A BASIS FOR CRITERIA OF SENSITIVITY, RESISTANCE AND TOLERANCE IN RELATION TO THE EFFECT OF CERTAIN PHARMACOLOGICAL SUBSTANCES AT DIFFERENT AGE PERIODS

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The concepts of sensitivity, resistance or tolerance are often used to compare the reactions of animals of different ages to the effect of pharmacological substances. These concepts are used indiscriminately, and the same index is usually used as the criterion, i.e., the difference in the values of the lethal doses [16 -21 and many others]. In many works, the data showing the percentage of lethality with the administration of pharmacological substances in doses ranging from the maximum tolerance to the absolute lethal are first processed by the method of cumulative frequencies, then expressed graphically and defined as curves of individual sensitivity [5, 7, 8, 9, 10 et al.]. I. A. Arshavskii's definition [1, 2, 3] of resistance as the ability of the organism to maintain a normal or even somewhat increased functional level due to the increase of true accommodative resistance to the active stimulant is based on research investigating the lability of the centers regulating the activity of the respiratory, cardiovascular and skeletal muscular systems under conditions of alteration in animals of different ages. This reaction enables the organism to preserve and sustain the condition usually known as homeostasis. The criterion of resistance used in our laboratory is the duration and degree of expression of the first phase of the parabiotic reaction.

In order to further develop and crystallize the concepts and criteria of sensitivity, resistance and tolerance to the action of pharmacological substances, we made a physiological analysis of the reactions of animals of different ages to the administration of certain pharmacological substances. These investigations enabled us primarily to differentiate between the concepts of sensitivity and resistance.

In the physiological sense, the concept of sensitivity is close to the notion of excitability, or the stimulation threshold. The minimal dose causing certain formations of the organism to react in a fashion specific to the given substance without eliciting a reaction from other formations should be regarded as the criterion of sensitivity to the action of pharmacological substances [13-15].

In the case of most pharmacological substances, there is great difference between the values of the threshold and lethal doses. The latitude between the minimum effective and the lethal doses of many pharmacological substances is completely different in the case of very young animals from that observed for adult animals. For example, the threshold dose of atropine blocking the cholinoreceptive substance of the heart for very young puppies is 1/500 of the same dose for adult dogs, while the minimum lethal dose for the former is only 1/2 of that for the latter [12]. However, the usually accepted method of comparing sensitivity according to the range of the lethal doses does not take these differences into account.

EXPERIMENTAL METHOD

In order to obtain more precise criteria of resistance and tolerance, we performed experiments on baby rabbits 3-8 days old and on adult rabbits. Chloral hydrate was injected intraperitoneally in doses of 5-800 mg/kg, each dose being administered to a group of 3-11 rabbits of the same age (except the doses of 5 and 10 mg/kg in the case of the adult rabbits). The rabbits for the experimental groups were selected not only according to age and weight, but also according to physiological conditions as determined by temperature and by electrocardiogram. The original temperature of the baby rabbits used in the experiments ranged from 35 to 38°, the cardiac rhythm, from 240 to 315 per minute. The animals' reactions were evaluated according to the electrocardiogram and from the changes in respiration and temperature.

EXPERIMENTAL RESULTS

A resistance type of reaction in a rabbit 3 days old, i.e., when the centers which regulate the activity of the respiratory and cardiovascular systems, as well as the centers of thermoregulation, maintain the original or an increased level of activity after the administration of 125 mg/kg chloral hydrate, is shown by the curves in Fig. 1 above the line representing the original level. The

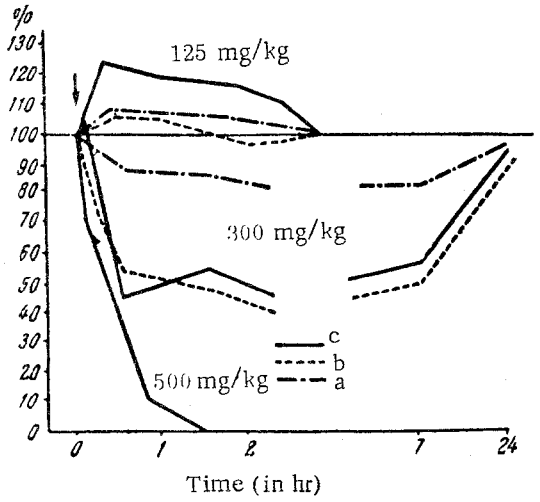

Fig. 1. Graph showing the changes in temperature (a), respiratory rhythm (b) and rhythm of heart contractions (c) characterizing the resistance type of reaction in rabbits aged 3-8 days to the administration of 125 mg/kg chloral hydrate (shown above line representing original level, taken as 100%). Below the line of the original level are shown the same indices for the tolerance type of reaction to the administration of 300 mg/kg chloral hydrate. The lowest curve represents the changes in the heart rhythm caused by the administration of a lethal dose of chloral hydrate (500 mg/kg).

