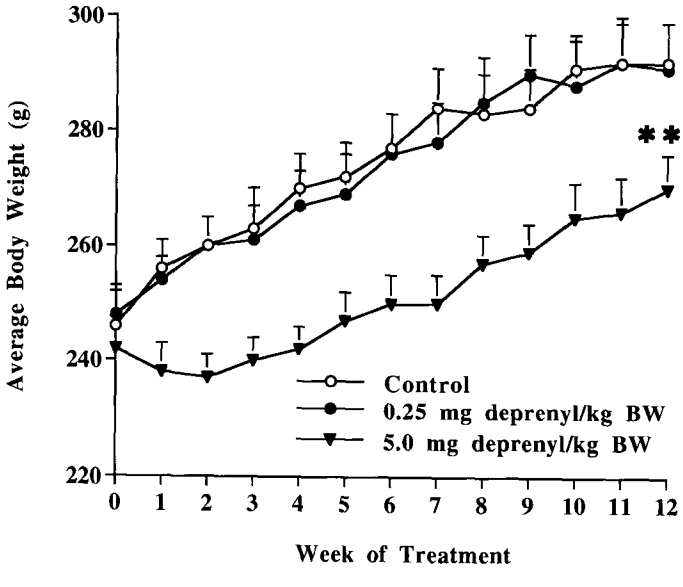

Fig. 7. Effects of deprenyl treatment on the body weight of rats with DMBA-induced mammary tumors. **Significantly ($p<0.05$) different from the control and 0.25 mg groups.

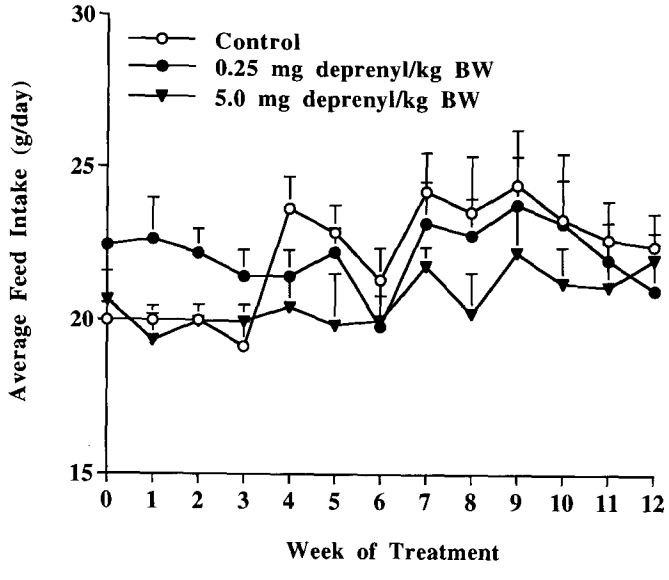

Fig. 8. Effects of deprenyl treatment on the feed intake in rats with DMBA-induced mammary tumors. Each point represents average feed intake quantified for one day in each week.

deprenyl prevented the development of mammary tumors possibly through neuroprotection and an enhancement of the tuberoinfundibular dopaminergic (TIDA) neuronal activity in the MBH *(20)*. The results from the present study confirm the tumoricidal effects of deprenyl and that this effect was associated with DA; an increase in the synthesis of DA in the hypothalamus accompanied by a decrease in the DA metabolism indicated by a reduction in the concentrations of DOPAC and HVA. This increase in the synthesis of DA most probably resulted in an increase in its release from the hypothalamus because TIDA neurons lack autoreceptors and the high-affinity DA transporter system; therefore, DA release is linked to the activity of MAO *(21,22)*. This conclusion is supported by the observation that deprenyl increases the release of DA both in vitro and in vivo from the MBH *(23,24)*. There was also an increase in the synthesis of serotonin and a decrease in its metabolism due to deprenyl treatment. It is well known that DA inhibits, while serotonin stimulates, PRL secretion. The decrease in PRL secretion associated with inhibition of mammary tumor growth suggests that the inhibitory effect of DA was stronger than the stimulatory effect of serotonin. The role of NE in PRL secretion is conflicting and not clear, but it is essential for luteinizing hormone secretion and other reproductive functions.

In addition to PRL, other hormones such as growth hormone (GH), thyroid hormones, insulin, and ovarian hormones interact with a number of growth factors including insulinlike growth factor-I (IGF-I), epidermal growth factor, and transforming growth factor to influence mammary tumorigenesis *(12,25)*. Administration of PRL along with GH enhanced the development of mammary tumors in rats and treatment with somatostatin analogs suppressed tumor volume and decreased IGF-I receptors in mice indicating that tumor growth can be regulated by GH and IGF-I *(12,26)*. The prevalence of mammary tumors was higher in transgenic mice expressing abundant GH possibly due to PRL-like actions of GH *(27)*. A better understanding of the effects of GH and IGF-I on tumor regression following deprenyl treatment may be obtained by quantifying serum GH and IGF-I levels and assessing their ability to control tumor growth.

