Criteria of Individual and Population-Wide Resistance to Acute Hypoxia

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It is shown that the geometric mean of survival time and the deviation of σ from τ are measures of a population's resistance to acute hypoxia; that a measure of the individual resistance of an animal to such hypoxia is Student's parameter for that animal; that the distribution of Student's parameter in a population is a lognormal distribution under any conditions; and that the number of animals with low resistance is always equal to the number of highly resistant animals. The procedure described makes it possible to limit the number of animals used in an experiment by recording with the requisite accuracy the proposed measures of resistance to acute hypoxia at the population and individual levels.

Key Words: *hypoxia; resistance; individual resistance*

Knowledge of individual variations in physiological parameters is necessary for defining the limits of age- and sex-specific variabilities in these parameters, the normal ranges of various responses, and the reserves of adaptive/compensatory mechanisms. The course of any disease is largely determined by individual responsiveness, which is based on congenital and acquired traits. As found in studies of responses to oxygen deficiency, there are individuals in any population of animals that survive when most of the test animals (even 95%) have died [2,3]. Animals differing in susceptibility to hypoxia exhibit substantial differences in behavioral, physiological, and metabolic variables [4,5].

Although several methods are now available for quantifying the results of experiments on animals with acute hypoxia [1-3], these methods are not without their shortcomings. Linear estimates are valid only when variations in the recorded parameters are small. Different procedures may yield discrepant results depending on the empirical coefficients used.

A relatively accurate method of linear analysis was proposed by Berezovskii [3] for rats separated, according to survival times at an altitude of 11,000 m, into groups with low, medium, and high resistance to hypoxia, using 30% deviations from the arithmetic mean of survival times calculated for all the rats tested over the same period as cutoff points for their separation into these groups. The cutoff points were set at equal intervals from the mean survival time and were shifted accordingly when its arithmetic mean changed. Berezovskii's method yields normal results if the deviations of survival times from the arithmetic mean are not large, whereas in the case of a nonlinear distribution where the minimal value differs from the maximal by one order of magnitude, this method produces a considerable deviation of the mean value from the center of the distribution curve.

The aim of the present study was to identify, by means of a strict mathematical analysis, criteria by which the resistance of an animal population to acute hypoxia can be characterized as completely as possible.

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MATERIALS AND METHODS

The study was conducted on 950 random-bred male white rats (body weight 150-200 g) in different seasons of the same year. A total of eight experiments lasting 9 to 20 days each were undertaken. The resistance of the rats to hypoxia was estimated in an altitude chamber where the air pressure was lowered to one-sixth of normal atmospheric pressure, which is equivalent to elevation to an altitude of 11,000 m above sea level. The rats were exposed to this pressure until a reversible respiratory arrest occurred, after which they were "brought down" and the normal atmospheric pressure was restored. The times during which the animals maintained their posture and survived at the indicated altitude were recorded, as was the time taken to regain the normal posture after the descent began. In the analysis of the data, survival time was treated as the main parameter because it was more variable than the time taken to lose or recover posture. A strict sorting of the data so as to arrange the animals in terms of increasing survival enabled us to determine the distribution and mutual correlations of the data.

RESULTS

The results of analyzing the data obtained for the entire rat population (*n*=950) are summarized in Table 1 and Fig. 3. The results of one of the eight experiments are illustrated in Figs. 1 and 2.

Our study demonstrated three important points. First, the survival time increased nonlinearly with the increase in the ordinal number of the sorted rat. Second, there was no significant correlation between the times of postural loss and recovery, since the coefficient of correlation between these two variables ranged from -0.14±0.09 to 0.2±0.08. The coefficients of correlation between survival time and time of postural recovery and between survival time and time of postural loss were positive and ranged from 0.18±0.08 to 0.5±0.06 and from 0.38±0.07 to 0.61±0.06, respectively. Third, the analysis of correlation functions indicated that the time of postural loss increased, on average, to a greater extent with increasing survival than did the time of postural recovery, although the scatters of these times were very large.

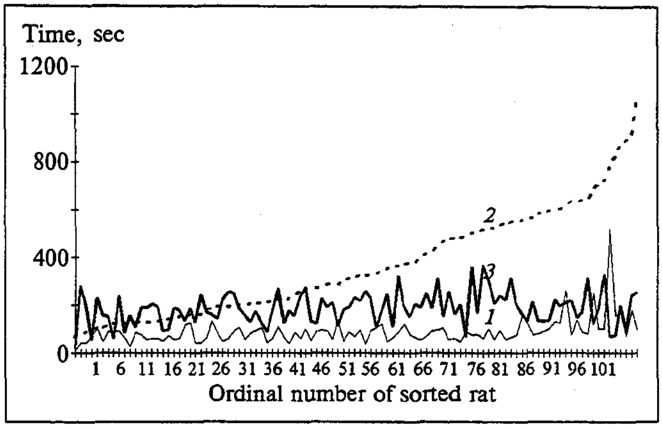

Fig. 1. Times of postural loss (*1*), survival (*2*), and postural recovery (*3*) as a function of the ordinal number assigned to each rat after the rats were sorted according to increasing survival times under conditions of acute hypoxia.