curves below the original level are those showing changes in the temperature and in the cardiac and respiratory rhythms of 5-day old rabbits after the administration of chloral hydrate in doses 300 and 500 mg/kg, which caused the lability of these systems to decrease. The latter reactions represent the protracted collapse typical of a very young organism, during which the nerve centers drop to a lower functional level under conditions of decreased body temperature [6, 11, 14].

With a dose of 300 mg/kg chloral hydrate, the collapse is reversible. This type of reaction indicates a condition of tolerance in the organism, which is to be understood as a reversible disturbance of homeostasis under conditions of intoxication.

Figure 2 gives electrocardiograms taken from baby rabbits (3 and 5 days old) showing reactions of the resistance (a) and tolerance (b) types and the reaction to the administration of a lethal dose (c).

The analysis conducted made it possible to establish that the range of the chloral hydrate doses under the influence of which the reaction characterized by maintenance of homeostasis (first phase) occurs in baby rabbits is very different from the analogous range for adult rabbits. The range of the doses causing the reversible second phase of the reaction and the range of the lethal doses also differ considerably in these two age groups (Table 1).

The absolute lethal dose of chloral hydrate for the baby rabbits was considerably smaller than that for the adult rabbits. A similar correlation between the lethal

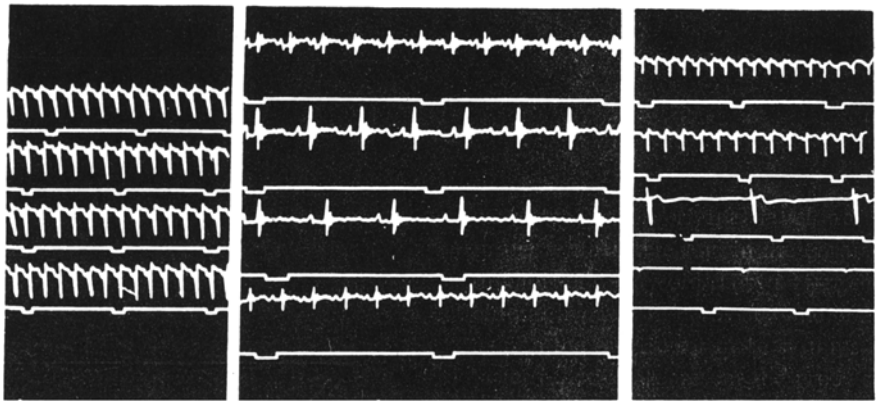

Fig. 2. Electrocardiograms of rabbits. a) 3 Days old before (top line) and 15 min, 1 hr 15 min and 2 hr 30 min after the administration of 125 mg/kg chloral hydrate (second, third, and fourth lines from the top, respectively); b) 5 days old before (top line) and 1 hr, 2 hr, and 24 hr after the administration of 300 mg/kg chloral hydrate (second, third and fourth lines from the top, respectively); c) 5 days old before (top line) and 20, 50, and 60 min after the administration of 500 mg/kg chloral hydrate (second, third, and fourth lines from the top, respectively). Time mark = 1 sec.

TABLE 1. The Different Ranges of Chloral Hydrate Doses Causing the First and Second Reaction Phases in Rabbits of Different Ages

Doses	Rabbits	
	3-8 days old	adult
	chloral hydrate doses (in mg/kg)	
Causing first reaction phase in all experimental animals	5—125	5—450
Producing variation of first reaction phase and reversible second phase	150—250	500—700
Causing reversible second phase of reaction in all animals	275—300	—
Causing variation of second reaction phase-reversible and irreversible	350—450	650—750
Absolute lethal	500	800

doses for rabbits of these two age periods has also been observed in the case of morphine [19, 20].

Table 2 gives the complete data on the baby and adult rabbits, expressed in absolute, integrated (according to Berens) and percentile terms .

On the basis of the data in Table 2, we constructed in Fig. 3 the curve of variation for the percent of death in baby rabbits (B_1) administered chloral hydrate in doses ranging from the maximum tolerance (300 mg/kg) to the absolute lethal (500 mg/kg) and an analogous curve for adult rabbits (B) given doses ranging from 600 to 800 mg/kg. Curves A_1 and A show the variation in the resistance and tolerance types of reactions in baby rabbits (A_1) and adult rabbits (A) given doses within the ranges specified in Table 1.