Recent studies have demonstrated that deprenyl is capable of reversing the age-related decline in noradrenergic innervation in the spleen of old rats and stimulating natural killer (NK) cell activity and Con A-induced interleukin-2 (IL-2) production by splenocytes and that such effects are not directly related to MAO inhibition *(28)*. In a recent unpublished study, we observed an increase in IL-2 and interferon-γ production, and NK cell activity by splenocytes from deprenyl-treated rats with DMBA-induced mammary tumors and, thus, leading us to speculate that the inhibition of tumor development observed in this study may also be due to this effect.

The nigrostriatal dopaminergic system in the striatum mainly controls motor functions in the body. It is not known whether the striatum has any influence on the growth of mammary tumors. Deprenyl treatment has been reported to increase the DA content, DA release in vitro, with no alterations in NE and serotonin levels in the striatum of young male rats *(6)*. In the present study, we found that the effects of deprenyl are not isolated to dopaminergic system but also include noradrenergic and the serotonergic systems in the striatum as demonstrated by an increase in the concentrations of NE and serotonin, and a decrease in the metabolism of DA.

Deprenyl has a wide spectrum of biological effects and these effects are manifested through changes in the central catecholaminergic and serotonergic systems. Although the exact mechanism of action is not clear, there is evidence that deprenyl inhibits neuronal re-uptake of DA and stimulates DA turnover in the striatum *(6)*. These effects are believed to be due to the ability of deprenyl to inhibit the activities of MAO-A and MAO-B in the neurons and glia of the brain *(6)*. Many studies have demonstrated that MAO-A and MAO-B have substrate specificity in degrading neurotransmitters. In general, MAO-A metabolizes serotonin and NE while MAO-B degrades phenylethylamine, and DA is believed to be a substrate for both MAO-A and MAO-B *(29,30)*. The inhibitory effect of deprenyl on MAO activity is dependent upon the dose and duration of the treatment. Usually the lower dose inhibits MAO-B, whereas the higher dose inhibits both MAO-A and MAO-B *(31,32)*. The present study also describes the ability of the lower dose of deprenyl to increase the synthesis of NE and serotonin, most probably by inhibiting the activity of MAO-A. This finding is in agreement with other studies in which administration of low dose of deprenyl for prolonged duration of treatment inhibited the activity of MAO-A *(17,32)*.

Diet restriction also causes regression of mammary tumor growth by altering the synthesis of DA and 5-HT in the hypothalamus and by inhibiting PRL secretion *(15,16)*. In the present study, treatment of tumor-bearing rats with deprenyl did not alter feed intake and therefore, the regression of mammary tumors was most probably due to the direct action of deprenyl on the central dopaminergic and serotonergic systems. This finding conforms to the previous finding in which treatment of old female rats for more than 8 mo did not alter body weight and feed intake *(17)*. The increase in body weight in rats treated with the higher dose of deprenyl was smaller, perhaps, due to the reduction in tumor size and tumor number. It has been shown that a decrease in body weight of more than 25% due to underfeeding can cause suppression of mammary tumor growth *(15,16)*.

Deprenyl is metabolized in the liver to amphetamine, methamphetamine, and desmethyldeprenyl. It is believed that the actions of deprenyl on central monoaminergic systems are not due to amphetamines when the rodents are treated with lower doses of deprenyl *(33)*. However, treat-

ment of rats and mice with higher doses of deprenyl results in anorexia and loss of body weight. An increase in body weight in the absence of changes in feed intake of deprenyl-treated rats may be due to an increase in basal metabolic rate and locomotor activity. Administration of deprenyl at a dose similar to that in the present study induced a moderate increase in exploration and rearing activities without any change in body weight and such effects are believed to be mediated through central noradrenergic and dopaminergic systems *(34)*. Further studies are essential to measure the basal metabolic rate, a reliable index of caloric availability, in order to determine the extent of involvement of nutritional component in tumor regression by deprenyl.

In summary, treatment of rats with DMBA-induced mammary tumors with deprenyl for 3 mo decreased PRL concentration, and suppressed tumor growth and tumor burden. We believe that these effects were produced, in part, through the inhibition of DA metabolism resulting in an enhancement of TIDA activity in the MBH.

