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Role of Dopamine in Malignant Tumor Growth

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The regulatory role of dopamine, a monoamine neurotransmitter and/or a neurohormone in controlling the secretion of several anterior pituitary hormones, cardiovascular, and renal functions, has already been extensively used by clinicians for therapeutic purposes. In addition to these important functions of dopamine, some recent reports also indicate its novel role in regulating malignant cell proliferation and controlling immune functions in tumor-bearing animals. Therefore, in this article, we discuss all the relevant information correlating dopamine and malignant tumor growth in order to understand the host-tumor relationship at the level of a neurotransmitter and/or a neurohormone.

Key Words: Dopamine; cancer; human; animal.

Introduction

Dopamine, an important member of the catecholamine family, is one of the major neurotransmitters in the mammalian brain. It also has an independent role in the periphery *(1,2)*. Moreover, the secretion of several anterior pituitary hormones as well as stimulation or inhibitions of several stimulatory and inhibitory factors have been found to be controlled by dopamine *(3,4)*. In addition, dopamine has a significant influence on the immunological defense system of the host either directly *(5–9)* or indirectly through the regulation of the secretion of prolactin (PRL) and growth hormone *(10–13)* because these hormones in turn have been shown to modulate the immune system *(14,15)*. Interestingly, some studies have shown alterations in the growth patterns of some experimental tumors by modulation of the central dopaminergic system *(12,16–23)*. It is also now well-known that in host-tumor interactions, various physiological stimuli such as hormones *(24–26)* and host reactions such as immunological defense *(27,28)* may have a role in influencing the growth and size of a malignant tumor. Moreover, reports are also available indicating the direct antiproliferative effect of dopamine and its analogs on malignant cell proliferation both in vivo *(6,7,29–37)* and in vitro *(38–43)*. Therefore, the role of dopamine as a potential regulator of malignant cell proliferation, functional activities of hormones, and the immune system in tumor-bearing hosts has been discussed.

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Indirect Alteration of Malignant Tumor Growth by Modulation of Dopaminergic System

Hormone-Dependent Tumors

Several experimental studies are available that indicate a correlation between central dopaminergic activity and malignant tumor growth. Significant stimulation in the growth of dimethylbenz*(a)*anthracene (DMBA)–induced mammary adenocarcinomas was observed in rats treated with a dopamine receptor antagonist: haloperidol. It was suggested that this drug stimulated malignant tumor growth in these animals by elevating their serum PRL level *(17,20,44)*. On the contrary, the growth of DMBA-induced mammary tumors was found to be significantly reduced in these animals following chronic treatment with the monoamine oxidase inhibitors pargyline and deprenyl *(17,21–23)*. These drugs act by lowering the serum PRL level in these animals by inhibiting the enzyme necessary for the metabolism of dopamine in the hypothalamus *(17,21–23,45)*. In addition, deprenyl also decreased the PRL level by increasing the synthesis of dopamine in the hypothalamus and also possibly prevented the development of these tumors through neuroprotection of tuberoinfundibular dopaminergic neurons in the mediobasal hypothalamus *(22,23)*. In these studies, the investigators suggested that central dopamine exerts its influence on these mammary tumors by inhibiting PRL release *(3,4,17,21–23,45)*. The PRL stimulates the mammary tumor growth directly as well as by regulating the activities of natural killer (NK) and lymphokine-activated killer cells, and the release of lysosomal enzymes and growth factors *(46,47)*. It appears that pretreatment of these animals with DMBA might have contributed to the increase in PRL secretion by altering the activity of

tuberoinfundibular dopaminergic neurons *(48)*. Interestingly, there are few reports that suggest the efficacy of dopamine agonists in the treatment of advanced breast cancer patients when these drugs were administered in combination with other anticancer agents. It was suggested that dopamine agonists acted indirectly by inhibiting PRL secretion in these patients *(49,50)*.

