QUANTITATIVE ASSESSMENT OF DRUG EFFICACY IN ADRENALIN-INDUCED HEART INJURY

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The protective or potentiating effect of drugs in relation to adrenalin-induced damage to the heart is manifested as a regular shortening or lengthening of the time taken for eosinophilia to develop compared with that following injection of adrenalin alone. This effect lies at the basis of quantitative evaluation of the efficacy of drugs in the treatment of heart damage.

KEY WORDS: heart injury; eosinophilia; effect of drugs.

Methods of quantitative evaluation of the efficacy of drug action used at the present time in experimental models of cardiovascular diseases do not take into account the initial state of the pituitary–adrenal system (PAS), one of the first systems of the body to react to extremal factors, and its responses to pharmacological agents. Yet we know that in stress situations changes in PAS function are accompanied by the regular development of an eosinopenic effect, followed by eosinophilia [1, 4-6], and this has been used to develop criteria for evaluation of drug action.

This paper gives the results of a morphological study of the structure of the heart after injury by adrenalin and also of the dynamics of changes in the peripheral blood eosinophil count, as an integrative indicator of PAS function. Administration of Inderal (propranolol), which reduces the cardiotoxicity of sympathomimetics, and of isadrine (isoproterenol), increasing cardiotoxicity [2], against the background of adrenalin could be used to assess not only the protective action of drugs, but also their potentiating action on heart injury.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-200 g with a peripheral blood eosinophil count of 220-340/μl at 9 a.m. The animals were divided into four groups, with six rats in each group. The rats of group 1 (control) received a subcutaneous injection of adrenalin in a dose of 3.75 mg/kg. The animals of group 2 received adrenalin in the same dose, followed 1-1.5 h later by a subcutaneous injection of isadrine, 5 mg/kg. The animals of group 3 received the same dose of adrenalin followed 1-1.5 h later by Inderal, 5 mg/kg. The rats of group 4 received adrenalin and physiological saline. The peripheral blood eosinophil count was determined in the animals of all groups at intervals of 3 h after injection of adrenalin (in a Goryaev's counting chamber, after staining by Hinkleman's method). Changes in the eosinophil count were subjected to statistical analysis and plotted graphically (Fig. 1). The efficacy of isadrine and Inderal therapy was assessed by calculating the ratio of the time taken for eosinophilia to develop in the animals of the control group to the corresponding time for animals of each experimental group. Additionally, on other animals divided into four similar groups, ordinary histological investigations of the structure of the heart were carried out to determine the degree of injury to the organ. The animals were killed in all groups at a time of marked eosinophilia, for it was shown previously that under extremal conditions more marked structural changes are found in the heart at that time [3].

EXPERIMENTAL RESULTS

Adrenalin was found to cause the development of structural damage to the heart in the form of foci of necrosis of muscle cells (Fig. 2a), which was sharply intensified after combined administration of adrenalin and the β-adrenomimetic isadrine (Fig. 2b). After administration of the β-adrenoblocker Inderal after adrenalin, the degree of structural damage to the heart was considerably reduced and foci of necrosis of muscle cells

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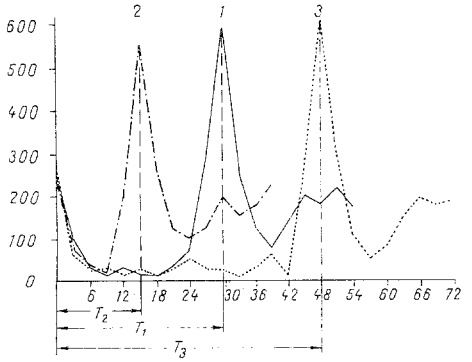

Fig. 1. Number of eosinophils in 1 μl peripheral blood of rats after injection of adrenalin (1), adrenalin and Inderal (2), and adrenalin and isadrine (3). Abscissa, time after injection of adrenalin (in h); ordinate, number of eosinophils in 1 μl blood.

