

## INCREASED SENSITIVITY OF TISSUES TO STIMULI IN AN AUTOTRANSPLANTED LIMB

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Changed reactivity of the tissues in an autotransplanted organ, especially in the first few months following the transplantation, can be apparent not only with respect to electric current stimulation (1) but also to chemical stimuli, including pharmacologic substances.

It is well known that denervated structures exhibit enhanced sensitivity to chemical stimuli. This is explained by lowering of the sensitivity threshold of denervated striated muscle to current as well as to adrenaline, acetylcholine, pilocarpine and other chemical substances [2] and also by metabolic disturbances and structural changes in proteins accompanying denervation of an organ [3].

The aim of the present investigation was to elucidate the degree and nature of altered reactivity of tissues in autotransplanted limb in dogs to administration of pharmacologic substances possessing different mechanisms of action; comparison was made of these changes in relation to different intervals of time following the operation\*.

### EXPERIMENTAL METHODS

Of substances with a cortical mechanism of action, sodium bromide, which enhances the inhibitory functions of the cortex, and caffeine, which increases the excitatory processes were tested. Acetylcholine and adrenaline were taken for comparative studies.

Sterile 5% solution of sodium bromide was given intravenously (10 mg per 1 kg body weight). Also intravenously was given a sterile 10% solution of caffeine, always in the amount of 3 ml for dogs weighing 12-15 kg.

Acetylcholine and adrenaline were administered subcutaneously: 0.015 g of the former and 2 ml of the latter in sterile physiologic solution 1:1,000.

The function of the transplanted limb was studied prior to administration of the substances and during 1½-2 hours following their administration.

In order to trace the dynamics of the action of a given substance on the motor nerves and muscles of the limb changes in the indicators were recorded at 5-7 minute intervals by means of chronaxie measurements.

The reactivity of the tissues of the autotransplanted limb was compared with the reactivity of the healthy limbs in the same dogs. Five experiments were carried out on each dog: 1 control, the rest with administration of adrenaline, caffeine, acetylcholine and bromide. Intervals between experiments were 6-7 days.

\*The operations were performed by N. P. Petrova of the Surgical Department.

The experiments were performed on 20 dogs, nine of which were operated (autotransplantation of the left hind limb), while the remainder constituted a control group of healthy dogs. Altogether 120 experiments were performed, with over 11,000 separate measurements of the rheobase and chronaxie for motor nerves and muscles of healthy and autotransplanted limbs in dogs.

## EXPERIMENTAL RESULTS

Introduction into the organism of pharmacologic substances exerted a general effect on the animals. Bromide, as a rule, produced drowsiness and sleep, with changes in the motor nerve and muscle rheobase and chronaxie. In experiments on healthy dogs administration of sodium bromide increased the rheobase in 47.2% of cases, in 32.6% the threshold of motor excitability changed within the limits of the original values and in 20.2% of cases it even showed a decrease. Motor nerve chronaxie was usually increased under the influence of bromide (84.6%).

Experiments with caffeine showed decrease of rheobase and increase of chronaxie of the motor nerves. Under the action of acetylcholine motor nerve rheobase and chronaxie were decreased  $1\frac{1}{2}$  times more frequently than in control experiments, while chronaxie was more often increased.

Changes in the rheobase and chronaxie of the limbs did not extend beyond the limits of normal. Rheobase changes were within the range of 1-30 v, chronaxie — 0.01-0.3  $\mu$ F. More frequent lowering of motor excitability threshold (rheobase) was characteristic for caffeine and adrenaline, while for bromide and acetylcholine more frequent increase in tissue chronaxie was characteristic.

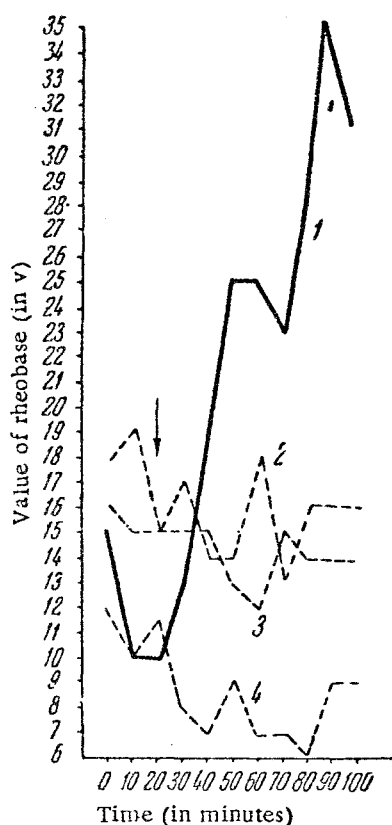


Fig. 1. Changes in limb muscle rheobase following administration of adrenaline; dog Orion.  
1) autotransplanted limb; 2), 3), 4) healthy limbs. Arrow indicates moment of adrenaline injection.

