GENERAL CHARACTERISTICS AND COMPARISON OF RADIOPROTECTIVE PROPERTIES OF ADRENOMIMETICS OF THE ARYLALKYLAMINE SERIES IN EXPERIMENTS ON MICE

V. I. Kulinskii and V. G. Yashunskii

UDC 615.849.1.015.25:547.589.4

The radioprotective effect of certain arylalkylamines (AAA), namely phenylephrine and its near analogs, when injected subcutaneously 15 min before irradiation in a dose of 800 rad was investigated in experiments on mice. The AAA were shown to have a low protective dose (25-50 μmoles/kg) and to give a stable and high radioprotective effect (survival rate 80-88%; dose reduction factor 1.3-1.4) and to have low toxicity (LD_{50} 4-8 mmoles kg). In their effectiveness the AAA studied are not inferior to aminothiols, and in the width of their pharmacological action ($K = LD_{50}/ED_{50}$ = 200-500) they surpass certain aminothiols and indolylalkylamines.

KEY WORDS: arylalkylamines; phenylephrine; radioprotectors.

For many years most investigators considered that catecholamines have a weak or moderate radioprotective action but, at the same time, are relatively toxic [1]. Later, one of us (V.I. K.) showed that under optimal conditions catecholamines are sufficiently effective protectors and that among them there are nontoxic substances with a therapeutic index of about 200 [5]. However, other adrenomimetics of the arylalkylamine (AAA) series have been studied only sporadically, and data on their radioprotective effect (RPE) are contradictory [3, 5, 9]. Recently, however, the AAA have begun to be regarded as promising protectors [8, 9, 13].

The object of the present investigation was a general assessment of AAA as protectors, with special reference to representatives of this class of known therapeutic application: phenylephrine, ethylephrine [7], norphenylephrine (M-octopamine) [12]. RPE and toxicity were studied and compared with those of typical representatives of the aminothiols and also with other protectors.

EXPERIMENTAL METHODS

Experiments were carried out on 1508 male CBA mice aged 3-5 months. The substances were injected in a volume of 10 ml/kg: AAA subcutaneously 15 min before irradiation and aminothiols intraperitoneally 7 min before irradiation. The conditions of irradiation and dosimetry were described previously [7]. Values of ED_{50} and LD_{50} were determined by the Litchfield–Wilcoxon–Ruth method [2]. The latitude of pharmacological action ($K = LD_{50}/ED_{50}$), the dose reduction factor (DRF) [2], and the protective index I [11, 14] were calculated.

EXPERIMENTAL RESULTS

The principal characteristics of RPE of the AAA tested are compared with those of aminothiols in Table 1. Data for the latter were close to those given in the literature. For instance, the therapeutic indices for aminothiols were 1.3-3 [1, 8, 11] and I=1.5-2.5 [11]. The AAA tested were evidently not inferior to aminothiols in the intensity of their RPE (the proportion of animals surviving, the value of DRF) but surpassed them considerably in their values of K and I, which reached 240-500 and 240-400 respectively. Closely similar values of the therapeutic indices were described previously [5] for isopropylnoradrenalin and phenylephrine in experiments on noninbred mice [5].

The fact that the values of K and I for AAA are 2 orders of magnitude higher than for aminothiols is attributable to two factors: 1) the lower toxicity (LD_{50} 2-5 times higher) and 2) the much lower optimal factor effec-

Department of Biochemistry, Krasnoyarsk Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Orekhovich.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 3, pp. 232-233, March, 1979. Original article submitted June 26, 1978.