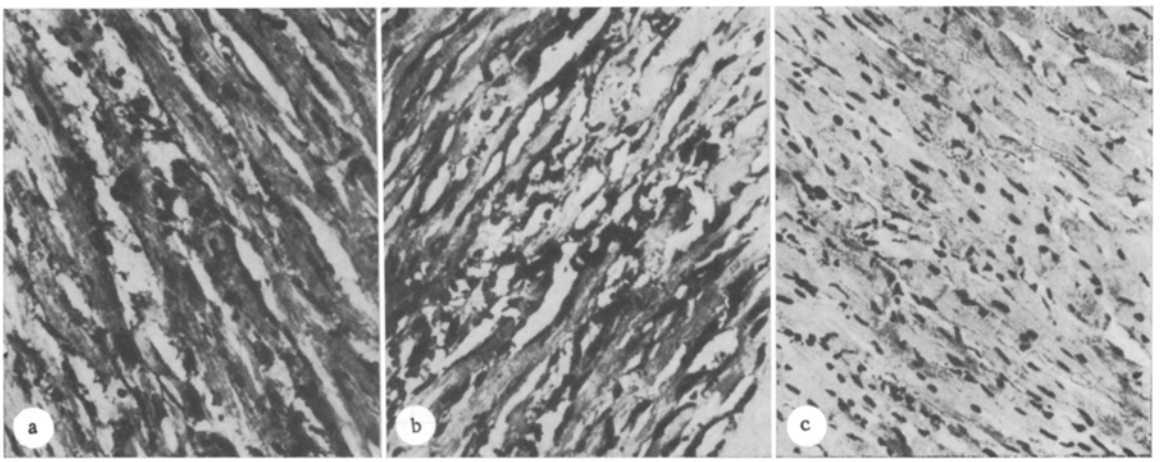

Fig. 2. Morphological changes in rat myocardium: a) 30 h after injection of adrenalin 3.75 mg/kg: partial homogenization of muscle fibers with swelling and fragmentation, pycnotic changes in nuclei of necrotic muscle cells; b) 48 h after injection of adrenalin 3.75 mg/kg and isadrine 5 mg/kg: unbroken homogenization of myocardial cells, multiple foci of necrosis of muscle cells, karyorrhexis, hemorrhagic foci; c) 15 h after injection of adrenalin 3.75 mg/kg and Inderal 5 mg/kg: homogeneous and swollen regions of muscle fibers with disappearance of cross-striation and enhanced acidophilia, condensed nuclei of muscle cells, no foci of necrosis of myocardiocytes present. Hematoxylin-eosin, 79×.

were absent (Fig. 2c). Injection of physiological saline into the rats after adrenalin did not change the harmful action of this sympathomimetic on the heart or the time taken for eosinophilia to develop.

The efficacy of isadrine and Inderal therapy was assessed by calculating the equation:

$$A = \frac{T_C}{T_0}$$

where A is the efficacy of action (activity) of the drug, T_C the time (in h) taken by animals of the control group to develop eosinophilia after previous eosinopenia under the influence of adrenalin only (the harmful agent); T_0 the time (in h) for animals of the experimental group to develop eosinophilia after administration of adrenalin followed by isadrine or Inderal.

Administration of isadrine, which potentiates the cardiotoxic action of adrenalin, to animals with adrenalin-induced cardiac injury was found to lengthen the time taken for eosinophilia to develop to 48 h (compared with 30 h after adrenalin alone). Injection of Inderal, which reduces the severity of heart damage, shortened

the time taken for eosinophilia to develop to 15 h. Calculation of the efficacy of action of isadrine and Inderal in adrenalin-induced heart injury gave values A = 0.62 for isadrine and A = 2 for Inderal, i.e., the former potentiates the harmful action of adrenalin whereas the latter has a protective action.

The investigations thus showed a regular relationship between the efficacy of action of the two drugs tested in adrenalin-induced heart injury and changes in the duration of phases of responses of the PAS, as reflected in an increase or decrease in the time required for eosinophilia to develop in response to injection of adrenalin.

In the writers' view, this principle of evaluation of the efficacy of drug action can be used to develop objective criteria characterizing the action of chemical compounds and pharmacological agents under a wide range of extremal conditions.

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EFFECT OF SODIUM HYDROXYBUTYRATE ON THE AMMONIA CONTENT IN RAT MUSCLES DURING PHYSICAL EXERTION

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In experiments on rats forced to swim while carrying a load, sodium hydroxybutyrate was found to have a normalizing effect on the ammonia content in the striated muscles, a biochemical indicator of physical fatigue. Whereas in control rats not receiving hydroxybutyrate swimming led to a marked (more than twofold) increase in the ammonia content in muscle tissue, in animals receiving prophylactic sodium hydroxybutyrate (one only or as a 2-week course) ammonia did not accumulate. It is suggested that by preventing the toxic effect of one of the end products of nitrogen metabolism, sodium hydroxybutyrate may alleviate the after-effects of muscular fatigue.

KEY WORDS: sodium hydroxybutyrate; physical exertion; nitrogen metabolism; striated muscle.

Sodium hydroxybutyrate has the property of increasing the resistance of the body to hypoxia [5, 15]. Analysis of the mechanism of this effect has shown that the compound reduces the degree of disturbance of oxidative processes induced by hypoxia [1, 6, 10] and also reduces the changes in nitrogen metabolism in nerve tissue characteristic of that state [2]. It has also been shown that if sodium hydroxybutyrate is given during repeated physical exertion separated by short intervals of rest a tendency is observed toward stabilization of working capacity at a certain level [4]. Hypoxia due to a deficient oxygen supply to the tissues, and the so-called motor hypoxia due to physical exertion, are known to have some common pathogenetic factors, one of

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