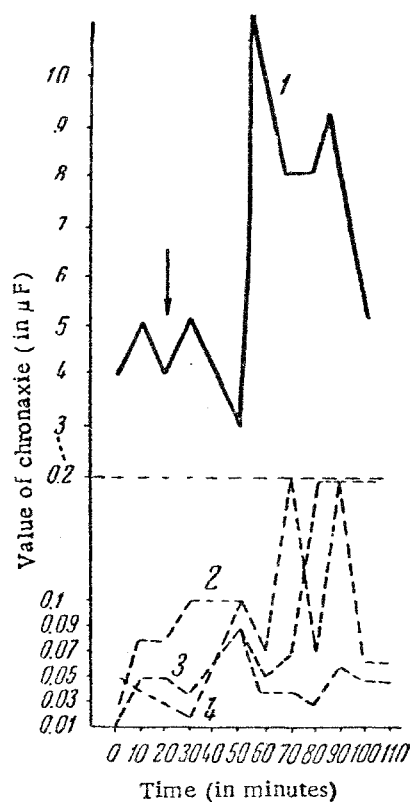


Fig. 2. Changes in limb muscle chronaxie following administration of adrenaline; dog Lisa.

Records similar to Fig. 1.

Greater sensitivity to pharmacologic substances was noted in autotransplanted limbs.

In the case of the dog Orion administration of pharmacologic substances 12-21 days postoperatively caused almost no changes in the rheobase and chronaxie of the healthy limbs. In the operated limb chronaxie of the denervated muscles increased from 5 to 8  $\mu$ F on introduction of bromide, and dropped from 7 to 4  $\mu$ F on introduction of caffeine. Acetylcholine increased the rheobase from 9 to 25 v and lowered the chronaxie from 7 to 3  $\mu$ F. Adrenaline produced a sharp increase in the devernated limb rheobase (Fig. 1).

In the case of the dog Lisa experiments were carried out 16-45 days following operation. Administration of bromide changed the rheobase of the healthy limbs from 22 to 15 v, of the operated limb - from 12 to 14 v. The muscle chronaxie of the healthy limbs showed a transient increase from 0.03-0.09 to 0.2 F; in the case of the operated limb it showed a persistent increase from 3 to 7  $\mu$ F. Caffeine produced a slight increase in the chronaxie of the healthy limbs and an increase from 4 to 7  $\mu$ F in the operated limb. Administration of acetylcholine produced no changes in the healthy limbs but decreased the chronaxie of the operated limb from 8 to 5  $\mu$ F. Particularly marked effect was exerted by adrenaline on denervated muscle: the already high chronaxie increased from 5 to 10  $\mu$ F following administration of adrenaline and continued to increase beyond the limits of its determination (Fig. 2).

In the dog Druzhok administration of caffeine did not alter the rheobase but decreased the chronaxie of the denervated muscles from 9 to 3  $\mu$ F, while administration of adrenaline raised it from 3 to 7  $\mu$ F; the chronaxie of the healthy limbs changed at the same time within the limits of original values. In the dog Seraya, 1 $\frac{1}{2}$  months after operation acetylcholine and adrenaline injections caused increases of the rheobase of the transplanted limb from 20 to 65 v and increase of muscle chronaxie from 4 to 10  $\mu$ F and higher. No such reactions of the left hind limb muscles were observed in these dogs prior to autotransplantation.

Such heightened reactivity of transplanted limbs is rarely encountered at later periods of the graft's "taking".

Tissue Sensitivity in Healthy and Autotransplanted Hind Limbs in Dogs to Pharmacologic Agents (Average Data) in Percentage of Original Values

Pharmacologic Agent	Rheobase in V		Chronaxie in $\mu$ F	
	healthy limb	Autotrans-planted limb	healthy limb	autotrans-planted limb
Bromide	230	250	100	600
Caffeine	65	45	100	100
Acetylcholine	200	175	70	600
Adrenaline	20	250	100	210

The dogs Silva and Lisa showed, 8 months postoperatively identical reactions to administration of bromide, caffeine, acetylcholine and adrenaline in the transplanted and healthy limbs. The dog Belyi, however, showed increased reaction to these substances after a similar interval.

The table gives average values for maximal tissue reaction to pharmacologic substances as percentages of values obtained from the same limb prior to administration of these. Judging by the rheobase, for example, tissue reactivity in the transplanted limb to adrenaline is 12 times greater than in the symmetrical healthy limb.

Chronaxie values indicate that the reactivity of the tissues in the transplanted limb to bromide and acetylcholine is increased 6 times compared with the healthy limb.

Thus increased, and at times altered, reactivity of tissues in autotransplanted limbs to adrenaline, acetylcholine, caffeine and bromide has been established. This heightened tissue reaction subsides as innervation is restored.

#### SUMMARY

120 experiments were made on 20 dogs to study the effect of adrenalin, acetylcholine, caffeine and sodium bromide (subcutaneous and intravenous) on the rheobase and chronaxie of motor nerves and muscles in healthy and autotransplanted limbs. The sensibility of denervated tissues towards the mentioned agents was shown to be increased and of a different nature; it decreased as the tissues' innervation recovered.

#### LITERATURE CITED

[1] B. Cannon and A. Rosenblueth, Increased Sensitivity of Denervated Structures. The Law of Denervation\* Moscow, 1951.

[2] Kh. S. Koshtoyants, Proteins, Metabolism and Nervous Regulation\*. Moscow, 1951.

\* In Russian.