CHANGES IN THE CONDITIONED REFLEX ACTIVITY OF DOGS DURING PROLONGED FEEDING WITH CHOLESTEROL AND METHYLTHIOURACIL

N. Kudryavtseva, T. Lovyagina, and T. Sinitsina

I. P. Pavlov Physiological Division and Division of Pathological Anatomy, Institute of Experimental Medicine (Director, Active Member AMN SSSR Professor D. A. Biryukov) of the AMN SSSR, Leningrad
(Presented by Active Member AMN SSSR P. S. Kupalov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 53, No. 4, pp. 46-49, April, 1962
Original article submitted April 4, 1961

This investigation marks the beginning of research into the changes occurring in the higher nervous activity of dogs in the process of development of experimental atherosclerosis of the blood vessels of the brain.

The method now used to produce experimental atherosclerosis in dogs is that proposed by N. N. Anichkov and T. A. Sinitsina [2], which is a modification of the method introduced by Steiner, Kendall, and Bevans [5]. In the Soviet modification the animals are fed simultaneously on a solution of cholesterol in sunflower oil and on methylthiouracil without the preliminary "thiouracil" period.

The aim of the present investigation was to study the higher nervous activity of dogs during simultaneous feeding with cholesterol and methylthiouracil. In addition we attempted to differentiate between the changes in conditioned reflex activity observed when the experiment was carried out in this manner and those found during administration of thiouracil preparations.

EXPERIMENTAL METHOD

Experiments were conducted on 3 dogs. By the character of their nervous processes, all the dogs were regarded as possessing a strong variant of the weak type of nervous system, with predominance of excitation. The work was carried out in a soundproof chamber. The secretion was recorded by means of a Ganicke-Kupalov hydropneumatic system. Each scale division corresponded to 0.1 ml of saliva. The unconditioned reinforcement consisted of 20 g of powdered meat and biscuit, mixed with water in the ratio of 1:1.

A system of conditioned reflexes was established in the dogs, as follows: positive conditioned reflexes to a metronome giving 138 beats per minute, a gurgle, and the light of a 60 w electric lamp. and an inhibitory conditioned reflex to a metronome giving 60 beats per minute. The stimuli were applied every 4 minutes and, as a rule, in a definite order. At the beginning of the experiment each dog received daily 30 g of a 30% solution of cholesterol in sunflower oil, and 1 g of methylthiouracil mixed with boiled meat (about 40 g). The dogs ate the food offered to them eagerly.

EXPERIMENTAL RESULTS

The changes in conditioned reflex activity in the experiments to produce atherosclerosis are indicated in Table 1.

It was found experimentally that on the 22nd day after the beginning of feeding with these substances the animals first showed signs of refusing to eat during the experiment. Subsequently (on the 27th day) the level of the dog's conditioned reflex activity fell sharply (see Table 1, Expt. No. 134).

Comparison of the control and experimental data (see Table 1) shows that the positive conditioned reflexes were greatly decreased: their total secretion before feeding on cholesterol and methylthiouracil was 99 scale divisions, and on the 27th day after the beginning of feeding it was 21 divisions. Successive inhibition was considerably increased, as shown by a sharp fall in the conditioned reflexes after the inhibitory stimulus (to the metronome-3 divisions, to the gurgle—0).

The appearance of phases of activity was frequently observed, and differentiation was considerably disinhibited. These findings indicated a disturbance of the animal's higher nervous activity.

TABLE 1. State of the Higher Nervous Activity of the Dog Naida

Serial no. of application of conditioned stimuli	Conditioned stimulus	Period of isolated action of conditioned stimuli (in seconds)	Period of delay of conditioned reflexes (in seconds)	Course of conditioned secretion in scale divisions per 15 seconds (recorded every 5 seconds)	Magnitude of conditioned reflex	Unconditioned secretion per minute
			Before beginning of experiment (Expt. No. 126)			
269	Metronome	30	4	1+7+5+3+5+3	24	160
138	Light	30	3	2+5+3+4+4+4	22	150
178	Gurgle	30	3	2+5+3+3+4+4	21	155
85	Metronome (-)	30	3	2+3+2+0+1+1	9	–
270	Metronome (+)	30	4	1+2+3+2+3+5	16	170
179	Gurgle	30	3	3+3+2+2+3+3	16	165
			During experiment (Expt. No. 134)			
285	Metronome (+)	30	14	0+0+1+1+3+2	7	140
141	Light	30	7	0+1+2+1+2+1	7	140
194	Gurgle	30	13	0+0+1+2+0+1	4	135
93	Metronome (-)	30	4	1+2+3+0+0+0	6	–
236	Metronome (+)	30	–	0+1+2+0+0+0	3	160
195	Gurgle	30	–	0+0+0+0+0+0	0	145

Legend: + corresponds to a positive stimulus, - to an inhibitory. The same legend applies to Tables 2 and 3.

