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31 May 1963

Radioprotection by Pressor Amidines

Abstract. *In the mouse, radioprotection is not always associated with the effect of hypertensive amidines and related amines. The protection resulting from this group of agents follows the pharmacological reduction of intercellular oxygen tension.*

After the observation that simple *S*-alkyl isothiuronium salts decrease radiosensitivity, Ashwood-Smith (*1*) tested some of its homologs in an attempt to relate structure to radioprotective action and to discover more promising agents. He found that activity diminishes rapidly as the *S*-alkyl substituent is lengthened beyond three carbon atoms. It is interesting that Fastier (*2*), in his excellent review of the structure-activity relationships of amidines, describes a loss of pressor action for *S*-alkyl isothiuroniums with alkyl substituent longer than three carbon atoms. The possible correlation of chemical structure, pressor activity, and radioprotection by these amidine derivatives led to a study of the effects of pressor amidines and pharmacologically related amines on the radiosensitivity of mice.

Table 1. Thirty-day survival data of mice receiving single doses of related pressor amines and amidines before irradiation to lethal doses of Co^{60} (1000 r).

Intraperitoneal administration		Animals (No.)	Survival (%)
Dose (mg/kg)	Time (min)		
	Controls		
		290	0
	2-Methylpseudo urea		
500	15	20	50
	Methyl guanidine		
150	5	20	5
	2-Amino pyridine		
25	15	30	0
	4-Amino pyridine		
3	15	15	0
	n-*Pentylamine*		
50	15	10	0
	n-*Hexylamine*		
40	15	10	0
	S-*ethyl isothiuronium*		
150	30	40	98
150	15	80	90
75	15	30	90
20	15	20	60
	*Papaverine · HCl**		
325	30	10	10
Papaverine · HCl, plus* S-*ethyl isothiuronium*			
325	30		
150	15	26	40
	Hypoxia†		
		42	5
Hypoxia, plus S-*ethyl isothiuronium*†			
150	15	20	5

* Subcutaneous administration. † Irradiated with 2200 r Co^{60}.

Young female mice (Bagg Swiss), weighing 20 to 25 g, were used. Ten control mice were irradiated simultaneously with each treated group and thereafter both groups were housed jointly. The radiation was done in a specially designed cobalt-60 irradiator which contained about 1200 curies of cobalt-60, half above and half below the radiation chamber. The mice were exposed in a plexiglass box which rotated through a flat radiation field of about 100 r/min. In the experiment with hypoxia, two treated and two control mice were irradiated simultaneously in a cobalt-60 Gammacell-220 (*3*) at about 1800 r/min. The irradiation chamber was gassed before and during exposure with a mixture of 5 percent oxygen and 95 percent nitrogen.

Each of the chemicals tested is known to increase blood pressure (*2*), but only two of these offered significant protection against lethal radiation. The survival data in Table 1 indicate that radioprotection by amidines is not directly associated with their pressor activity. In an attempt to explain this disparity, additional investigations were conducted with *S*-ethyl isothiuronium as a test compound.

The results in Table 1 show that *S*-ethyl isothiuronium is radioprotective when used over a wide dose range and for a considerable period of time. Also, papaverine, a known pharmacological antagonist (*2*) significantly reduced the protective effect of a massive dose of *S*-ethyl isothiuronium. Other agents—reserpine, atropine, phenergan, and dibenzyline—had no influence on *S*-ethyl isothiuronium action. The favorable therapeutic ratio and the response to a specific antagonist are parallel to actions established for serotonin (*4*), which is thought to decrease radiosensitivity through oxygen-dependent pathways. A similar mechanism may explain the action of *S*-ethyl isothiuronium since our data show that it fails to increase the radioprotection afforded mice by the optimal reduction of intercellular oxygen.

The experimental results suggest that pressor amidines offer radioprotective activity through a pharmacological mechanism which leads to a lowered oxygen tension of radiosensitive tissues.

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15 April 1963

Glycogen Deposition in the Liver Induced by Cortisone: Dependence on Enzyme Synthesis

Abstract. *The deposition of liver glycogen in starved rats given a single dose of cortisone is inhibited by puromycin and actinomycin. The former agent interferes with induced enzyme formation in general, and the latter with the cortisone-induced rise in liver enzyme levels. The results suggest that the regulatory effect of cortisone on carbohydrate metabolism may be brought about by its action on the cellular concentration of certain enzyme proteins.*

Adrenocortical hormones, which influence the rate of certain metabolic processes in vivo, do not appear to act as simple inhibitors or activators of enzymic reactions in vitro. Therefore, Knox, Auerbach, and Lin (*1*) suggested that hormone action may be brought about by changes in the actual concentration of the protein moiety of specific enzyme systems. The dependence on enzyme synthesis of the acute stimulation of glycogen deposition by cortisone in the liver of starved rats has now been tested.

Recent data suggest that the rise of enzyme activity induced by cortisone reflects an increase in the rate of *de novo* enzyme synthesis. The accumulation of liver tyrosine transaminase (*2*), glutamic-alanine transaminase (*3*), and tryptophan pyrrolase (*4*) has been measured immunochemically. Correspondingly, the administration of an inhibitor