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Mitogenic Effect of Several Interleukins, Neuromediators and Hormones on Human Glioblastoma Cells, and its Inhibition by the Selective Anticancer Agent PB-100

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Zusammenfassung

Wir untersuchten in vitro die Wirkung von sechs verschiedenen im Gehirn vorkommenden Substanzen auf menschliche Zellverbände: U251-BCNU resistente Glioblastomzellen, die von einem hochgradig bösartigen Gehirntumor stammen, und deren normales Pendant, CRL 1656 Astrozyten. Die Zytokine IL-4 und IL-10 (allein oder zusammen mit IL-6), die Katecholamin-Neuromediatoren Dopamin und Adrenalin sowie die Steroid-Hormone Progesteron und Testosteron regten alle die Vermehrung der Glioblastomzellen stark an, wohingegen sich die normalen Astrozyten viel weniger vermehrten. Das selektive Antikrebsmittel PB-100 hemmte diese stimulierende Wirkung. Darüber hinaus tötete es je nach Dosierung über 98% der bösartigen Zellen ab, während die normalen Zellen nicht beeinträchtigt wurden.

Schlüsselwörter

BCNU (1,3- bis [2-chloroethyl] -1 nitrosourea), PB-100 (Flavopereirine), DNA (Desoxyribonukleinsäure), IL-4 (Interleukin-4), IL-6 (Interleukin-6), IL-10 (Interleukin-10).

Summary

We investigated in vitro the effect of six different substances present in the brain on two human cell lines: U251-BCNU-resistant glioblastoma cells, derived from a highly malignant cerebral tumor, and, as their normal counterparts, CRL 1656 astrocytes. The cytokines IL-4 and IL-10 (alone or together with IL-6), the catecholamine neuromediators dopamine and epinephrine, the steroid hormones progesterone and testosterone all significantly stimulated multiplication of the glioblastoma cells, but enhanced to a much lesser extent multiplication of normal astrocytes. The selective anticancer agent PB-100 inhibited these stimulatory effects. In addition, it could dose-dependently kill over 98% of the malignant cells while not affecting normal cells.

Keywords

BCNU (1,3- bis [2-chloroethyl] -1 nitrosourea), PB-100 (flavopereirine), DNA (desoxyribonucleic acid), IL-4 (interleukin-4), IL-6 (interleukin-6), IL-10 (interleukin-10).

Introduction

Numerous biological substances involved in normal physiological processes may enhance cancer cell proliferation. In many cases, the unbalance caused by excessive production of a substance boosts tumor development, and often the tumor itself is the overproducer, setting in motion a self perpetuating process. For instance, we showed that U 251 cells derived from the highly malignant human brain tumor, BCNU resistant glioblastoma, produce much higher amounts of interleukin-6 (IL-6) than the CRL 1656 astrocyte line chosen as their normal (noncancer) counterparts [1]. We also demonstrated that IL-6 exerts a differential effect on malignant and normal cell multiplication, highly increasing that of glioblastoma cells, but also to a lesser extent that of astrocytes [2]. This means that in vivo the influence of such mitogens on tumor development may also spread to bystander normal cells.

In previous experiments we had traced such effects to the activity of carcinogens and physiological carcinogen-like mitogens on DNA secondary structure [3–6] (see Discussion). As an outcome of this research, we were able to find a number of selective anticancer agents of natural origin, which bind to cancer DNA but not to normal DNA and in this way are nontoxic for normal cells. There is a particularly urgent need for such selective agents in brain tumor therapy as the few known anticancer drugs which cross the blood-brain barrier are toxic for normal cells [7,8].

We recently showed that our anticancer agent PB-100 may kill in vitro up to 99% U251 glioblastoma cells while it has no effect on CRL 1656 astrocytes at the same concentration [2]. In addition, PB-100 dose-dependently inhibits the mitogenic activity of the key multifunctional cytokine, IL-6, glioblastoma cells and astrocytes; cellular IL-6 production is not abolished by the drug, but its levels are brought and/or kept down to physiological values [2].

In this paper, we investigate the differential effect on U251 glioblastoma cells and CRL 1656 astrocytes of six substances involved in crucial physiological processes, notably in the brain: the cytokines IL-4 and IL-10, which take part in the regulation of IL-6 production; two neuromediators, the catecholamines L-dopa and epinephrine; and the steroid hormones progesterone and testosterone, which in addition to their natural activities are also used for cancer therapy. The effect of PB-100 on malignant and normal

cell proliferation in the presence of these agents is then discussed.

Materials and Methods

Chemicals and biological molecules

Grade A chemicals: Prolabo, Lyon, France. Trypsin, RPMI 1640 culture medium, fetal calf serum, glutamine: Gibco, Grand Island, NY, USA. Recombinant human IL-4 and IL-10: Pepro Tech. Inc., USA. IL-6: Boehringer Mannheim, Germany. Progesterone, testosterone, dopamine, epinephrine: Sigma Chemical Co., St. Louis, MO, USA. PB-100 was purified in our laboratory.

Cell lines

Human BCNU-resistant glioblastoma cell line U251: Swedish Cell Collection, Uppsala, Sweden. Normal astrocyte line CRL 1656 Mpf: American Type Culture Collection, Rockville, MD, USA.

Culture techniques

Cells were grown at 37°C in an incubator. Stock cultures were maintained by continuous passage in RPMI 1640 medium containing 10% fetal calf serum. Culture medium was changed three days after seeding and subsequently twice a week. Absence of mycoplasma and bacteria was checked every three months. For experiments, each cell type was subcultured in 6-well tissue culture plates (9.8 cm^2 wells) starting from a $4x10^4$ inoculum. Cell viability, determined using trypan blue, was 99% to 100% at start of experiments.

