EFFECT OF SOME NEUROTROPIC SUBSTANCES ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS*

I. K. Shkhvatsabaya

From the Institute of Therapeutics (Director: Prof. A. L. Myasnikov, Member Acad. Med. Sci. USSR), Acad. Med. Sci. USSR, Moscow.

(Received June 7, 1955. Presented by A. L. Myasnikov, Member Acad. Med. Sci. USSR)

The present paper described the results of a study of the effects of changes in the functional state of the central nervous system, caused by the action of neurotropic drugs, on alimentary cholesterolemia and on the evolution of experimental atherosclerosis in rabbits.

We have been able to find only scanty references to this problem in the literature. Of these, Yu. T. Pushkar's report [2] is of interest; he found that luminal retards the development of cholesterol atherosclerosis, and that phenocoll strongly intensifies lipid infiltration of blood vessels, and enhances blood cholesterol levels.

Langen [4] found that administration of barbiturates (veronal, luminal) in various doses to rabbits led to pronounced lipemia and to high blood cholesterol values, in both chronic and acute experiments.

T. D. Tsibekmakher's clinical observations [3] point to lowering of blood cholesterol after administration of luminal, whereas phenocoll had the opposite effect; these effects were observed after single doses of the drugs.

We have studied the effects of caffeine, chloral hydrate, and amytal on alimentary cholesterolemia and on development of lipoidosis of blood vessels in rabbits with cholesterol atherosclerosis induced by the method of N. N. Anichkov [1]. In some of our experiments we made systematic observations of the dynamics of blood pressure changes in the carotid artery, which was partly exteriorized, to a skin flap for the purpose.

EXPERIMENTAL METHODS

Four series of experiments were performed on sexually mature rabbits of the same age, weighing 2.5 to 3 kg. The experiments lasted for 97-100 days, during which time the rabbits received daily doses of 0.2 g of cholesterol per kg body weight.

The first (control) group consisted of 9 rabbits, receiving cholesterol only. The second group of 5 rabbits received, additionally, daily subcutaneous doses of 0.1 g of caffeine for 80 days (injections began on the first day of the experiment, and were interrupted for 5 days after every 20 days). Caffeine, in contrast to phenocoll, has no depressive action on the central nervous system when used for prolonged periods.

The third group (5 rabbits) were given 40-60 daily doses of 0.1 g of chloral hydrate beginning on the 20th day of cholesterol feeding, and with breaks of 5 days after every 10-15 days of chloral hydrate administration. This dosage of chloral hydrate caused no marked soporific effects.

*Presented at the 6th Annual Scientific Meeting of the Institute of Therapeutics, Acad. Med. Sci. USSR, January 28, 1955.

The fourth group (5 rabbits) were given 40 subcutaneous injections of amytal beginning with the 18th day of cholesterol feeding (at a dosage level of 0.035 g of amytal per kg body weight; a break of 4-5 days was made after every 5 days of amytal injection); these dosage levels caused prolonged and sustained sleep, without toxic effects.

Changes in the nervous activity of animals of the fourth group due to the action of amytal were followed by the conditioned defensive reflex method, as applied in A. A. Volokhov's and A. D. Speransky's laboratories.

Blood cholesterol was determined every 15-18 days for all animals, by Grigaud's method. The animals were killed by air embolism at the end of the experimental period, and were autopsied. The aortas were removed, and stained with Sudan, by the method of V. D. Tsinzerling.

EXPERIMENTAL RESULTS

Group I (control). Blood cholesterol values varied widely for different animals, from 450-550 mg-% for some to 800-900 mg-% for others. High values were achieved by the 30-45th day of cholesterol feeding.

Blood pressure remained fairly steady throughout the experiments, varying withing the limits 100-120 mm. Atheromatous changes were well marked in most of the animals.

Group II (cholesterol + caffeine). The blood cholesterol levels found in this group did not differ greatly from those of the control group. There was, nevertheless, a certain tendency toward lower values (500-550 mg-% in 3, and 290-320 mg-% in 2, rabbits, at the end of the experiment). Caffeine had a slight hypotensive action; the fluctuations in blood pressure in this group were wider than for the control and other groups.

The animals of Groups I and II became progressively more active, irritable, and at times aggressive, as cholesterol feeding continued. These changes were more pronounced in caffeinized rabbits, who also showed considerable tenseness of body muscles, with occasional slight tremor of particular muscle groups.

Atheromatous changes in this group were somewhat less pronounced than in Group I, and lipoid infiltration of blood vessels was less massive and extensive.

