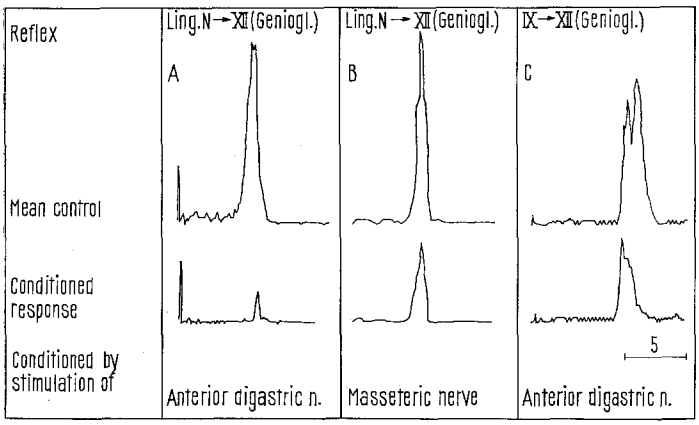

Fig. 1. Effect of electrical stimulation of trigeminal proprioceptive afferents on reflexes to the protruder of the tongue (genioglossus). Reflexes were elicited by single test stimuli to the lingual nerve (A, B) or the glossopharyngeal nerve (C), and recorded from the proximal portion of the severed hypoglossal branch to the ipsilateral genioglossus muscle. The computer-determined 'mean control' reflexes are shown in the upper part of the figure. If conditioning stimulation to ipsilateral trigeminal proprioceptive afferents in the anterior digastric nerve (A, C) or the masseteric nerve (B) preceded the test stimulus by the optimal conditioning-test interval of 15 msec, the reflexes were considerably depressed ('conditioned responses'; lower part of figure). Each tracing was computed from 50 individual responses. Time calibration: 5 msec.

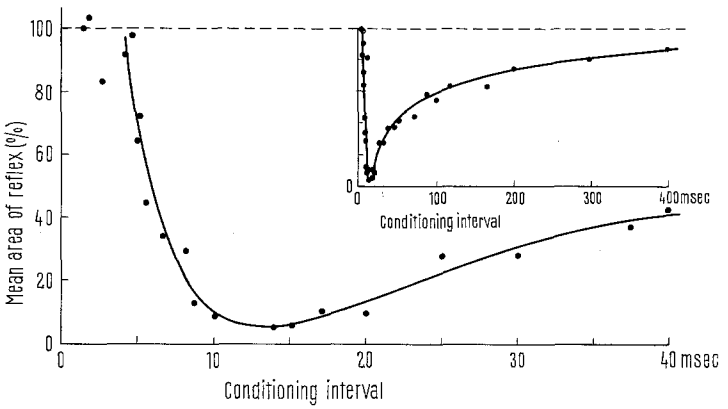

Fig. 2. Time course of reflex inhibition showing the effect of electrical stimulation of trigeminal proprioceptive afferents on reflexes to the genioglossus. Reflexes were elicited by single test stimuli to the lingual nerve and recorded from the hypoglossal branch to the ipsilateral genioglossus. Conditioning stimulation was applied to the ipsilateral anterior digastric nerve. Each point on the curve was computed from 50 individual responses. The smaller inset illustrates the remarkable duration of the inhibitory phase (400 msec or longer).

afferent activities in proprioceptive fibers are responsible for the observed inhibitory effect. This view is supported by the fact that natural stimulation of proprioceptors in the masseter or anterior digastric muscle produced identical effects as did electrical stimulation of the nerves of these muscles[3]. The remarkable duration of the time course of reflex depression suggest the involvement of a presynaptic inhibitory mechanism. There is experimental evidence that such a mechanism exerts its influence on the central endings of primary sensory neurons in cranial nerves. SAUERLAND and THIELE[3] demonstrated that activation of trigeminal proprioceptive afferents leads to presynaptic depolarization of lingual and glossopharyngeal nerve terminals.

