POSSIBLE "ANTIRADIOPROTECTIVE" EFFECT OF CATECHOLAMINES

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Isoprenaline considerably reduced the radioprotective action of high doses of noradrenalin and phenylephrine; this effect was completely abolished by the β-adrenolytic propranolol. Propranolol potentiated the radioprotective effect of noradrenalin and adrenalin, but not of phenylephrine. The "antiradioprotective effect" (or component of action) of the catecholamines, mediated through β_1 receptors, is postulated. By blocking this effect, the full potential prophylactic activity can be exhibited. A combination of dibenamine, propranolol, and noradrenalin combines a high protective effect (73%) with low toxicity (the dose of noradrenalin used is 320 times less than LD_{50}).

The possibility that the same substance may combine opposite properties is well known. For instance, the catecholamines (CA) have opposite effects on the contraction of smooth muscles for secretion of insulin, depending on whether they act through α- or β-adrenergic receptors [10, 17].

It has been suggested that some effects of CA can prevent the full exhibition of their radioprotective action. These side effects would naturally be easier to demonstrate when their basic activity is maximal. To detect these effects, isoprenaline (N-isopropylnoradrenalin) was injected after high doses of noradrenalin (NA) or phenylephrine, equivalent to the saturation dose on the curve of radioprotective action. The other method used, administration of propranolol, was based on preliminary observations indicating that this β-adrenolytic substance increases the protective effect of adrenalin (A) [7].

EXPERIMENTAL METHOD AND RESULTS

Experiments were carried out on 810 male albino mice aged 2-4 months. The hydrotartrates of 1-A and 1-NA and the hydrochlorides of DL-isoprenaline, DL-phenylephrine, dibenamine, and DL-propranolol were used; all doses were calculated as base. The compounds were injected subcutaneously in a volume of 8 ml/kg: dibenamine 18-22 h, propranolol 30-40 min, A, NA, and phenylephrine 15-20 min, and isoprenaline 5-8 min before irradiation. The animals were irradiated in a dose of 806 rad ($LD_{98/30}$) at 190 kV, without an additional filter, and at a dose rate of 420 rad/min [6]. Differences between series were assessed by the χ^2 criterion, and LD_{50} was determined by the method of Litchfield and Wilcoxon [1].

The results are given in Table 1. Where the original radioprotective effect was small, isoprenaline increased it, but not to more than 60%. However, when large doses of NA or phenylephrine (1.84 and 8.2 mg/kg respectively), giving maximal prophylactic activity, were used the additional administration of isoprenaline gave the opposite effect, reducing the radioprotective effect by half. This was not due to the toxicity of the combination (no animals died 1-3 days after administration, and all the unirradiated control mice survived), nor was it the simple result of summation of action of the amines, because no such effect was obtained with a combination of NA (1.84 mg/kg) and phenylephrine (8.2 mg/kg); 50% of the animals survived.

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TABLE 1. Effect of Isoprenaline and Propranolol on Radioprotective Effect of Synpathomimetics; Survival after 30 Days Is Shown (in percent)

Radioprotector	0,9% NaCl	Noradrenalin		Adrenalin	Phenylephrine	
		0,92	1,84	1	4,1	8,2
	2±1 (178)	28±9,0 (25)	60±6,6 (55)	34±8,0 (35)	41±8,7 (32)	60±9,8 (25)
Isoprenaline	28±6,6* (43)	58±2,2† (60)	32±9,3† (25)	55±7,7 (42)	60±9,0 (30)	25±17† (20)
Propranolol	0 (10)	87±6,2* (30)	73±8,1 (30)	65±11‡ (20)	40±11 (20)	—

Note. Number of experiments in parentheses. Statistical significance calculated relative to results in first column.

*$P < 0.001$.

†$P < 0.05$.

‡$P < 0.1$.

The decrease in the radioprotective action of NA by isoprenaline in a dose of 1.84 mg/kg was completely prevented by propranolol ($P < 0.025$); 70% of the mice receiving this triple combination survived ($n = 30$), a result in full agreement with the protective effect of NA itself against the background of propranolol (73%; $P > 0.9$). This shows that this effect of isoprenaline is mediated through the β receptors.

The ability of isoprenaline, itself a radioprotector, to diminish the prophylactic activity of sympathomimetics, is conventionally described as an "antiprotective" effect. It has been suggested that this side-effect may also appear in a latent form in the action of other CA, preventing the complete manifestation of their primary radioprotective effect. Since the "antiprotective" activity of isoprenaline was manifested through the β receptors, experiments were carried out (Table 1) in which sympathomimetics were given in conjunction with propranolol, a powerful and specific β adrenolytic [2].

It is evident that propranolol, which itself did not protect the animals, considerably (by three times) potentiated the radioprotective effect of NA in a dose of 0.92 mg/kg. The effect of the equimolar dose of A was increased to a lesser degree (twice), and the protective action of phenylephrine was unchanged. These results are in agreement with the hypothesis that CA possesses a certain β effect which prevents the complete manifestation of their radioprotective action. Propranolol, by blocking β receptors, prevents the development of this "antiprotective" component, thus leading to production of the greatest possible radioprotective effect.

An alternative explanation of the potentiating action of propranolol is the hypothesis that it blocks the CA depots, because cocaine increases the prophylactic effect of CA [8]. However, the following facts conflict with this hypothesis: 1) propranolol increased the radioprotective activity of NA in a dose of 0.92 mg/kg more strongly than cocaine (87% survival compared with 56%; $P < 0.05$), whereas the cocaine-like properties of propranolol are only weak or are completely absent [12, 18]; 2) the effect of NA and A in doses of the order of 1 mg/kg, against the background of propranolol, increased the pure effect of double doses of CA (60 and 40% respectively; for NA, $P < 0.005$); this also contradicts the original assumption [7] that blocking β receptors increases the quantity of active A; 3) inetol (netalid), a much weaker blocking agent of β receptors than propranolol [2], but preventing depot formation more strongly [12, 18], does not potentiate the radioprotective effect of CA [7]. All these facts support the hypothesis of an "antiprotective" component of action, because the decrease in the effect of propranolol in the series NA > A >> phenylephrine is parallel to the affinity of these sympathomimetics not only for the depots [13], but also for β_1 receptors [13-15].

This hypothesis naturally requires additional experimental verification and an explanation of the biochemical nature of the phenomenon. Of the β_1 effects already known, lipolysis is interesting, since oxidized derivatives of unsaturated fatty acids possess definite radiomimetic properties [6] and can provide a basis for the formation of prostaglandins, which prevent many effects of CA [11]. Careful attention must also be paid to the fact that CA, unlike most radioprotectors, increases the oxygen demand of the body [4, 16]. This may increase the oxygen tension in the tissues and, consequently, prevent the shift toward the reduced state of the cell and an increase in the level of SH groups characteristic of increased radioresistance [3].

This explanation is supported also by another difference between A and most protectors. The very slight decrease in redox potential [4, 9] and the absence of an effect on the level of SH groups in the spleen [5]. The possible incorporation of 3',5'-AMP, which can also play an important role in the radioprotective effect [8], likewise must be investigated.

These results suggest that when the pharmacodynamics of radioprotectors is studied, not only the toxic effects but also possible "antiprotective" reactions must be taken into account. The desirability of combining these two approaches is supported by the results of using a combination of dibenamine, propranolol, and NA in a dose of 0.92 mg/kg, giving an increase of 2.5 times in the radioprotective effect (up to 78%; n = 30), while at the same time the toxicity is greatly reduced (LD_{50} of NA given in conjunction with these adrenolytics is 294 ± 22 mg/kg, or 320 times the protective dose).

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