Growth stimulation and inhibition

Increasing concentrations of filtration-sterilized substances under test were added to cultures and incubated for 48h. Then 0.05 ml trypsin solution in 0.05% EDTA were added to each well and, following a five minute incubation, trypsinization was stopped by addition of 4 ml RPMI per well. Cells were detached from culture plates and counted with a Coulter counter. All experiments were performed three times and each in triplicate.

Results

Effects of interleukin-4 and interleukin-6 on in vitro multiplication of human U 251 glioblastoma cells and CRL 1656 normal astrocytes

After recently demonstrating that in vitro IL-6 differentially stimulates multiplication of these two cell lines, more markedly enhancing that of U 251 cells [2], we investigated the effect of two cytokines involved in the regulation of IL-6 synthesis: IL-4 and IL-10.

Tab. 1 shows that, when tested separately, these cytokines both induce a dose-dependent increase of glioblastoma cell multiplication. Using IL-4, malignant cell number increase reaches 26% for a cytokine concentration of 0.5 ng/ml and 70% for 10 ng/ml. Using IL-10, increase of glioblastoma cell number ranges from 36% for a cytokine concentration of 1 ng/ml and 60% for 20 ng/ml. For these same cytokine concentrations, normal cell number increase is much lower, ranging respectively from 2.75% to 20% for IL-4 and from about 7.25% to 13% for IL-10.

Tab. 2 indicates results of experiments in which IL-4 on one hand and IL-10 on the other was tested together with IL-6, a much more active cell proliferation enhancer. When IL-6 is tested alone, a concentration of 0.2 ng/ml is sufficient to induce a 70% increase of glioblastoma cell number. As it can be seen from data in the table, this cell number increase falls by 74% using 5 ng/ml IL-4 and by only 50% using 10 ng/ml IL-4. IL-6 alone induces a 42% increase of

Tab. 1: Effects of IL-4 and IL-10 on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grown for 48h at 37°C in the absence and presence of ng/ml concentations of IL-4 or IL-10. Cell number increase (%): mean values of three separate experiments.

Interleukines	U 251 Cell number increase %	CRL 1656 Cell number increase %
IL-4 ng/ml		
0	---	---
0.5	26.0 ± 9.89	2.75 ± 0.45
1	28.3 ± 5.86	6.95 ± 1.70
5	50.0 ± 11.19	16.06 ± 2.88
10	70.0 ± 3.83	20.01 ± 1.48
IL-10 ng/ml		
0	—	—
1	36.0 ± 1.53	7.27 ± 3.45
5	38.0 ± 2.79	6 75 ± 3.84
10	50.0 ± 2.76	10.19 ± 0.54
20	60.0 ± 1.93	13.10 ± 4.15

Tab. 2: Effects of IL-4, IL-6 and IL-10 on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grown for 48h at 37°C in the absence and presence of ng/ml concentrations of IL-4, IL-6 or IL-10, used either alone or together as indicated. Cell number increases (%): mean values of three separate experiments.

Interleukines		U 251 Cell number increase %	CRL 1656 Cell number increase %
IL-6 ng/ml + IL-4 ng/ml			
0	0	---	---
0	5	8.47 ± 11.29	6.42 ± 2.88
0.2	0	71.17 ± 2.07	42.47 ± 3.14
0.2	5	18.02 ± 3.83	16.30 ± 5.67
0.2	10	37.90 ± 3.18	20.07 ± 4.43
IL-6 ng/ml + IL-10 ng/ml			
0	0	---	—
0	10	2.72 ± 2.76	3.39 ± 0.64
0.2	0	71.17 ± 2.07	42.47 ± 3.14
0.2	10	31.62 ± 3.92	9.55 ± 2.66
0.2	20	28.81 ± 1.18	15.54 ± 1.48

normal astrocytes; this increase is reduced by 61% using 5 ng/ml IL-4 and by 50% using 10 ng/ml IL-4. IL-6 induced enhancement of malignant and normal cell multiplication is similarly reduced using IL-10: for glioblastoma cells 10 ng/ml IL-10 decrease this enhancement by 55% and 20 ng/ml IL-10 by 60%; corresponding figures for normal astrocytes are 72% and 60%, implying that IL-10, contrary to IL-4, differentially controls IL-6 activity on glioblastoma cells and normal astrocytes. Taken together, these results suggest a complex competition between IL-6 and the other two cytokines. Our data are in agreement with results obtained by other authors in different biological systems [9–12].

Effects of dopamine, epinephrine and PB-100 on in vitro multiplication of human U 251-BCNU-resistant glioblastoma cells and CRL 1656 normal astrocytes

In view of their central activity in the brain, we investigated the effect of dopamine and epinephrine on multiplication of glioblastoma cells and astrocytes. It is both dose-dependent and differential. Fig. 1 indicates dopamine mitogenic activity. Enhancement of tumor cell multiplication begins with 10 ng/ml dopamine and becomes maximum for 200 ng/ml. Astrocyte multiplication slightly increases using 10 ng/ml dopamine, reaches a maximum of 20% for 50 ng/ml and then progressively drops back to control values for 200 ng/ml dopamine.