Materials and Methods

Animals

Female Sprague-Dawley rats, 35–40 days old were obtained from Harlan Sprague-Dawley Inc., Indianapolis, IN. They were housed in air-conditioned, temperature controlled (23 ± 2°C) animal quarters (photoperiod 0500 to 1900 h) and were provided with feed and water *ad libitum*. At the age of 50–55 d, they were injected with a single dose of a lipid emulsion (1 mL) containing 7,12-dimethylbenzanthracene (DMBA; Upjohn Co, Kalamazoo, MI) through the tail vein. Most of the rats developed mammary tumors within two months after DMBA administration. After tumor appearance, when each rat had at least one tumor 1–2 cm in diameter, the rats were housed in individual cages and randomly divided into three different groups.

Treatment

Rats in group 1 ($n = 9$) were injected with 0.9% saline that was used as the vehicle for injection of deprenyl (Selegiline hydrochloride, Somerset Pharmaceuticals Inc., Denville, NJ) to groups 2 and 3. Rats in group 2 ($n = 10$) were injected with 0.25 mg of deprenyl/kg BW and rats in group 3 ($n = 9$) were injected with 5.0 mg of deprenyl/kg BW All the injections were given sc every day, for 12 wk. Tumor diameter, tumor number, body weight, and feed intake were measured every week throughout the treatment period. Tumor diameter was calculated by averaging two perpendicular diameters measured by vernier calipers. Percentage change in tumor diameter was calculated using the equation (Average diameter in $cm_{week\ n}$ – Average diameter in $cm_{week\ 0}$) × 100.

At the end of the treatment period, the animals were sacrificed (0800–1000 h), and the MBH and the ST were dissected out. The MBH was dissected out using the posterior part of the optic chiasm as the anterior limit, the anterior part of the mammillary bodies as the posterior limit, and the lateral hypothalamic sulci as the lateral limits. The ST was dissected out using the external walls of the lateral ventricles as the internal limits and the corpus callosum as the external limit. Each MBH and striatum block was stored in 200 µL of 0.1 *M* $HClO_4$. The samples were stored at –70°C until analyzed for catecholamines, indoleamine, and their metabolites by high performance liquid chromatography with electrochemical detection (HPLC-EC).

Trunk blood was also collected to assay serum prolactin concentration. Blood samples were centrifuged and serum was collected and stored until PRL concentrations were determined by RIA.

PRL RIA

Serum samples in duplicate were assayed for PRL using reagents supplied by NIDDK *(17,18)*. Radioiodinated PRL was obtained from Hazelton (Vienna, VA) and PRL antibody and standard were obtained from the NIDDK. The reference preparation for PRL was NIDDK-rPRL-RP3 with a potency of 30 IU/mg. The assay had a sensitivity of less than 10 pg, an interassay variability of 4.8 ± 1.1%, and an intraassay variability of 6.2 ± 1.2%.

HPLC-EC

The HPLC-EC procedure has been described in detail before *(8–11)*. Briefly, at the time of analysis, the samples were thawed at 60°C for 1 min, then homogenized and centrifuged to collect the supernatant that was used for the determination of neurotransmitters and protein. The supernatant (25 µL) from each sample was mixed with 10 µL of the internal standard (isoproterenol) and injected onto a C18, 5 µm particle size, 250 mm long analytical column (BioAnalytical Systems, West Lafayette, IN). The column was kept in a CTO-6A column oven (Shimadzu, Columbia, MD) at a constant temperature of 37°C. The mobile phase, consisting of monochloroacetic acid (14.15 g/L), octanesulfonic acid (0.3 g/L), ethylenediaminetetraacetic acid (0.25 g/L), sodium hydroxide (4.675 g/L), acetonitrile (3.5%), and tetrahydrofuran (1.4%), was pumped through the HPLC system with the help of a LC-6A pump (Shimadzu, Columbia, MD) at a flow rate of 1.6 mL/min. The sensitivity of the LC-4B amperometric detector (BioAnalytical Systems, West Lafayette, IN) was 1 nA full scale and the potential of the working electrode was 0.65 V in channel 1 with respect to an Ag/AgCl reference electrode. The data were analyzed using a C-R4A Chromatopac integrator (Shimadzu, Columbia, MD). Protein concentrations in supernatants were determined by bicinchoninic acid assay (Pierce, Rockford, IL), and neurotransmitter concentrations were expressed in terms of µg protein. Differences between groups were determined using ANOVA. Parameters that attained significance following ANOVA ($p < 0.05$) were further analyzed by Fisher's least significant difference test.

Acknowledgments

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