Left of curve A_1 in Fig. 3 lies the dosage range of 5-275 mg/kg, which includes the doses to which all or some of the baby rabbits of each experimental group reacted by increased mobility of the nerve centers. We call this the range of resistance. The range of tolerance, or the doses ranging from 150 to 450 mg/kg, to which all or some of the rabbits of the experimental groups reacted by a reversible transition to the second reaction phase, lies between the curves A_1 and B_1. The range of resistance for the adult rabbits is shown by the horizontal shading left of curve A (5-700 mg/kg); the vertical shading between curves A and B represents the range of tolerance, and the diagonal shading to the right of curve B shows the range of lethal doses.

Curves A and A_1 cannot be said to depict all cases of the resistance type of reaction, because this reaction was observed in the baby rabbits with the administration of doses less than 125 mg/kg, and in adult rabbits, with doses less than 450 mg/kg, beginning with a dose of 5 mg/kg.

It is the ranges of resistance, which differ for each age group, rather than the curves A and A_1 which give the most complete picture of resistance, just as tolerance is best characterized by the range of tolerance for each age group as well as by the curves B and B_1. Curves A and A_1 are both the right margin of the ranges of resistance and the left margin of the ranges of tolerance; the

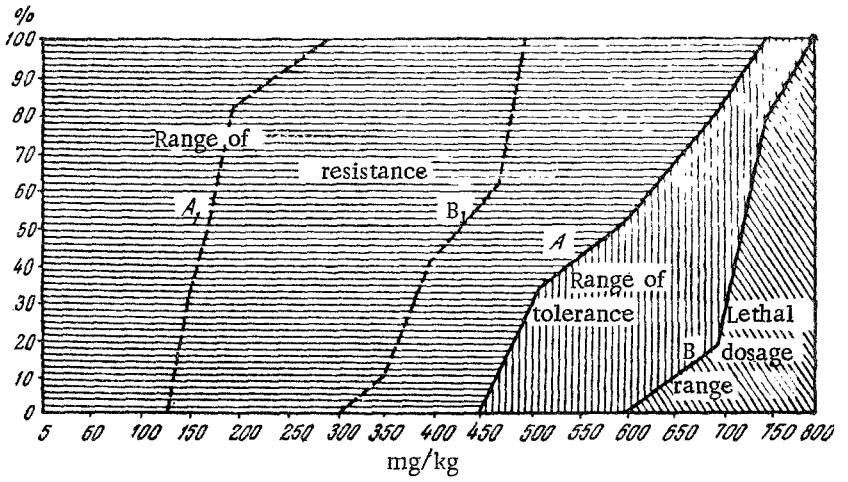

Fig. 3. Variation curve of resistance-tolerance (A) and variation curve of tolerance lethality (B) for adult rabbits. Horizontal shading) range of resistance for adult rabbits. The dotted lines drawn inside the range of resistance of the adult rabbits are the variation curve of resistance-tolerance (A_1) and the variation curve of tolerance-lethality (B_1) for baby rabbits. The shading and notations on Fig. 3 concern the adult rabbits.

TABLE 2. Variation of Resistance and Tolerance Reactions and Lethal Issues in Rabbits with the Administration of Chloral Hydrate

Dose (in mg/kg)	Total No. rabbits	Reaction phases: in absolute nos. first	in absolute nos. 2nd.	in integrated form first	in integrated form 2nd.	in percent first	in percent 2nd.	Lethality of rabbits: in absolute numbers alive	in absolute numbers dead	in integrated form alive	in integrated form dead	in percent alive	in percent dead
A. Rabbits 3–8 days old													
5	4	4	0	25	0	—	—	4	0	—	—	—	—
10	3	3	0	21	0	—	—	3	0	—	—	—	—
50	3	3	0	18	0	—	—	3	0	—	—	—	—
100	4	4	0	15	0	—	—	4	0	—	—	—	—
125	4	4	0	11	0	100,0	0	4	0	—	—	—	—
150	5	2	3	7	3	70,0	30,0	5	0	—	—	—	—
175	5	3	2	5	5	50,0	50,0	5	0	—	—	—	—
200	6	1	5	2	10	16,7	83,3	6	0	—	—	—	—
250	4	1	3	1	13	7,1	92,9	4	0	—	—	—	—
300	6	0	6	0	19	0	100	6	0	23	0	100,0	0
350	9	0	9	0	28	—	—	7	2	17	2	89,5	10,5
375	3	0	3	0	31	—	—	2	1	10	3	76,9	23,1
400	6	0	6	0	37	—	—	3	3	8	6	57,2	42,8
450	11	0	11	0	48	—	—	5	6	5	12	29,4	60,6
500	6	0	6	0	54	—	—	0	6	0	18	0	100,0
B . Adult rabbits													
5	2	2	0	31	0	—	—	2	—	—	—	—	—
10	2	2	0	29	0	—	—	2	—	—	—	—	—
50	3	3	0	27	0	—	—	3	—	—	—	—	—
150	3	3	0	24	0	—	—	3	—	—	—	—	—
200	3	3	0	21	0	—	—	3	—	—	—	—	—
300	3	3	0	18	0	—	—	3	—	—	—	—	—
450	6	6	0	15	0	100,0	0	6	—	—	—	—	—
500	6	2	4	9	4	69,2	30,8	6	—	—	—	—	—
550	3	2	1	7	5	58,3	41,7	3	—	—	—	—	—
600	4	3	1	5	6	45,4	54,6	4	0	9	0	100,0	0
700	5	2	3	2	9	18,2	81,8	4	1	5	1	83,3	16,7
750	4	0	4	0	13	0	100	1	3	1	4	20,0	80,0
800	6	0	6	0	23	—	—	0	6	0	10	0	100,0

