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STIMULATION BY THE DOPAMINE AGONIST AMPHETAMINE AND INHIBITION BY THE DOPAMINE ANTAGONIST HALOPERIDOL OF EXPERIMENTAL CARCINOGENESIS INDUCED BY METHYLCHOLANTHRENE IN THE RAT

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Facts about the role of CNS monoamines in cancerogenesis have been accumulated for a number years. The present investigation was designed to investigate the effect of stimulation by the dopamine agonist amphetamine and inhibition by the dopamine antagonist haloperidol and the antineoplastic drug (cyclophosphamide) on survival time and the incidence of metastasis in tumor-bearing rats. We used 70 Wistar rats in the experiment. The tumors were induced by 3-methylcholanthrene. After surgical extirpation of the tumors different groups of animals were treated with amphetamine, haloperidol, cyclophosphamide or nothing. Autopsy and histological examinations were performed in all animals. From the amphetamine group of animals 75,0% survived over 120 days versus 31,2% of the animals from the haloperidol group, 68,8% from the cyclophosphamide group and 50% of the control group (only surgical removal of tumors). In the amphetamne treated group, 83,3% of the animals were without metastases, compared with the haloperidol group (40,0% without metastases), the cyclophosphamide group (45% without metastases) and the control group (27,3% without metastases).

The mechanism of the antineoplastic effect amphetamine and other monoamine stimulators included the interaction of influences both on the metabolism of the central nervous system and the tumor. Most probably, the modulation of the neurotransmitters affected carcinogenesis not only by regulation/disregulation of brain homeostasis, but also via direct action on intracellular processes during cell development and differentation.

Key words: experimental carcinogenesis, monoamines, amphetamine, haloperidol.

INTRODUCTION

The theory that stress and emotional turmoil are related to cancer has been debated for decades. Recent experimental, psychological and epidemiological literature indicates that the development of some forms of cancer can be related to certain cognitive, emotional and behavioral characteristics such as helplessness, depression, denial and inability to express one's feelings and needs

(Grossarth Maticek et al, 1982). Retrospective and prospective behavioral cancer studies have revealed that psychological stressors may play a pivotal role in the initiation and progression of malignant neoplasia (Grossarth Matiček et al, 1988, Baltrusch, 1990). Considerable evidence from basic and clinical research has implicated disturbance of catecholamine function in the pathophysiology of many neurological and psychiatric disorders (Rakić, 1984) and their relationship to cancer incidence (Grossarth-Maticek et al., 1991). Many experimental data indicated that some CNS drugs had a favorable effect on tumor-bearing rats (Weiss et al., 1981, Rakić et al. 1994), while psychotonic drugs had a definite antineoplastic effect (Popov et al., 1994).

The present investigation was designed to examine the effect of stimulation by the dopamine agonist, amphetamine, and inhibition by the dopamine antagonist, haloperidol, and the antineoplastic drug (cyclophosphamide) on survival time and incidence of metastasis in tumor-bearing rats.

MATERIAL AND METHODS

We used 70 wistar rats in the experiment over the last 2 years. The animals were injected with 1% 3-methylcholanthrene suspension in 10% Tylose, subcutaneously under the dorsal skin of the neck in doses of 3 mg/animal. Within 6-9 months, after a single injection, the rats developed tumors, at the site of injection. Surgical removal was performed when the tumors, had reached a size of 1-3 cm. Different groups of animal were then treated either with intraperitoneal amphetamine (5 mg/kg divided in two daily doses), intraperitoneal haloperidol (5 mg/kg divided in two daily doses), cyclophosphamide (single dose of 50 mg/kg for females and 100 mg/kg for males).subcutaneously or left untreated (control). Autopsy and histological examinations were done in all animals.

RESULTS

Survival time (more than 120 days) was the greatest in group B 75,0% (amphetamine treatment after surgical removal of tumors) versus 31,2% for group C (haloperidol treatment after surgical removal of tumors), 50% for group A (only surgical removal of tumors) and 68,8% in group D (cyclophosphamide treatment after surgical removal of tumors) as shown in Table 1.