Epinephrine (Fig. 2) already markedly enhances glioblastoma cell multiplication at a concentration of 10 ng/ml, inducing a maximum two fold increase at 20 ng/ml; effect then slightly decreases, but cell multiplication remains high above control values. Epinephrine poorly affects astrocytes with maximum activity at 50 ng/ml.

It may be seen from Figs. 3 and 4 that inhibition of glioblastoma cell multiplication by PB-100 is dose-dependently decreased by increasing concentrations of dopamine and epinephrine. Thus, the 98% inhibition caused by 50 µg/ml of PB-100 alone drops to 75% using 10 ng/ml dopamine or epinephrine. PB-100 does not suppress the

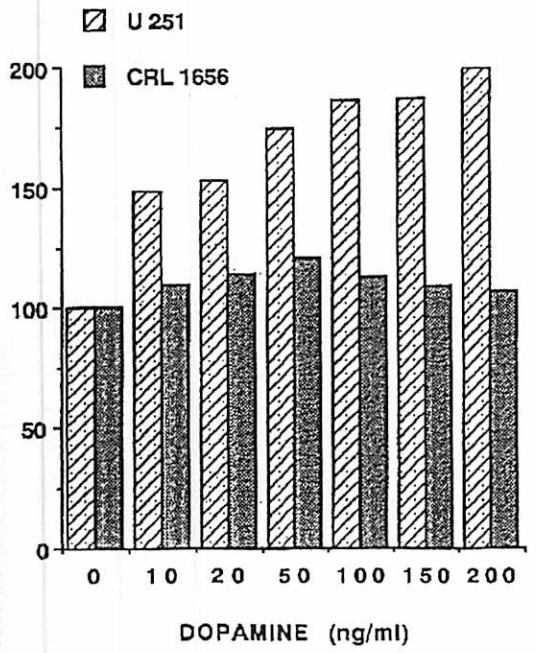

Fig. 1: Effects of dopamine on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grwon for 48h at 37°C in the absence and presence of increasing ng/ml concentrations of dopamine. Number of cells (% variation): mean values of three separate experiments. U 251 SD: ± 8.34. CRL 1656 SD: ± 4.74.

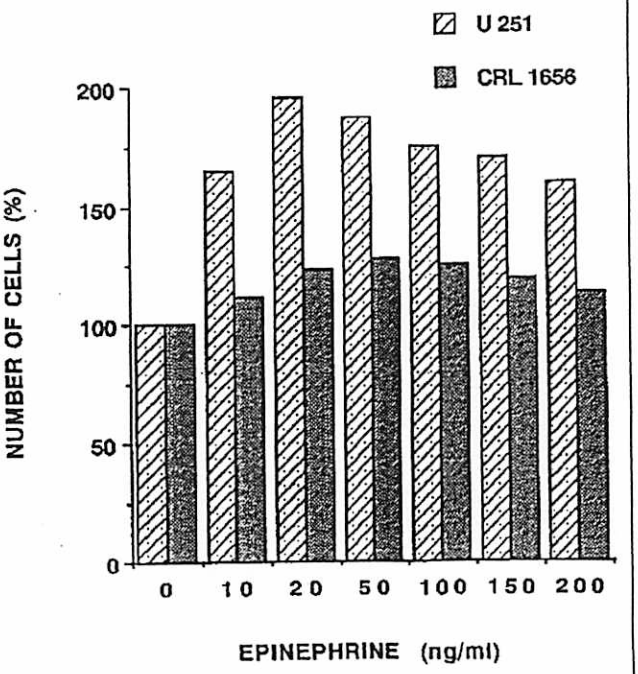

Fig. 2: Effects of epinephrine on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Experimental conditions are the same as in Fig. 1. Epinephrine was used at increasing ng/ml concentrations as indicated. Cell number (% variation): mean values of three separate experiments. U251 SD: ± 7.86. CRL 1656 SD: ± 7.22.

