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Short Communication

Cytotoxicity of *p*-Chloroamphetamine in Dimethylhydrazine-Induced Carcinomata of Rat Colon

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Summary. *Previous studies have shown that several serotonin-related compounds are cytotoxic to dimethylhydrazine-induced carcinomata of the colon of rat. This paper reports the cytotoxicity of another serotonin-related compound, p-chloroamphetamine.*

Introduction

Recent studies in our laboratory have shown that the rate of cell proliferation in chemically induced adenocarcinomata of rat colon can be influenced by a variety of biogenic amines [9, 10, 12, 13]. One of these amines, 5-hydroxytryptamine (5-HT), has been shown to be an important stimulus for tumour cell proliferation [12], and toxic congeners of 5-HT, such as 5,6- and 5,7-dihydroxytryptamine [11, 14], and some 5-HT-receptor blocking drugs (cyproheptadine and methysergide) [1] are cytotoxic to the tumour. *p*-Chloroamphetamine (PCA) has been shown to cause long-term depletion of 5-HT in various neural tissues [6, 7], and this effect has been attributed to cytotoxicity in 5-HT-metabolising tissues [5]. This paper reports the cytotoxicity of PCA in dimethylhydrazine (DMH)-induced tumours of rat colon.

Materials and Methods

Male Sprague-Dawley rats were fed Clarke King Nu-pig pellets and tap water ad libitum and housed at 21–24° C (except during the 24 h immediately after injection of PCA) with artificial lights from 07.00–21.00 h and darkness from 21.00–07.00 h. Rats were given weekly SC injections of DMH (Aldrich Chemical Company, Inc. Milwaukie, Wisconcin) at a dose of 21 mg/kg, as previously described [2, 8].

After 20 weeks the DMH injections were discontinued, and following a further interval of 6 weeks, 16 animals were given SC injections of PCA (Regis Chemical Company, Chicago, Illinois) at a dose of either 1 or 10 mg/kg and then housed for 15–24 h at a temperature of 15–19° C [6]. At intervals ranging from 15–48 h after treatment animals were killed by decapitation and tissues taken for microscopy. Control animals received the same regimen of DMH treatment but were not injected with PCA.

Evaluation of Cytotoxicity. Tumours of the transverse or descending colon were then prepared for histological examination. Estimation of the numbers of necrotic and of nonnecrotic cells in histological sections of tumours were made in the following way. Sections of tumours were examined at 400× magnification and the number of necrotic and nonnecrotic cells per visual field were counted with the aid of an eyepiece with a rectangular graticule. Each successive visual field at 0.3-mm intervals along two mutually perpendicular axes extending from edge to edge of the histological section was examined in this way and the mean percentage of necrotic cells per tumour was calculated. Between 1,000 and 2,000 cells were scored per tumour. Only cells with a distinctly pyknotic nucleus, i.e., one lacking the normal vesicular chromatin pattern, were recorded as necrotic. Results from each group of tumours treated in a particular way were conflated and the mean standard error for the percentage of necrotic cells was calculated. The statistical significance of the apparent difference between treatment means was estimated by the application of Student's *t*-test.

Results

In DMH-induced tumours taken from control rats, an average of 9% of tumour cells were judged to be necrotic. In tumours taken from animals treated with PCA for 24 or 48 h, a statistically significant increase in the percentage of necrotic cells was observed (Table 1).

Discussion

The preceding results show that PCA, like cyproheptadine, methysergide, 5,6-dihydroxytryptamine and 5,7-dihydroxytryptamine is cytotoxic in DMH-induced ade-

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Table 1. Percentage of necrotic cells in DMH-induced adenocarcinomata of rat colon following treatment with *p*-chloroamphetamine

Dose of *p*-chloroamphetamine (mg/kg)	Interval from treatment to sacrifice (h)	Percentage of necrotic cells		*P*
		Mean ± SE		
Nil (control)	–	9	1	–
1	24	44	9	< 0.02
10	15	26	8	0.2–0.1
	24	42	9	< 0.05
	48	41	12	< 0.05

nocarcinomata. However, the mechanism of toxicity for each of these agents in tumour cells remains obscure. Whilst reviews on the neurotoxicity of dihydroxytryptamines [4] and PCA [5] have recently been published, the dearth of information available on tumour amine metabolism makes extrapolation of the debate regarding cytotoxicity in neural tissues to the observations in the current study quite untenable.

The potential clinical usefulness of amine-related cytotoxic agents in human large-bowel cancer must be viewed in light of the rather dismal current situation with chemotherapy in this disease. Judging from meticulously conducted clinical trials, the cytotoxic drugs in use at present do little, if anything, to prolong the life of patients with disseminated bowel cancer [3]. In the one clinical case so far treated, 5,7-dihydroxytryptamine exhibited no detectable antitumour effect, nor were any serious side effects observed (Tutton and Schwartz, unpublished observation). The effect of various amine-related cytotoxic drugs on human colorectal tumours growing in xenograft in immune-suppressed mice is currently being investigated in this laboratory.

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