Table 1. Survival time > 120 days

Groups	n	Survival time >120 days	
		Number	%
A	22	11	50.0
B	16	12	75.0
C	16	5	31.2
D	16	11	68.8

A - Only surgical removal of tumors - control group
B - Amphetamine treatment after surgical removal of tumors
C - Haloperidol treatment after surgical removal of tumors
D - Cyclophosphamide treatment after surgical removal of tumors

The incidence of metastasis for the animals which had a survival time of more than 120 days, indicated that in group B there were minimal metastases (83,3% of the animals were without metastasis), compared with group C (40,0% of the animals without metastasis), group A (27,3% without metastasis) and group D (45,4% without metastasis) as shown in Table 2.

Table 2. Incidence without metastasis (for animals which had a survival time > 120 days)

Groups	n	Without metastasis	
		Number	%
A	11	3	27.3
B	12	10	83.3
C	5	2	40.0
D	11	5	45.4

A - Only surgical removal of tumors - control group
B - Amphetamine treatment after surgical removal of tumors
C - Haloperidol treatment after surgical removal of tumors
D - Cyclophosphamide treatment after surgical removal of tumors

The statistic analysis is shown in Table 3.

Table 3. Fisher test

Groups	Groups				
	A	B	C	D	
A	########	0.083	0.137	0.139	SURVIVAL
B	0.009*	########	0.014*	0.283	
C	0.377	0.106	########	0.032	
D	0.238	0.062	0.404	########	
INCIDENCE OF METASTASIS					

* - statistical significance

DISCUSSION

Quite a number of retrospective (Bahnson, 1969, Le Shan, 1966) and prospective studies of psychosomatic factors in cancer have been published. Among many major topics, research on the relationship between psychological factors and cancer has burgeoned (Reed and Jacopsen, 1988. Thomas and Duszynski, 1974). The results from a number of recent experiments are being interpreted at two levels: namely, in terms of their immediate relevance to clinical concerns and in terms of the support they offer for particular theoretical principles and/or constructs. Psychological factors alter brain homeostasis followed by a decreased level of catecholamines, particularly in the hypothalamus (Weiss et al., 1981), and thus exert an influence on cancerogenesis.

Thus, in our investigation rats in group B which, after surgical removal of tumors, received amphetamine, the survival time and the incidence of metastasis were much more favourable than in group C (treated with haloperidol after surgical removal of tumors). In the cyclophosphamide treated group, despite a good survival time, there was a high incidence of metastasis. It is evident that surgical removal of tumors accompanied by treatment with amphetamine (dopamine stimulation) or cytostatics prolonged survival time. Moreover, the

effects of amphetamine were more significant for there was low incidence of metastasis in surviving animals, which was not the case when treating them by cytostatics only. The effects of amphetamine, and some other monoamine stimulative drugs such as piracetam (Rakić et al., 1994, Popov et al., 1994), have special significance because they do not interfere with cell proliferation and subsequently no primary or secondary resistance develops, contrary to the case with most chemotherapeutics.

The mechanism of the antineoplastic effects of psychoactive drugs includes an interaction of influences both on the metabolism of the central nervous system (CNS) and the tumor. The results of von Metzler (1986) indicated that tumor growth might be inhibited by altering the transmitter content in the CNS and that the transmitters, stimulated by CNS drugs, could participate in repair mechanisms. Most probably, the modulation of neurotransmitters exerted an influence on cancerogenesis not only through regulation/disregulation of brain homeostasis, but also via direct effects on intracellular processes during cell development and differentiation. The transfer of information from a tumor at the periphery to the CNS and conversely, from the CNS to a tumor may use a humoral or neuronal route to neuronal cells effecting central disorder. Our results indicate that CNS drugs could produce a reverse transfer from neuronal to non-neuronal cells leading to a decreased tumor rate or occasionally affecting remission.

REFERENCES

1. *Bahnson C. B. and Bahnson M. B.* 1969. Ego defences in cancer patients. *Ann. N. Y. Acad. Sci., 164*, 549-559.

2. *Baltrusch H. J. F.* 1990. Psycho-oncology Letters, Vol 1, No 3, 18.

3. *Grossarth-Maticek R, Siegrist J, Vetter H.* 1982. Interpersonal repression as a predictor of cancer. *Sci. Med. 16,* 493-498.