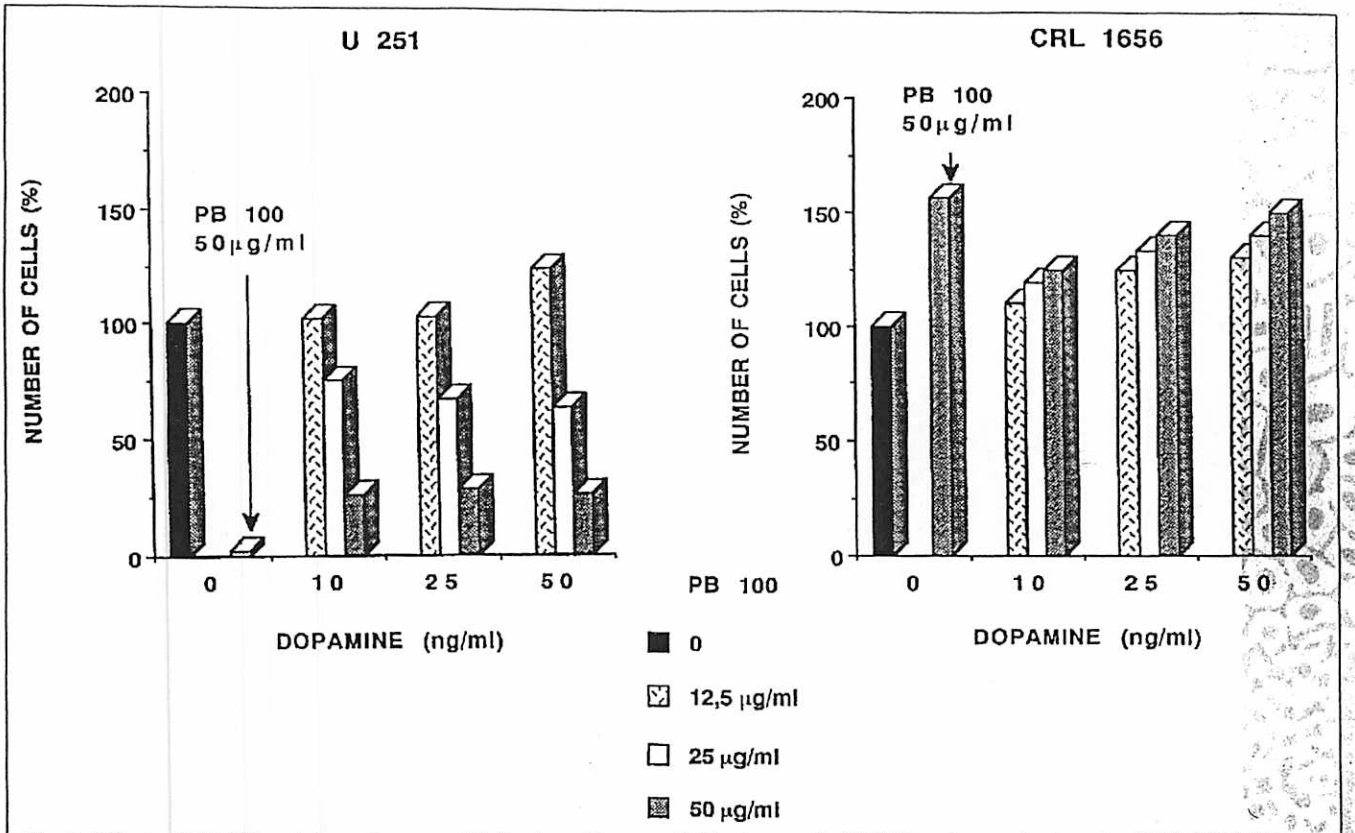

Fig. 3: Effects of PB-100 and dopamine on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grown for 48h at 37°C in the absence (controls) and presence of indicated concentrations of dopamine (ng/ml) and PB-100 (µg/ml). Number of cells (% variation): mean values of three separate experiments. U 251 SD: ± 3.97. CRL 1656 SD: ± 7.52.

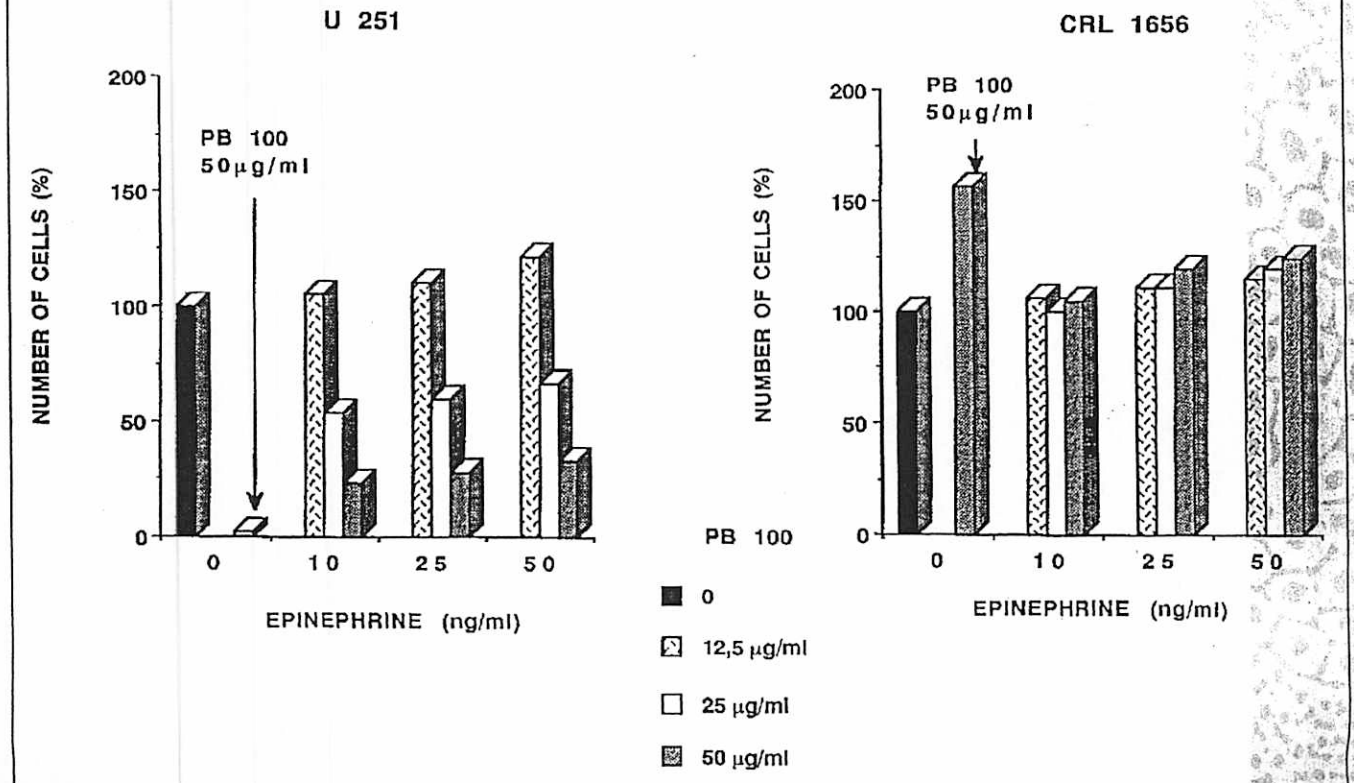

Fig. 4: Effects of PB-100 and epinephrine on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Experimental conditions are the same as in Fig. 3. Epinephrine was used at ng/ml concentrations and PB-100 at µg/ml concentrations. Cell number (% variation): mean values of three separate experiments. U 251 SD: ± 5.85. CRL 1656 SD: ± 7.11.

much slighter effect of dopamine on normal astrocyte multiplication. L-dopa, which only slightly stimulates glioblastoma cell multiplication (data not shown), is not transformed into dopamine in the brain though, in other tissues, it is decarboxylated, yielding dopamine, which in turn is turned into epinephrine and norepinephrine [13–15].