Proprioceptors in the masseter (jaw closer) and anterior digastric muscle (jaw opener) are activated during mastication. Afferent activities from both muscles produce one and the same effect: a remarkable and long-lasting reduction of the reflex activity to the protruder of the tongue, i.e. a decrease in protrusive tongue action. This phenomenon constitutes a very effective protective mechanism for the anterior portion of the tongue during masticatory activity. It appears that this protective mechanism already commences during the opening phase of the mouth[4].

Zusammenfassung. Die Reflexaktivität des Protrudors der Zunge (M. genioglossus) wurde durch die Aktivierung propriozeptischer afferenter Fasern im N. trigeminus bedeutend herabgesetzt. Polysynaptische Reflexe zum M. genioglossus wurden entweder durch Reizung des N. lingualis oder des N. glossopharyngicus ausgelöst. Bedingende elektrische Reizung der Nerven verschiedener Kaumuskeln induzierte eine bis zu 500 msec andauernde Hemmung dieser Reflexe.

E. K. SAUERLAND and N. MIZUNO

Departments of Anatomy and Oral Medicine and the Brain Research Institute, Center for Health Sciences, University of California at Los Angeles, Los Angeles (California 90024, USA), 29 April 1970.

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[4] This research was supported by grants No. NS 06819-04 and No. MH 10083 from the United States Public Health Service. The authors are indebted to the UCLA Brain Research Institute for the use of the computer facilities. Dr. Mizuno's present address: Department of Anatomy, School of Dentistry, Hiroshima University, Hiroshima City, Japan.

Exercise, Blood Lactate and Food Intake

In man and other animals bouts of exercise are followed by a period of hypophagia which is succeeded by the restoration of energy balance within 1 to 2 days[1,2]. During exercize blood concentrations of lactate increase from a normal of 0.5–1.0 m*M* up to 15 m*M*[3], and we have shown that a 30-min i.v. injection of L-lactate (1.3–1.5 mmoles/kg) into monkeys, causing a maximum blood lactate concentration of 2.5 m*M*, decreased their food intake about 40% during subsequent feeding[4]. Since the lactate levels quickly returned to normal, the hypophagia appears to be a

residual effect. The present study was designed to test the possible influence of exercise and/or lactate on the metabolism of the medial hypothalamus as a possible explanation for the sustained depression of food intake. We theorized that an increase in blood lactate levels produced by severe exercize or injection of lactate causes the release of a factor which increases the glucose metabolism rate and activity of the ventromedial area of the hypothalamus (VMH) for several hours.

The action of gold thioglucose (GTG) in producing lesions in the VMH is closely related to the rate of glucose metabolism[5,6]. Mice made diabetic with alloxan do not develop VMH lesions after GTG injections unless also given insulin[7], and insulin-insensitive but hyperglycemic and hyperinsulinemic obob Bar Harbor mice are much less sensitive to the VMH effect of GTG[5]. Consequently, to measure the rate of glucose metabolism, a histological determination of the lesioning effect of GTG on the VMH of mice was made.

To test the effect of exercize on medial hypothalamic metabolism, alloxan-diabetic mice (65 mg/kg i.v.) were run on a treadmill at rates of 12 to 16 m/min for 60 min. Group 2 was run 15 min, injected i.p. with 0.8 mg/g GTG, and run another 45 min. Three groups of mice, 3, 4, and 5, were trained by running 60 min for 5 to 7 days. On the last day of training Group 3 was injected with GTG after 15 min of the 60-min exercize period; Groups 4 and 5 were injected 2 and 4 h after exercize, respectively. All mice were shown to have glucosuria and hyperglycemia. The brains were removed 1 to 3 days after GTG injection for histological preparation[5].