TABLE 2. Conditioned Reflex Activity of the Dog Naida in the Period of Highest Serum Cholesterol Concentration (1780 mg %)

Serial no. of application of conditioned stimuli	Conditioned stimulus	Period of isolated action of conditioned stimuli (in seconds)	Period of delay of conditioned reflexes (in seconds)	Course of conditioned secretion in scale divisions per 15 seconds (recorded every 5 seconds)	Magnitude of conditioned reflex	Unconditioned secretion per minute
442	Metronome (+)	30	6	0+2+2+1+2+2	9	165
302	Light	30	4	1+1+1+2+5+5	15	160
434	Gurgle	30	5	0+1+2+2+2+2	9	155
218	Metronome (-)	30	–	1+1+1+1+1+1	6	–
443	Metronome (+)	30	–	0+0+0+0+0+0	0	140

One month after the beginning of feeding with cholesterol and methylthiouracil the dog had gained 1.8 kg, and after 8 months 4 kg, and this weight gain was maintained until the end of the investigations.

The period of feeding with these substances continued for 22 months, and throughout this time the serum cholesterol concentration was 204 mg %, and after 7, 10, 14, and 22 months the corresponding figures were 210, 336, 382, and 1780 mg %. Thus the serum cholesterol rose gradually for 14 months and was not very high, but at the end of the experimental period the blood cholesterol concentration increased sharply (to $8\frac{1}{2}$ times its original level).

During the period of the highest blood cholesterol concentration the dog's conditioned reflex activity was unchanged from that in the initial period of feeding with cholesterol and methylthiouracil (see Table 1, Expt. No. 134). It was characterized by a changeable level of conditioned reflexes, phases, disinhibition of differentiation, considerable successive inhibition, and frequent refusals to eat during the experiment. Table 2 shows that the positive conditioned reflexes were much below their original level (see Table 1, Expt. No. 126), and that successive inhibition was well marked. The unconditioned reflexes underwent no significant change in the course of the experimental period.

TABLE 3. Changes in the Conditioned Reflex Activity of the Dog Trezor under the Influence of Methylthiouracil

Conditioned stimulus	Magnitude of conditioned reflexes (in scale divisions)	
	Before taking methylthiouracil	After taking methylthiouracil
Metronome (+)	28	7
Bell	18	11
Light	30	6
Metronome (-)	7	12
Metronome (+)	18	0
Bell	18	3

Similar changes in conditioned reflex activity were also observed in another dog (Fantik), on which similar experiments were conducted.

The third dog (Trezor), after the establishment of a definite background of conditioned reflexes, received 1 g methylthiouracil alone for 4 months, the same dose as the previous animals. The changes in the higher nervous activity of the dog Trezor were very similar to those described above, although this dog did not receive cholesterol (Table 3).

In the work to which reference has already been made, V. I. Gunin [1] and, later, D. S. Tendler [3] and others showed that prolonged feeding of dogs with methylthiouracil or its derivatives causes severe disturbances of conditioned reflex activity—a decrease in positive reflexes, phase phenomena, disinhibition of differentiation, successive inhibition, and so on; these dogs gained in weight. These workers showed histologically that changes of the colloid goiter type take place in the thyroid gland. These changes accounted for the modification of the higher nervous activity.

It may be assumed from the findings cited above that the change in the higher nervous activity which we observed during the period of prolonged feeding of the dogs with cholesterol and methylthiouracil, and also the increase in weight of the animals, were associated with the modification of thyroid function by methylthiouracil. It does not therefore seem possible to study the changes in higher nervous activity of dogs in the initial period of development of atherosclerosis of the cerebral vessels when produced in this manner, for all the abnormalities are masked by disturbances resulting from changes in the thyroid function.

Postmortem examination of the dog Naida showed severe atherosclerotic changes in the coronary arteries. Plaques were also found in the aorta and the renal, femoral, and superior mesenteric arteries. No atherosclerotic plaques were found in the arteris of the brain. In the dog Fantik, in spite of the considerable hypercholesteremia (520 mg %), atherosclerotic plaques were absent and only a permeation of the vascular walls with lipids was observed.

In all three dogs the thyroid gland showed considerable changes of the colloid goiter type, indicating hypofunction of the gland.

We thus conclude from the data in the literature and from our own experimental findings that the changes in the higher nervous activity of dogs fed simultaneously with cholesterol and methylthiouracil are primarily the result of hypofunction of the thyroid gland.

SUMMARY

Changes in the higher nervous activity of dogs fed cholesterol and methylthiouracil simultaneously for a prolonged period of time occur mainly at the expense of the thyroid hyperfunction.

Therefore, it was impossible to trace the changes in the reflex activity of dogs at the initial period of experimental induction of the atherosclerosis of the brain vessels with the aid of the method involving a simultaneous cholesterol and methylthiouracil feeding because all the deviations were masked by disturbances occurring at the expense of thyroid hyperfunction.

LITERATURE CITED

1. V. I. Gunin, Abstracts of Proceedings of the Second Conference of Students' Scientific Societies of Medical, Pharmaceutical, and Stomatological Institutes [in Russian], Moscow (1952), p. 13.
2. T. A. Sinitsina, In: Annual Report of the Institute of Experimental Medicine of the AMN SSSR [in Russian], Leningrad (1958), p. 383.
3. D. S. Tendler, The Effect of Methylthiouracil and Functional Disturbances of the Thyroid Gland Caused by its Use on Extero- and Interoceptive Conditioned Reflexes. Author's abstract of candidate dissertation [in Russian], Leningrad (1952).
4. S. Neuschlosz, Biochem. Z. (1930), Bd. 225, S. 115.
5. A. Steiner, F. Kendall, and M. Bevans, Am. Heart J. (1949), Vol. 38, p. 34.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