Transplanted and Other Tumors

In addition to these indirect inhibitory effects of dopamine on PRL-dependent malignant tumors in the rat, a unique correlation between dopamine concentration in different regions of the brain and malignant tumor growth has been demonstrated in our laboratory. Irrespective of the histological type of the tumor, an inverse correlation between experimental transplanted tumor growth and dopamine content in corpus striatum, hypothalamus, and cerebral cortex of the brain has been observed in mice *(16,51–53)*. Although the precise nature of the relationship between the lowered levels of dopamine in these brain regions and the progress of tumor growth in these animals is not yet clear, a disturbance in the otherwise balanced immune network by neuromodulatory substances may be the explanation. The increase in chronic PRL secretion owing to the decrease in the dopaminergic activity in the hypothalamus may have inhibited the generation of cytotoxic killer cells from T-lymphocytes and NK cell antitumor cytotoxicity in these animals *(54,55)*. Similarly, dopamine depletion in the corpus striatum increases metenkephalin and proenkephalin content in the striatum, which in turn may have suppressed the immune system in these tumor-bearing mice *(9,11)*. A recent study by Uomoto et al. *(56)* is also consistent with our observations. They showed a significant decrease in dopamine in corpus striatum, hypothalamus, and cerebral cortex following colon carcinoma in mice. However, they correlated this change in brain dopamine during tumor growth with anorexia and a decrease in the nigrostriatal as well as mesocortical and mesolimbic dopaminergic activities with a reduction in the locomotor activity in these animals. They also suggested that the decrease in the dopaminergic activity in the diffuse forebrain regions of these animals was similar to the neurochemical changes found in advanced cancer patients suffering from delirium, one of the main psychiatric symptoms of the disease *(56)*. Note that a significantly lower incidence of lung, prostate, and colon cancers is seen in patients with schizophrenia *(57–59)* in whom hyperactivity of the central dopaminergic system has been suggested *(60)*.

In addition to the role of central dopamine in the development and growth of transplanted and PRL-dependant malignant tumors, some evidence is available indicating its role in the carcinogen-induced malignant tumors of other organs. Gurkalo and Zabezhinski *(61,62)* showed that the dopamine receptor agonist apomorphine inhibited *N*-nitroso diethylamine (NDEA)–induced hepatocarcinogenesis in mice, and the dopamine receptor antagonist haloperidol stimulated the process of carcinogenesis in these animals. Because NDEA prolonged apomorphine-induced behavior owing to stimulation of central dopamine receptors, these investigators suggested that apomorphine may have inhibited hepatocarcinogenesis by stimulation of central dopamine receptors. They also hypothesized that corpus striatum and mesolimbic systems of the brain might have a role in controlling cell proliferation and neoplastic transformation *(61,62)*. This speculation, although interesting, was not substantiated by definite scientific experiments.

Although none of the evidence from these experiments suggests any mechanism by which central dopamine may influence the growth of malignant tumors in distant peripheral organs, results from our laboratory demonstrated a unique mechanism by which altered central dopamine may influence the growth of peripheral malignant tumors. It was observed that mice treated with 1-methyl-4 phenyl-1,2,3,6,-tetrahydropyridine (MPTP), which selectively and irreversibly damages the central dopaminergic system, there was a significantly increased growth of Ehrlich carcinoma when compared to non-MPTP-treated controls *(12)*. The underlying mechanism was suggested to be significant depression of T-lymphocyte proliferation, decreased IgG and IgM secretion by B-lymphocytes, decreased NK cell activity, and loss of tumor cell–killing ability by cytotoxic T-cells *(12)*. This inhibition of immune effector cells following destruction of the central dopaminergic system might be owing to the increase in the secretion of PRL, somatostatin, metenkephalin and proenkephalins, which in turn inhibited the activities of these cells *(9)*. Therefore, it can be suggested that central dopamine indirectly influences malignant tumor growth by controlling the secretion of other hormones and cytokines.

There are also some contradictory results indicating that modulation of dopaminergic activity by the dopamine receptor agonist bromocriptine stimulates stomach carcinogenesis in rats *(63)* and the antagonist haloperidol inhibits colon carcinogenesis in mice *(64)*. Because it is known that the serotonin and dopamine systems interact *(65)*, serotonin is a potent stimulator of gastrointestinal cells *(66)*, dopamine inhibits the parasympathetic system *(67)*, which in turn has a protective role in these carcinogen-induced malignant tumors *(63,64,68,69)*, Iishi et al. *(63)* suggested that bromocriptine, by stimulating the release of serotonin in the stomach and by inhibiting the gastric parasympathetic system, may have stimulated stomach cancer in these animals. Moreover, they suggested that haloperidol, by acting centrally, significantly reduced the total calorie intake and body weight of these mice and thereby prevented colon carcinogenesis in these animals, because decreased total calorie intake and body weight is found to lower the incidence of colon cancer in these animals *(64,70)*. In addition, haloperidol blocked the inhibitory effect of dopamine on the parasympathetic system, thereby inhibiting colon cancer in mice

(64). Thus, it is apparent from these studies that dopamine may not have a direct role in the process of carcinogenesis and also that its action varies according to the site and the carcinogen used for the experiment.