As shown in the Table, exercize increased the frequency of lesions from 0 to 60% in untrained diabetic mice. The

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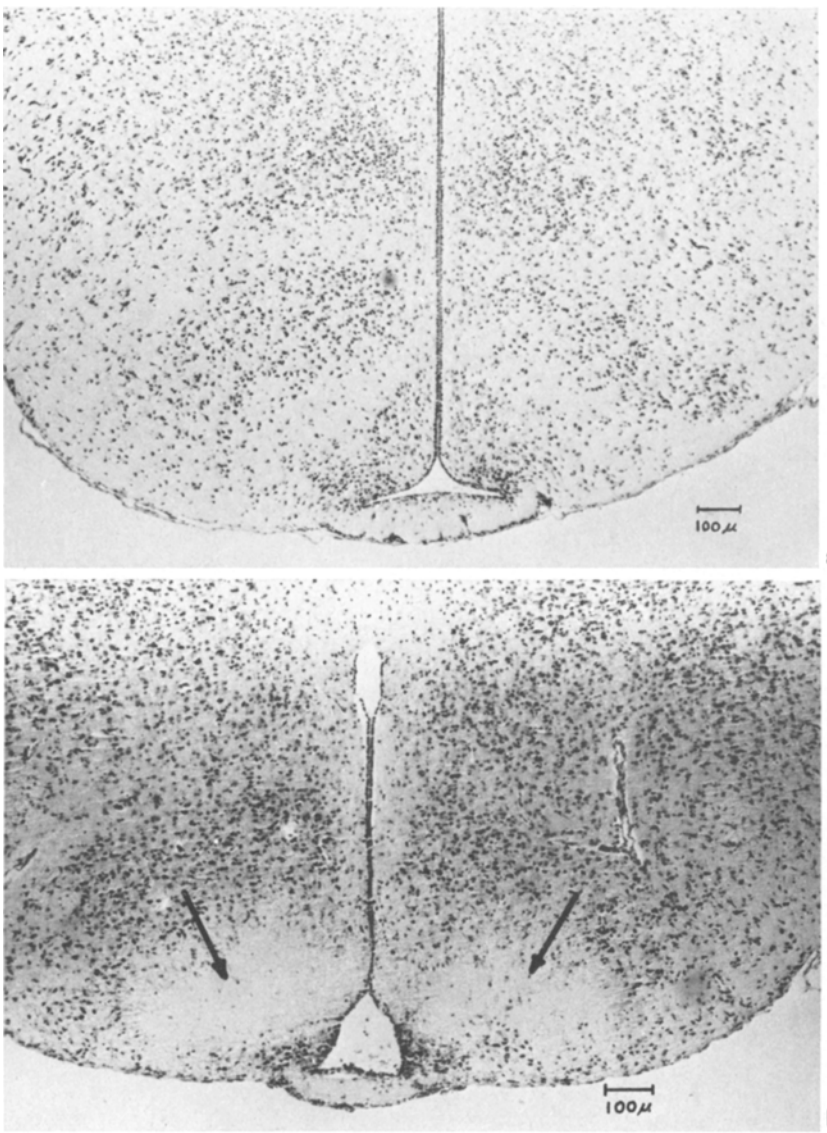

Photomicrographs of the hypothalamus of diabetic mice injected i.p. with 0.8 mg/g body weight of goldthioglucose. A) Showing no lesion, is from a mouse in Group 1. and B) showing severe bilateral lesions is from a mouse in Group 9.

size of the lesions varied from small to complete VMH ablation. The low incidence of lesions in Group 3 may be related to an increased ability to metabolize the lactate due to training. In the Figure are photomicrographs of the VMH of the brain of diabetic mice, one exercized and the other not exercized. It should be noted that none of the unexercized mice (Group 1) developed VMH lesions following GTG injection, while 15 of 24 normal mice given doses of only 0.3 mg/g body weight developed lesions.

In a second experiment untrained diabetic mice (Group 6) were injected i.p. with 2.5 μmoles/g of Na lactate (pH = 7.34) and 30 min later with 0.8 mg/g GTG. Groups 7, 8, 9 and 10 were trained as described above and on the day following the training period were first injected with 2.5 μmoles/g of Na lactate and then 0.8 mg/g GTG 0.5, 2, 4 and 8 h later, respectively. These mice also developed lesions in the VMH, even up to 8 h after lactate injection (Table). Sodium propionate, 2.5 μmoles/g (pH = 7.34), was not effective in mediating the GTG lesions of the VMH of diabetic mice.