Survival time proved to be a more reliable and stable parameter for use in physiological evaluations than the times of postural loss and recovery. The nonlinear distribution of survival times (ST) became normal when they were expressed in the logarithmic form, log(ST) (Fig. 2). The black area in Fig. 2 corresponds to the life of the animals during the experiment; all animals remained in the experiment up to point 1.845 and were leaving the experiment in the interval between points 1.845 and 3.027. As

TABLE 1. Results of Analyzing Survival Times (ST) of Rats Using Linear and Nonlinear Estimations

No. of rats	Linear estimation after Berezovskii			Nonlinear estimation					Change in mean ST, sec
	range between		arithmetic mean of ST, sec	range between		geometric mean of:		σ_ε	
	minimal ST	maximal ST		log(ST) minimal	log(ST) maximal	log($\overline{ST}$)	$\overline{ST}$, sec		
123	50	920	298	1.698	2.984	2.338±0.030	218±15	0.335	80
139	66	914	246	1.819	2.960	2.318±0.023	208±10	0.275	38
104	70	1066	371	1.845	3.027	2.497±0.028	314±19	0.290	57
113	50	865	274	1.698	2.937	2.384±0.026	242±14	0.278	32
115	62	665	282	1.792	2.822	2.415±0.024	260±14	0.257	22
115	55	845	262	1.740	2.926	2.358±0.026	228±14	0.286	34
125	90	1090	395	1.954	3.037	2.554±0.021	358±17	0.240	37
116	55	665	188	1.740	2.752	2.235±0.024	171±8	0.265	17

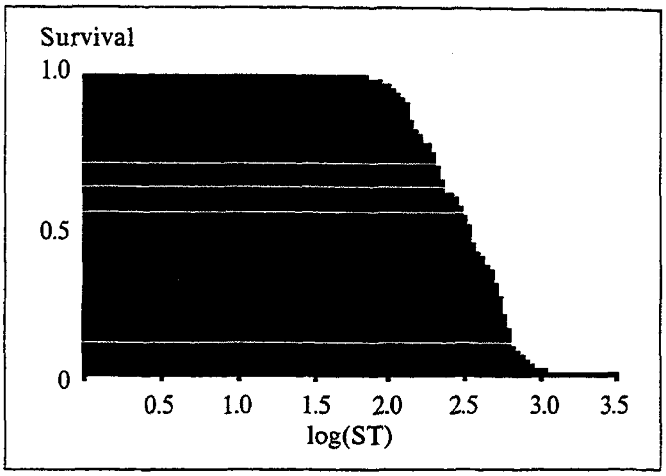

Fig. 2. Log survival times (ST).

can be seen in this figure, the withdrawal of animals from the experiment can be approximated with reasonable accuracy even by a straight line - by connecting point 1.845 with point 3.027. Disadvantages of such graphic analysis are the difficulties involved in visually detecting differences between the beginning and end of a decline in the characteristic under study and in estimating the rate and mean value of the decline. Exact parameters of the distribution and new criteria for estimates were obtained by subjecting the data to a detailed nonlinear mathematical analysis in order to evaluate the physiological state of animals under conditions of acute hypoxia.

During acute hypoxia, the mean survival time $(\overline{ST})$ of an animal population, defined as the arithmetic mean of survival times recorded for individual animals, is equal to the period over which a reversible respiratory arrest develops in one half of the population:

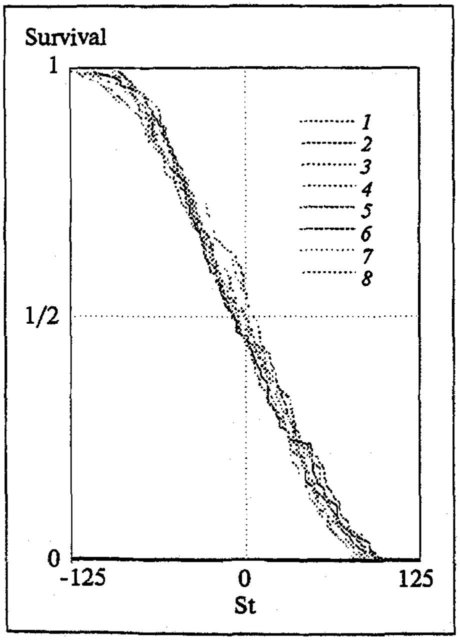

Fig. 3. Individual criterion of resistance to acute hypoxia (*St*) for all test rats in the eight experiments.

$$\overline{ST} = \sqrt[n]{\prod_{i=1}^{n} ST_i}$$

where n is the ordinal number of the animal.