Effects of progesterone, testosterone and PB-100 on in vitro multiplication of human U 251 glioblastoma cells and CRL 1656 normal astrocytes

At ng/ml concentrations both progesterone and testosterone dose-dependently stimulate glioblastoma cell multiplication. It may be seen from Tab. 3 that for progesterone malignant cell number already increases by about 44% with 5 ng/ml hormone, plateaus at around 50% from 15 to 50 ng/ml and finally reaches 67% with 100 ng/ml. Effect of testosterone starts at the same 5 ng/ml concentration, inducing a 30% increase of glioblastoma cell multiplication; this increase then plateaus at 37% between 15 and 25 ng/ml and rises to 57% at 100 ng/ml. The two hormones have little effect on normal astrocytes, progesterone being slightly more active than testosterone.

In the absence of the hormones, dose-dependent PB-100 inhibition of glioblastoma cell multiplication ranges from 60% for a 25 µg/ml concentration of the anticancer agent to 98% for 50 µg/ml. In the presence of either progesterone or testosterone, these figures fall to about 25% and 50% using the above respective PB-100 concentrations (Figs. 5 and 6). This is indicative of competition between PB-100 and the steroid hormones.

Discussion

Although it is not often reported, many important biological substances differentially enhance malignant and normal cell multiplication. They are more mitogenic for cancer than for normal cells, and in many cases this activity is amplified because the tumor tissues themselves overproduce the mitogen. This is the case for instance for the cytokine interleukin-6 (IL-6), known to be a growth factor for various malignancies [16,17]. In a recent paper, we showed that in vitro human BCNU-resistant U 251 glioblastoma cells not only produce more IL-6 than CRL 1656 normal (noncancer) astrocytes, but respond twice as well to the cytokine's mitogenic effect [1]. We also demonstrated that our selective anticancer agent PB-100, which is able to kill over 98% glioblastoma cells at µg/ml concentrations while not affecting normal astrocytes, could inhibit IL-6 mitogenic activity in both cell types as much as it was in above physiological levels [1].

Results presented here describe the differential effect in vitro of six other biological substances which are present and active in the brain and might thus influence brain tumor development.

The cytokines IL-4 and IL-10 are closely involved in IL-6 regulation [18–20]. Both are mainly produced by Th-2 lymphocytes, which are implicated in allergy and hypergammaglobulinemia. Like all cytokines they have multiple and varied effects. Among its various activities, IL-4 is a powerful regulator of the production of other cytokines such as IL-1, IL-6, IL-8, TNF, INF gamma. Almost all types of cells carry IL-4 receptors. Some mouse tumors secrete high amounts of IL-

Tab. 3: Effects of progesterone and testosterone on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grown for 48h at 37°C in the absence and presence of ng/ml concentrations of either progesterone or testosterone. Cell number increase (%): mean values of three separate experiments.

Steroid Hormones	U 251 Cell number increase %	CRL 1656 Cell number increase %
Progesterone ng/ml		
0	—	—
2	44.3 ± 6.85	10.92 ± 11.38
15	50.0 ± 6.55	15.50 ± 7.47
25	53.3 ± 6.17	16.83 ± 12.24
50	54.9 ± 1.15	13.03 ± 7.76
100	67.2 ± 5.75	11.05 ± 5.92
Testosterone ng/ml		
0	—	—
5	31.0 ± 3.75	7.1 ± 2.43
15	37.3 ± 10.28	7.9 ± 5.13
25	37.4 ± 3.32	6.6 ± 6.43
50	46.0 ± 3.39	4.9 ± 7.04
100	57.3 ± 5.48	4.9 ± 4.78

Tab. 4: Effects of IL-4, IL-10 on presence of PB-100 on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grown for 48h at 37°C in the absence (controls) and presence of indicated concenrations of IL-4 and IL-10 (ng/ml) and PB-100 (µg/ml). Number of cells (% variation): mean values of three separate experiments.