The results of the above experiment are evidence that the metabolism of the VMH of the diabetic mice following exercize or injection of lactate was changed in a manner similar to that of a diabetic mouse given insulin. Although we have no evidence that there is a relationship to these experiments, it is interesting that a factor released by muscle during exercize has insulin-like activity on glucose metabolism on various tissues including the brain (8, 9, 10). It is especially relevant that such a factor has been found in the urine of trained rats up to 12 h after the session of exercize[8]. It may be that this factor or one with similar properties is released by increased plasma levels of lactate and has insulin-like activity on the VMH which increases the metabolic and presumably the firing rate. Since it is a long-acting factor, it may cause a sustained hypophagia through the suppression of the lateral hypothalamic area activity by the increased VMH activity.

The importance of exercize in the treatment of diabetes has long been stressed[11]. Our experiments suggest that, in addition to the improvement of glucose utilization generally observed, exercize may also be beneficial in controlling the development of obesity not only by increasing energy expenditure but also by preventing excessive food intake[12].

Zusammenfassung. Erhöhte Lactatmengen im Plasma können während körperlicher Anstrengung die Freisetzung eines Stoffes verursachen, welcher, ähnlich wie Insulin, im mittleren Hypothalamus wirkt. Dieser Stoff könnte auch an der Auslösung der Hypophagie, welche nach körperlicher Anstrengung auftritt, beteiligt sein.

C. A. Baile, W. Zinn
and Carol McLaughlin

Department of Nutrition, Harvard School of Public Health, Boston (Massachusetts 02115, USA), 3 July 1970.

The effect of exercize or lactate on the lesioning of the ventromedial hypothalamus by goldthioglucose (GTG) in mice made diabetic with alloxan

Group	*n*	Blood glucose (mg/100 ml)[a]	Condition	GTG injection time After exercize (min)	After lactate[b] (min)	Lesions (%)
1	9	398 ± 91	U[c]	N[e]		0
2	5	514 ± 33	U	0		60
3	11	477 ± 37	T[d]	0		18
4	5	534 ± 98	T	120		60
5	5	531 ± 27	T	240		0
6	5	411 ± 50	U		30	40
7	5	487 ± 55	T		30	40
8	5	437 ± 55	T		120	40
9	5	397 ± 20	T		240	80
10	5	558 ± 128	T		480	40

[a] Day of injection. [b] 2.5 μmoles/g body weight. [c] Untrained. [d] Trained. [e] Not exercized or injected with lactate.

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[12] This work was supported, in part, by grants-in-aid from the National Institute of Neurological Diseases and Blindness No. NB-01941, National Institute of Arthritis and Metabolic Diseases No. AM-02911 and the Fund for Research and Teaching, Department of Nutrition, Harvard School of Public Health.

Physiologic and Pharmacologic Responses of Mammalian Vascular Smooth Muscles During Electric Field Stimulation

Previous studies[1-4] have shown that brief pulses of 60 Hz alternating current field stimulation (AC) cause contraction of various types of isolated smooth muscle. A portion of the response in vascular smooth muscle appears to be due to the release of endogenous catecholamines, principally norepinephrine[1,5]. We will demonstrate that essentially steady-state levels of contraction can be achieved during continuous AC stimulation, and that voltage-response curves can thus be generated. These curves are depressed by 'direct' smooth muscle relaxants, by an alpha-adrenergic blocking agent, and by ultra-violet radiation, which is known to reduce active tone[6]. Evidence will be presented that the non-catecholamine mediated portion of the AC response is due to stimulation of the excitable membrane, and perhaps to direct activation of the excitation-contraction coupling mechanisms.

Materials and methods. Spiral strips of aorta from rabbits killed by cervical concussion were suspended under a tension of approximately 3 g in a constant temperature bath, according to established methodology[7]. The bathing medium was Krebs bicarbonate solution