TABLE

Degree of Lipoidosis in Rabbit Aortas

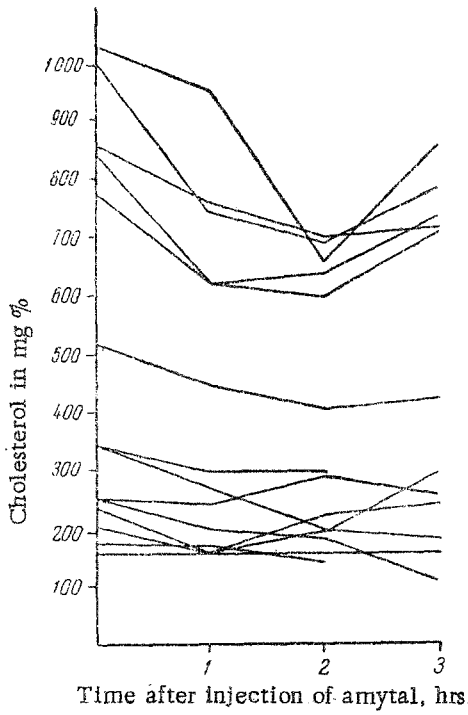
Control group		Experimental groups					
		cholesterol + caffeine		cholesterol + chloral hydrate		cholesterol + amytal	
No. of rabbit	degree of lipoidosis	no. of rabbit	degree of lipoidosis	no. of rabbit	degree of lipoidosis	no. of rabbit	degree of lipoidosis
4	++	1	+	6	+	20	+
13	+++	2	++	8	+	4	+
14	++++	3	+++	12	++	22	++
15	++++	7	++++	17	—	23	+
18	+++	10	+++	—	—	24	—
19	++++						
26	++++						
27	++						
32	+						

Group III (cholesterol + chloral hydrate). Only relatively small elevations in blood cholesterol (250-300 mg-%) were found in this group, and the variations were inconsiderable. In one rabbit only was a sudden rise observed, at the end of the experiment (from 300 mg-% to 600 mg-%).

Blood pressure fell gradually, without any violent fluctuations. The animals became progressively more inactive and indifferent to handling during feeding, blood sampling, etc. At the given dosage, chloral hydrate did not appear to exert any soporific action.

Only small atheromatous changes were found in the aortas of the animals of this group, and the degree of lipoidosis was also small (+, ++). Atheromatous plaques were found chiefly in the ascending part of the aorta.

Group IV (Cholesterol and Amytal). This group is of particular interest. Sleep supervened 10-30 minutes after the injections, and was fairly profound, lasting for 2.5-5 hours. It was noticed that, beginning with the 20-30th day of administration of amytal its action became much more rapid, sleep following 5-10 minutes after the injection. Considerable behavior changes were seen beginning with the 15-20th day of administration; the animals became drowsy and inactive, and were only half awake for most of the time.



Fluctuations in blood cholesterol after injection with amytal depending on the initial cholesterol content of the blood of different rabbits.

Conditioned reflex activity was followed in all the 5 rabbits of this group throughout the experiment. Distinct and relatively stable conditioned reflexes were elaborated after 15-20 associations, which is the usual number, and we proceeded to elaborate differentiation after 25 associations.

The animals of this group had low blood cholesterol values, the levels for two of them (Nos. 23 and 24) being practically the same at the end as at the beginning of the experiment (60-75 mg-%); there was a moderate fall in blood pressure, and the changes in the aorta were insignificant. These animals gave clearcut conditioned reflex responses.

Rabbit No. 21, which suffered from an intensely irritated skin condition, had very high blood cholesterol values (up to 1020 mg-%), and parallel changes in blood pressure were observed (from 50-75 to 120-125 mm). However, towards the end of the experiment blood cholesterol began gradually to fall, to a final value of 480 mg-%; this coincided with a pronounced alleviation of the irritation. Aortal changes were only slight in this animal (+), as in the other rabbits of this group (see Table).

We also performed 14 acute experiments on changes in blood cholesterol and blood pressure 1, 2, and 3 hours after a single injection with amytal. Rabbits which had initially a high blood cholesterol content showed a distinct and considerable fall in this value, by over 30% of the initial level, by the second hour, as a rule. With lower initial blood cholesterol the effect was much smaller, and in some cases there was even a slight rise. Hypotensive action was manifested mostly in rabbits which had high initial blood pressures (see Figure).

DISCUSSION OF RESULTS

Our findings provide incontrovertible evidence of the effect of neurotropic drugs, which modify the functional state of cortical and subcortical formations, on alimentary hypercholesterolemia and on lipoid infiltration of arteries.

The intensity of the latter condition is not critically dependent on the blood cholesterol content, although a certain parallellism is to be seen in particular animals whose blood cholesterol fluctuates widely in either direction; no correlation can be seen for rabbits with an average blood cholesterol content, and the same applies, to a lesser degree, to blood pressure variations.

Administration of caffeine causes only insignificant lowering of alimentary hypercholesterolemia, as compared with the controls, and only slightly reduces lipoidosis of the arterial walls.

Prolonged barbiturate sleep, and, to a smaller degree, sedative doses of chloral hydrate, bring about a considerable lowering of alimentary hypercholesterolemia, and prevent or reduce the intensity of aortic lipoidosis.

A single dose of amytal causes lowering of blood cholesterol and blood pressure in hypercholesterolemic animals; the magnitude of the effect depends on the initial values, being more pronounced in animals with high blood pressure and cholesterol content.

LITERATURE CITED

[1] N. N. Anichkov, and V. D. Tsinzerling, Atherosclerosis (In Russian) (Moscow, 1953) pp. 7-18.

[2] Yu. T. Pushkar, ibid., pp 121-127.

[3] T. D. Tsibikmakher, ibid., pp 148-149.

[4] C. D. De Langen, Acta med. Scand., 97, 427-439 (1938).