Compounds	U 251 Cell number increase or decrease%	CRL 1656 Cell number increase or decrease%
PB 100 + IL-4 µg/ml ng/ml		
0 0	—	—
0 10	+46.50 ± 6.79	+20.35 ± 3.74
12.5 10	-4.57 ± 3.95	-2.01 ± 3.49
25 10	-46.01 ± 2.38	+8.44 ± 5.17
50 10	-76.81 ± 2.05	+10.69 ± 4.99
PB 100 + IL-10 µg/ml ng/ml		
0 0	—	—
0 20	+77.97 ± 8.05	+6.80 ± 4.48
12.5 20	+22.20 ± 4.97	+0.44 ± 1.99
25 20	-72.29 ± 5.65	+5.67 ± 1.30
50 20	-64.27 ± 1.68	+9.11 ± 0.92

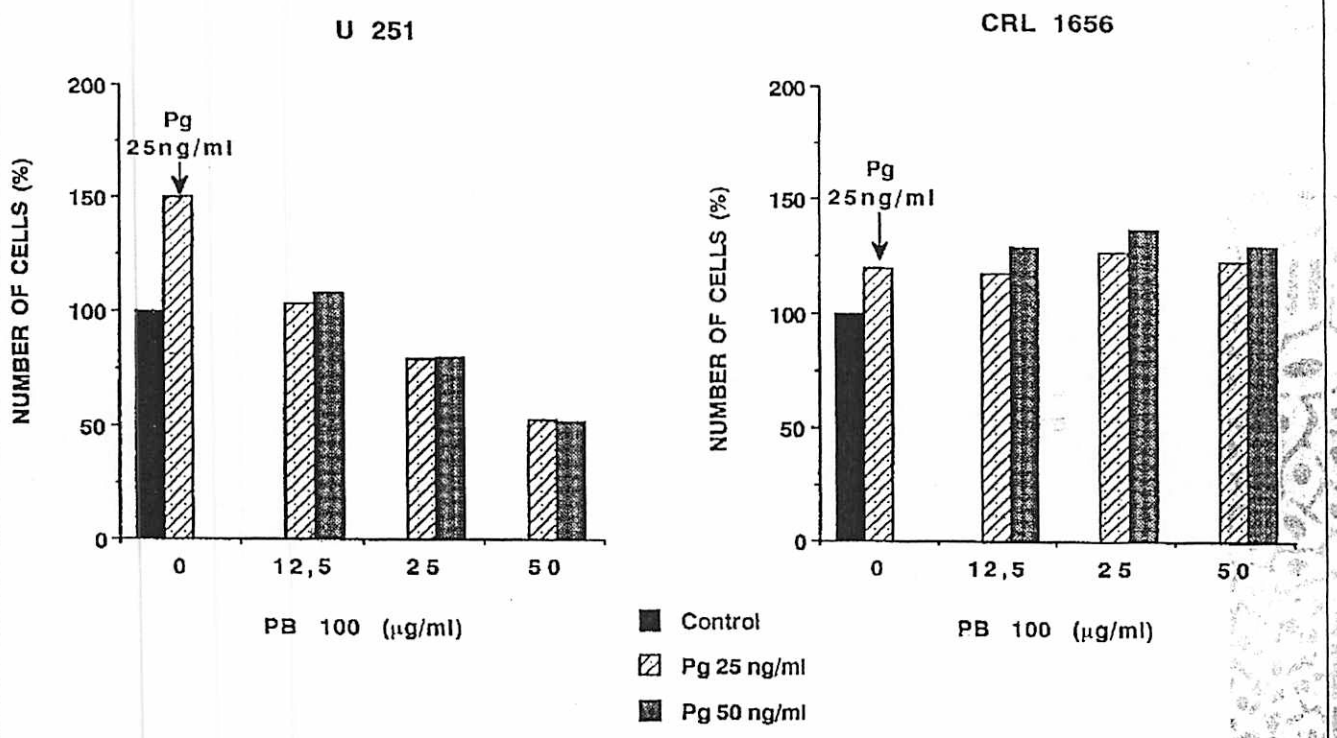

Fig. 5: Effects of PB-100 and progesterone on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Human BCNU-resistant glioblastoma cells (U 251) and normal astrocytes (CRL 1656) were grown for 48h at 37°C in the absence (controls) and presence of ng/ml concentrations of progesterone and µg/ml concentrtions of PB-100. Cell number (% variation): mean values of three different experiments. U 251 SD: ± 9.99. CRL 1656 SD: ± 9.54.