4. *Grossarth-Maticek R, Eyseck H. J., Vetter H.* 1988. Personality type, smoking habit and their interaction as predictors of cancer and coronary heart disease. *Person. Ind Diff., 2,*479-495.

5. *Grossarth-Maticek R, Eysenck H. J, Rakić Lj.* 1991. CNS and cancer, Anticarcinogenesis and Radiation Protection. *Ed. Nygaard and Upton, Plenum Press, New York,* 429-35.

6. *Le Shan L.* 1966. An emotional life-history pattern associate with neoplastic disease. *Ann N. Y. Acad.Sci., 125,* 780-793.

7. *Popov I, Spužić I, Rakić Lj.* 1994. Monoamines stimulation in experimental carcinogenesis. Jugoslav. Physiol. Pharmacol. Acta. 30, 1, 89-91.

8. *Rakić Lj.* 1984. Systems regulation behavior, *Mir, Moscow,* 1-109.

9. *Rakić Lj, Grossarth-Maticek R, Popov I. P.* 1994. The Central Nervous System and Cancer - Monoamine hypothesis. *Dtsch. Zschr. Onkol 26, 6,* 150-157.

10. *Reed W. H, Jacopsen P. B.* 1988. Emotion and cancer - New perspectives on an old question. *Cancer, 62,* 1871-1879.

11. *Thomas C. B, Duszynski K. R.* 1974. Closeness to the parents and family constellation in the prospective study of five disease states: mental illness, malignant tumor, hypertension and coronary heart disease. *John Hopkins Med. J., 134,* 257-270.

12. *Von Metzler A.* 1986. Carcinogenesis and the CNS. *Cancer detection and prevention, 9,* 259-277.

13. *Weiss J, Goodman P, Losito B, Corrigan S, Charry J, Bailey W.* 1981. Behavioral depression produced by an uncontrollable stressor. Relationship to norepinephrine, dopamine and serotonin levels in various regions of rat brain. *Brain Res. Rev., 3,* 107-205.

STIMULACIJA DOPAMINSKIM AGONISTOM AMFETAMINOM I INHIBICIJA DOPAIMSKIM ANTAGONISTOM HALOPERIDOLOM U EKSPERIMENTALNOJ KANCEROGENEZÍ INDUKOVANOJ METILHOLANTRENOM KOD PACOVA.

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SADRŽAJ

Poslednjih godina, sve je više podataka o uticaju monoaminskih neurotransmitera CNSa na kancerogenezu. Naše istraživanje je imalo cilj da uporedi efekat dopaminske stimulacije amfetaminom, dopaminske inhibicije haloperidolom i davanje citostatika ciklofosfamida u odnosu na preživljavanje i metastaziranje u eksperimentalnoj kancerogenezi kod metilholantrenom indukovanih tumora pacova. Sedamdeset Wistar pacova je upotrebljeno. Posle tumorske indukcije 3-metilholantrenom, rađena je hirurška ekstirpacija primarnog tumora, da bi se zatim životinje delile u različite grupe koje su primale amfetamin, haloperidol, ciklofosfamid ili su predstavljale kontrolnu grupu (nisu primale ništa). Sve životinje su na kraju bile obdukovane i histopatološki je verifikovana metastatska diseminacija. Najduže preživljavanje je postignuto u amfetaminskoj grupi gde duže od 120 dana preživljava 75% životinja, 31,2% u haloperidolskoj, 68,8% u ciklofosfamidskoj i 50% u kontrolnoj grupi. U amfetaminskoj grupi 83,3% životinja koje preživljavaju 120 dana su bile bez metastaza u odnosu na 40,0% u haloperidolskoj, 45,4% u ciklofosfamidskoj i 27,3% u kontrolnoj grupi.

Razlika u preživljavanju i metastaziranju u korist monoaminskih stimulatora može se tumačiti antitumorskim efektom koji monoamini ostvaruju preko promena u CNSu kao i promenama u metabolizmu tumora, ostvarujući svoj uticaj ne samo na procese regulacije/deregulacije moždane homeostaze već i direktno na intraćelijske procese u toku ćelijskog razvoja i diferencijacije.