 000714888/79/8703-0220$07.50

TABLE 1. Comparative Characteristics of Arylalkylamines and Aminothiols in Experiments on Mice (M ± m)

Substance	DRF	LD_{50}, μ moles/kg	ED_{50}, μ moles/kg	Latitude of pharmacological action (K)	Protective dose, μ moles/kg	Survival rate, %	Protective index (I)
Cystamine	1,42±0,12	2270±249	333	6,8	670	75±10	5,9
AET	—	1660±100	250	6,6	600	75±10	6,6
R,S-phenylephrine	1,29±0,082	5290±746	13±4,9	400	25	88±4	400
R(-)-phenylephrine	—	4120±182	8,3±1,22	500	25	87±4	310
R,S-ethylephrine	—	6570±59	—	—	50	80±13	240
R,S-norphenylephrine	1,39±0,087	8800±415	36±6,2	240	50	83±6	320

tive dose (12-27 times lower). According to data in the literature, indolylalkylamines are less toxic than aminothiols: Their therapeutic index is 10-30 [10] and I = 18-20 [11]. Consequently, indolylalkylamines occupy an intermediate position between the aminothiols and the AAA studied. Phenylephrine, however, and closely related substances from this point of view surpassed not only the classical representatives of the two main classes of radioprotectors. The effective protective dose of AAA (25-50 μmoles/kg) was close to the minimal values for radioprotectors described in the literature, namely 16 μmoles/kg [11], and the values of LD_{50} were just as high as those for nontoxic protectors Adchnon and Thiola (5800 and 12,270 μ moles/kg respectively) [11]. The last two substances, however, are inferior in their RPE to the classical protectors. It has recently been shown that the protective dose of Thiola is much higher than was hitherto considered, namely 4600 μmoles/kg [4], so that the value of I is only 3.5. An advantage of the AAA tested in this combination of two important features: high effect with low protective dose and low toxicity, responsible for the high values of K and I.

It will be noted that among the requirements which extend to radioprotectors a rational value of the therapeutic index is considered to be not less than 3 [8, 9], and the scale of effectiveness of radioprotectors based on the value of I ends at values of 15 or above [11]. Phenylephrine and its analogs satisfy these requirements.

Consequently, the AAA studied in experiments on mice are in fact effective and nontoxic radioprotectors: The gap between the protective and lethal doses, expressed by K and I, is sufficiently wide for them. The further investigation of substances of this series in the context of the study of chemical and biological principles and mechanisms of their protective effect (activation of receptors, the role of metabolic enzymes, and so on) would be interesting.

LITERATURE CITED

1. Z. Bacq. Chemical Protection Against Ionizing Radiation [in Russian], Moscow (1968).
2. M. L. Belen'kii, Elements of Quantitative Evaluation of a Pharmacological Effect [in Russian], Leningrad (1963), pp. 81-107.
3. T. Yu. Yul'yuchenok, A. A. Stolyarchuk, K. S. Shadurskii, et al., Farmakol. Toksikol., No. 5, 600 (1976).
4. M. M. Konstantinova and L. Revez, Radiobiologiya, 17, 839 (1977).
5. V. I. Kulinskii, "Metabolism of biogenic monoamines in irradiated animals and mechanisms of their radioprotective effect," Doctoral Dissertation, Khar'kov (1970).
6. V. I. Kulinskii, Radiobiologiya, 18, 178 (1978).
7. M. D. Mashkovskii, Therapeutic Substances [in Russian], Vol. 1, Moscow (1977), pp. 254-256.
8. P. P. Saksonov, V. S. Shashkov, and P. V. Sergeev, Radiation Pharmacology [in Russian], Moscow (1976).
9. N. N. Suvorov and V. M. Shashkov, Chemistry and Pharmacology of Substances for the Prevention of Radiation Injuries [in Russian], Moscow (1975).
10. S. P. Yarmonenko, N. N. Suvorov, B. B. Karochkin, et al., Radiobiologiya, 10, 78 (1970).
11. V. G. Yashunskii, Usp. Khim., 44, 531 (1975).
12. J. H. Hengstmann, W. Konen, G. Konen, et al., Eur. J. Clin. Pharmacol., 8, 33 (1975).
13. R. L. Prewitt and X. J. Musacchia, Int. J. Radiat. Biol., 27, 181 (1975).
14. R. D. Westland and J. L. Holmes, J. Med. Chem., 11, 1190 (1968).