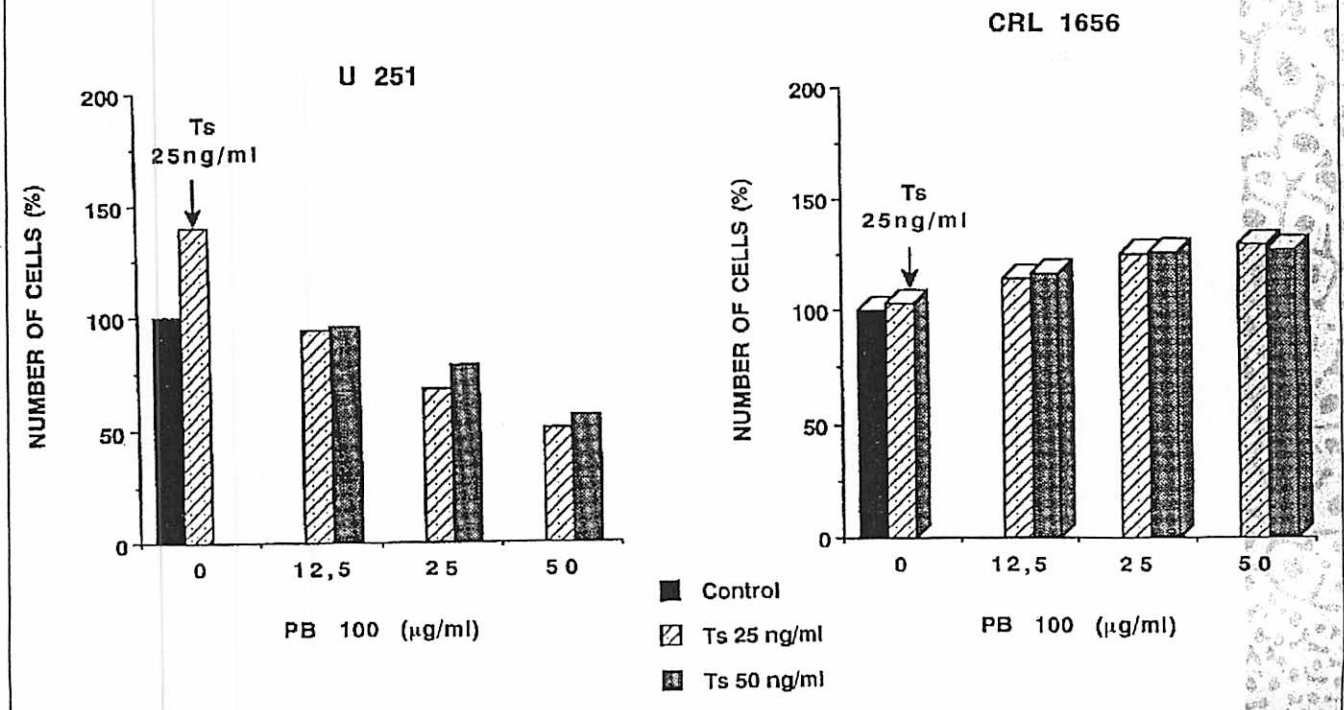

Fig. 6: Effects of PB-100 and testosterone on multiplication of human glioblastoma cells (U 251) and normal astrocytes (CRL 1656). Experimental conditions are the same as in Fig. 5. Testosterone was used at ng/ml concentrations and PB-100 at µg/ml concentrations. Cell number (% variation): mean values of three separate experiments. U 251 SD: ± 4.86. CRL 1656 SD: ± 10.10.

4. This cytokine was reported to inhibit IL-6 induced myelomatous cell proliferation and to exert an anticancer activity in mice through cytotoxic CD 8+ cell activation [21,22] and it was tested with some success in patients suffering from resistant tumors [23,24].

Th-2 and B lymphocytes, but also activated monocytes-macrophages, are IL-10 producers. Addition of IL-4 inhibits this monocyte IL-10 production. A number of mouse and human tumors were reported to synthesize IL-10 [25].

In this paper we demonstrate that both IL-4 and IL-10 dose-dependently increase the amount of glioblastoma cells by up to about 60% and that of normal astrocytes by only up to 10–20% (Tab. 1). Enhancement of both glioblastoma cell and astrocyte multiplication by IL-6 was antagonized by either IL-4 or IL-10, maximum decrease of mitogenic effect being 70% in glioblastoma cells and 40% in normal astrocytes (Tab. 2). These differential effects might be linked to distinct cytokine receptor levels in malignant and normal cells. IL-6 is a more powerful mitogen than the other two cytokines, being active at pg/ml concentrations, while IL-4 and IL-10 prove mitogenic at ng/ml concentrations. PB-100 at µg/ml concentrations still dose-dependently inhibits cancer cell multiplication in the presence of IL-4, IL-6 and IL-10; yet these cytokines compete to some extent with the anticancer agent (Tab. 4).

The catecholamine neuromediators ephinephrine and dopamine, which are essential to the central nervous system, were reported to exert a dose-dependent, tissue specific modulating effect on RNA synthesis by brain chromatin; they were postulated to bind either to DNA itself or to chromatin acidic proteins [13]. In our experiments, these catecholamines exhibit in vitro a differential mitogenic effect on glioblastoma cells and normal astrocytes, too, being much more active on the first than on the second type of cells. They are also dose-dependently effective at ng/ml concentrations. And the stimulatory activities of both epinephrine and dopamine compete with the inhibitory effect of PB-100 on malignant cell multiplication (Figs. 1 to 4).

We observed similar, differential dose-dependent activities at ng concentrations when testing progesterone and testosterone (Figs. 5 and 6). Steroid hormones, which are used for chemotherapy of certain human hormone dependent cancers, are known for their ability to behave as carcinogens for their physiological target tissues when they are present in excessive or unbalanced amounts [26–28], and nuclear receptors for testosterone and estradiol are also present in many non target human organs, such as the brain [29–31]. The interplay of cytokines, catecholamines and steroid hormones seems implicated in the regulation of multiple cerebral processes [29,30,33].

In vitro all of the six tested substances have in common the following properties: they are mitogenic for both cancer and normal cells, but much more for the first than the second; they are active at very low, ng/ml concentrations; and they compete in some way with PB-100. Does this competition occur at receptor level? Interleukins and catecholamines bind to cell-surface receptors, while steroid hormones bind to nuclear receptors. We recently showed that PB-100 readily enters glioblastoma cells and rapidly concentrates in their nucleus, particularly in nucleoli, but cannot even cross the cell membrane of normal astrocytes (manuscript in preparation). We might assume that part of the inhibition of the mitogens by PB-100, especially that concerning enhancement of normal cell multiplication, could take place at cell membrane level.