Direct Antiproliferative Effect of Dopamine on Malignant Tumor Cells In Vivo and In Vitro

In Vivo

In vivo experiments from our laboratory and others have shown significant antitumor properties of dopamine. Wick *(32–35)* demonstrated significant inhibition of experimental melanoma and leukemia by dopamine and its analogs. He also found that less toxic dopamine analogs could increase the survivability of these tumor-bearing animals more than dopamine itself *(32–35)*. Interestingly, he also found significant efficacy of this neurotransmitter and or neurohormone in the treatment of patients suffering from advanced melanoma *(36–37)*. Similarly, we showed significant inhibition of experimental carcinoma and sarcoma in mice by dopamine and its analog. Moreover, we found, in our experiments that dopamine was more effective in inhibiting sarcoma than carcinoma *(6,7,29–31,71)*. However, in these in vivo experiments, pharmacological doses of dopamine were administered and the antitumor property of dopamine was suggested to be mediated through some nonspecific cytotoxic effects of dopamine against tumor cells, such as inhibition of DNA polymerase *(30,41,72)*; increased intracellular lysosomal enzyme activity *(30)*; and stimulation of the functional activities of different effector cells of the immune system by stimulating the tumoricidal activities of peritoneal macrophages *(5)*, NK cells *(6)*, and cytotoxic T-cells *(7)*. The observations of Shibata et al. *(73)* also showed that dopamine might have a potential for promoting rat two-stage forestomach carcinogenesis, while inhibiting glandular stomach carcinogenesis. They suggested that dopamine prevented glandular stomach carcinogenesis by directly inhibiting DNA synthesis. This is further supported by another group that showed dopamine as an endogenous inhibitor of cell proliferation in pyloric mucosa of the stomach of the gerbil *(74)*.

Some recent observations from our laboratory also strongly support the notion that dopamine receptors when present in malignant tumor cells may play a significant role in the growth regulation of these cells. Our results indicated a significant decrease in D_2 dopamine receptor expression in human malignant stomach tissues and D_1 dopamine receptor expression in human colon cancer tissues together with its second-messenger cyclic adenosine monophosphate (cAMP) in these malignant human colon tumors when compared to age- and sex-matched normal and benign controls. This alteration of dopamine receptor expression in malignant cells also correlated well with the degree of invasiveness of the tumor *(75,76)*. These results may be of significance because a recent study demonstrated dopamine as an inhibitor of cell proliferation in the stomach of the gerbil through D_2 dopamine receptors *(74)*, and there are also several reports indicating the growth-inhibitory role of cAMP and its analogs on colon and other human tumor cell lines *(77,78)*.

In Vitro

Like in vivo results, several in vitro results also indicate significant growth inhibition of different tumor cell lines following dopamine treatment. The growth of tumors of neural origin such as neuroblastoma is specifically sensitive to dopamine. Their growth inhibition by dopamine treatment may be mediated through dopamine receptors present on the tumor cell surface or by autooxidation of dopamine resulting in the generation of reactive oxygen species that are cytotoxic to these cells. These results therefore suggest the possibility of using dopamine or its agonists as therapeutic agents against this malignant tumor *(39,40,79)*. Although several other malignant cell lines such as adenocarcinoma of the breast, melanoma, leukemia, squamous cell carcinoma of the head and neck, and small cell carcinoma of the lung have also been shown to be inhibited by dopamine, its analogs, and its agonists *(38,41–43,80)*. However, the detailed intracellular signaling pathway following stimulation of dopamine receptors in these cell lines remains to be elucidated. These results are further strengthened by recent reports indicating that dopamine can inhibit the growth of some nonmalignant tumor and immortalized cell lines when these cell lines were transfected with dopamine receptors *(81,82)*. Interestingly, there are also reports indicating that although the D_2 dopamine receptor agonist bromocriptine partially reverses *p*'-glycoprotein-mediated vincristine resistance in vitro, it also transcriptionally activates the multidrug resistance gene through D_2 dopamine receptors *(83,84)*. Although the majority of these reports indicate a growth-inhibitory role of dopamine in malignant tumors, there are some reports suggesting that dopamine can stimulate mitogenesis in glioma cells *(85,86)*. Thus, it appears that dopamine may have a tumor-inhibitory role only in some specific tumor types depending on the site and presence of dopamine receptors in them. It will therefore also be interesting to determine whether this action of dopamine is dependent on the histopathology of the tumor.

Future Directions

The evidence accumulated so far indicates a possible role of dopamine and its receptors on the development and growth of some malignant tumors. Evidence in many of these areas is based on experimental models and is at a preliminary stage, but it opens up new frontiers in understanding the host-tumor relationship directly at the level of dopamine receptors and indirectly through dopamine-mediated control of other hormones, cytokines, and neurotransmitters. It will therefore now be pertinent to screen malignant tumors for the presence of a specific class of dopamine receptors and then to eluci-

date their signaling pathways. In addition, we also require stable tumor cell lines that can express dopamine receptors in order to correlate the dopamine receptor–mediated signaling pathway and cell proliferation. Future in-depth studies on dopamine receptor–mediated signal transduction in malignant cells and its influence on oncogene and tumor suppressor gene expression may provide new insights into the mechanisms of malignant tumor growth and development. This approach may ultimately lead to the development of a new therapy by targeting dopamine receptors and their signal transduction pathways in malignant cells.

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