The boundaries (cutoff points) between the groups of animals with low, medium, and high resistance to hypoxia are related to the geometric mean of ST by the following rule: the geometric mean of ST in a population is equal to the square root of the product of these cutoff points.

In addition to the geometric mean of ST, a population of animals with acute hypoxia has another characteristic, namely, the scatter of animals in terms of log($\overline{ST}$), which is the standard deviation of σ from τ:

$$\sigma_\tau = \sqrt{\frac{1}{n}\sum_{i=1}^{n} [\lg(ST_i) - \lg(\overline{ST})]^2}$$

where $\log(ST_i) = \tau_i$.

It will be much easier to observe variations in the values obtained by expressing all experimental results in terms of a few parameters. This can be done by making use of Student's parameter (*St*), which is equal to the individual deviation of $\log(ST_i)$ for each animal from the mean log(ST) expressed as the deviation of σ from τ:

$$St_i = \frac{1}{\sigma\tau} \lg\left(\frac{ST_i}{\overline{ST}}\right)$$

Since Student's parameter can be calculated and ascribed to each animal, this parameter is a natural characteristic of the individual resistance to acute hypoxia shown by a given animal at the instant of measurement.

In our study, a total of 950 measurements of survival time at 11,000 m above sea level were made during different seasons of one year. By performing Student's test for the survival time of each animal in the population under study and then arranging the animals in order of increasing survival time, we can obtain a data array characterizing the viability of the population.

In Fig. 3, the points obtained for the eight experiments all lie on a single curve of survival under acute hypoxia (at a pressure equal to one-sixth of normal atmospheric pressure) and satisfy Kolmogoroff's significance test.

As can be seen in Table 1, our nonlinear estimates of mean survival time are up to 30% more accurate than the linear estimates by Berezovskii's method.

This study thus indicates that the time of postural loss is not related to the time of postural recovery and suggests that the number of animals with low resistance to acute hypoxia in a population is always equal to the number of highly resistant animals. The data indicate further that criteria of this resistance in a population are the geometric mean of survival time and the deviation of σ from τ; that a criterion of individual resistance of an animal to acute hypoxia is Student's parameter for that animal; and that the distribution of Student's parameter in a population is lognormal under any circumstances.

With the procedure described above, experimental findings can be treated in strict mathematical terms, avoiding the use of empirical coefficients. Moreover, the resistance to acute hypoxia can be recorded with the requisite accuracy at the population and individual levels by using a limited number of animals in the experiment. The use of this procedure can probably be extended to follow responses of animals to other adverse factors such as stress and environmental pollution.

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Participation of Opioid and Serotoninergic Brain Receptors in Amphetamine-Induced Stereotypy and Hyperthermy

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The inbred rat strains WAG and Fischer-344 were found to differ in the duration of amphetamine-induced stereotypy and the degree of hyperthermy elicited by this drug, the stereotypy lasting longer in WAG rats and the hyperthermy being more pronounced in Fischer-344 rats. A comparison of interstrain differences in the amphetamine effects, in receptor binding, and in the pharmacological activity of receptor agonists suggests that the μ-opiate system of the brain may be involved in the manifestation of amphetamine-induced stereotypy, while its serotoninergic system may mediate the elevation of body temperature caused by this drug.

Key Words: *amphetamine; stereotypy; thermoregulation; serotonin; morphine; clonidine*

Animals differ in their sensitivity to narcotic substances [3,4], and these differences appear to be governed by molecular/genetic mechanisms that determine neurochemical distinctions in the receptor binding and metabolism of narcotics and in the mediation of their effects. A pivotal role in the effects of psychostimulants is played by complex reactions of monoamine systems of the brain [1,2,5]. On the other hand, animals differing with regard to properties of the brain's opioid receptors and/or receptor binding of monoamines may also differ in their susceptibility to the development of addictive behavior [6].

Our previous studies [6] revealed differences in receptor binding between the WAG/G and Fischer-344 strains of rats. Thus, WAG rats were found to

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