Yet the common feature shared by the mitogens and the anticancer agent is the ability to modify DNA secondary structure. Years ago as an outcome of long series of experiments comparing cancer cell DNAs with their normal counterparts [3–5], we demonstrated that 260 nm UV absorbance of cancer DNA was always higher than that of the corresponding normal DNA, meaning that cancer DNA contained numerous broken H-bonds, and that long stretches of its strands were thus permanently separated. This had several implications: one was that the isolated strand stretches were becoming easily accessible to multiple endogenous or exogenous molecules, and another was that the newly exposed strands carried many normally unused initiation sites for replication and gene expression, accounting for enhanced multiplication and dysregulated protein synthesis. In contrast, non malignant DNA strands separate only transiently and locally for replication and gene expression so that its chains are "closed" most of the time and much less accessible than the "open", receptive chains of cancer DNA. We demonstrated a close correspondence between increase of cancer DNA UV absorbance (hyperchromicity), enhancement of in vitro cancer DNA replication and increased cancer cell multiplication [1,5]. We reported that many substances, including known carcinogens and natural substances with carcinogen-like activity, such as steroid hormones, were more highly active on cancer than on normal DNA [5]. Indeed, this stood out as a characteristic property of carcinogens. These findings account for the higher mitogenic effect exerted on

glioblastoma cells than on normal astrocytes by interleukins-4, -6, and -10, dopamine and epinephrine, progesterone and testosterone.

After devising an in vitro test (Oncotest) based on our fundamental findings we looked for, and found, a number of natural substances which were able to bring back together the separated cancer DNA strands as evidenced by the decrease of these agents induced in UV absorbance, DNA replication and cancer cell multiplication [1,2,4]. The characteristic property of these anticancer molecules is that they bind to malignant DNA, but not to normal, noncancer DNA, and thus do not affect normal cells. They are both highly selective for malignant cells and nontoxic for normal, even rapidly dividing cells, which are usually damaged by classic chemotherapy and radiotherapy.

The selective anticancer agent PB-100 is a plant derived beta carboline alkaloid, chemically well defined [4]. We demonstrated lately [34] that it binds to G and A rich DNA clusters. Such clusters are known to exist around most initiation sites for DNA replication or gene expression (mRNA synthesis). We must remember that due to extensive strand separation such initiation sites have become both numerous and accessible in malignant DNA [26]. This can explain why one compound, PB-100, is able to inhibit the mitogenic activities of molecules as different as cytokines, catecholamines and steroid hormones, which are active on genes distributed at different locations throughout the genome.

As a practical application of experiments described in this paper, attention should be paid to levels of the various tested mitogens in patients suffering from brain tumors, for not only can these agents increase malignant cell proliferation, but they can also affect normal bystander cells. PB-100 proves highly active on BCNU-resistant glioblastoma cells and is only very partially inhibited by the tested carcinogen-like mitogens. However, drug dosage must take account of this inhibition. In view of its selectivity and efficacy, and its ability to cross the blood-brain barrier, PB-100 should prove useful in brain cancer therapy.

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Tagungskalender

30. Krebskongreß der Deutschen Gesellschaft für Onkologie e.V.
Termin:
26.–27.10.1996
Ort:
Baden-Baden
Leitung:
Prof. Dr. Josef Beuth
Auskunft und Anmeldung:
Deutsche Gesellschaft für Onkologie
Institut für Medizinische Mikrobiologie und Hygiene der Universität zu Köln
Goldenfelsstr. 18–21,
60935 Köln
Tel. (0221) 478-30 62
Fax (0221) 43 81 56

1st International Dresden Symposium on Immunotherapy of Cancer
Termin:
May 31st–June 1st, 1996
Ort:
Dresden
Auskunft:
Medical Faculty Technical University of Dresden, Department of Surgery, Mrs. Türke, Fetscherstraße 74, D-01307 Dresden

5th Melanoma Workshop
Termin:
June 15–16, 1996
Ort:
Hamburg
Auskunft:
Holger Voigt, M.D., Melanoma Research Project, 31 B Dammtorstraße, D-20354 Hamburg, Germany

Minimal Residual Cancer: Methodical Challenge, Biology, and Clinical Significance for Oncology and Transplantation Medicine
Termin:
June 23–25, 1996
Ort:
Munich
Auskunft:
INTERPLAN, Convention & Visitor Service, Sophienstraße 1, D-80333 München

8th International Symposium, „Advances in Orthomolecular, Immunologic and Anti-Aging Medicine"
Termin:
June 28–30, 1996
Ort:
Mallorca, Spain
Auskunft:
American Biologics, 1180 Walnut Avenue, Chula Vista, California 91911
Phone (619) 429-8200, Fax (619) 429-8004

1. Kongreß der Deutsche Gesellschaft für Palliativmedizin
Termin:
27. und 28. September 1996
Ort:
Köln
Auskunft:
Deutsche Gesellschaft für Palliativmedizin, Kongreß-Sekretariat Prof. Dr. E. Klaschik/K. Schneider, Malteser Krankenhaus, Von Hompesch-Str. 1, 53123 Bonn

2nd Congress of the European Association for Neuro-Oncology
Termin:
October 6–9, 1996
Auskunft:
Congress & Tourismus Zentrale, Am Congress Centrum, D-97070 Würzburg

Skin Cancer and UV-Radiation
Termin:
3.–6. October 1996
Ort:
Bochum
Auskunft:
Verkehrsverein Bochum e.V., Postfach 10 28 30, D-44728 Bochum

2. Deutscher Kongreß für Radioonkologie, Strahlenbiologie und Medizinische Physik
Termin:
16.–19.11.1996
Ort:
Baden-Baden
Auskunft:
Deutsche Gesellschaft für Radioonkologie e.V.,
Pressestelle, Hoppe-Seyler-Str.,
72076 Tübingen

ECCO 9
Termin:
14.–18. September 1997
Ort:
Hamburg
Auskunft:
ECCO 9, Federation of European Cancer Societies (FECS), Avenue E. Mounier 83, B-1200 Brussels