best name for them is therefore "variation curves of resistance-tolerance" (or "resistance–tolerance curves" for short). The best name for curves B and B_1 is " rance–lethality curves".

Figure 3 shows that both the curves for the adult rabbits (A and B) slant more sharply to the right than the curves for the baby rabbits (A_1 and B_1). Both the A and B curves for the adult rabbits lie considerably to the right of the lethal dosage range for the physiologically mature baby rabbits. The size of the range of resistance for adult rabbits shown in Fig. 3(5-700 mg/kg) is notable, being considerably greater than the ranges of resistance and tolerance combined for baby rabbits. Conversely, the range of doses to which adult rabbits react by the second, reversible, reaction phase is not only narrower than their own range of resistance, but narrower than the range of tolerance for baby rabbits.

Their wider range of resistance indicates that the resistance of adult rabbits is much higher than that of baby rabbits, since maintenance of the original condition or increase in the lability of the thermoregulator, respiratory and cardiovascular systems and preservation of homeostasis can, under conditions of alteration, occur in the former within a wider range of effects than in baby rabbits.

One cannot conclude from the relatively narrow range of tolerance of the adult rabbits that, in spite of their higher resistance to chloral hydrate, their tolerance for it is less than that of baby rabbits. Such a paradoxical conclusion is impossible, due to the fact that the right margin of the range of tolerance (curve B in Fig. 3) is located within a higher range of doses than is the right margin of the range of tolerance for baby rabbits (curve B_1 on Fig. 3).

The data presented in this article allow one to regard the range of doses within which the maintenance of homeostasis is possible as a criterion of resistance, and the range of doses within which reversible disturbance of homeostasis is observed, as a criterion of tolerance.

A criterion based on the comparative values of the lethal doses is not adequate to compare sensitivity and resistance, nor can it fully characterize the differences in the tolerance of the very young organism for pharmacological substances.

Relying on the criteria mentioned, we established that in the case of chloral hydrate, both the resistance and tolerance of baby rabbits are lower than those of adult rabbits. The range of chloral hydrate doses within which the condition of homeostasis is maintained in adult rabbits is considerably wider than the range of resistance for baby rabbits. Moreover, the right margin of the range of resistance for adult rabbits lies between doses much higher than the absolute lethal doses for baby rabbits.

When comparing the sensitivity, resistance and tolerance of an organism at various ages in relation to any pharmacological substance, one must differentiate between these concepts and study the physiological reactions to doses ranging from the threshold to the lethal; research as to the effect of doses and concentrations lying within the range of resistance is highest in practical importance, as the latter approximates the concept of the therapeutic range.

SUMMARY

An attempt was made to differentiate the concepts and criteria of sensitivity, resistance and tolerance of animals of different ages using the example of chloral hydrate action. The concept of sensitivity is very close to the physiological notion of excitability; the minimal dose which provokes primary reaction on definite tissues or organs, to which other formations fail to react, should be regarded as a sensitivity criterion. The range of doses within which animals of various ages respond by reactions of increased functional mobility of the nerve centers and by maintenance of homeostasis is taken as a resistance criterion. Tolerance is to be understood as a condition of disturbed homeostasis, reversible under the action of a definite range of doses, this range being regarded as a criterion of tolerance. The criterion based on contrasting lethal doses is not adequate to draw a comparison between sensitivity and resistance in animals of various ages to characterize their tolerance.

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