THE EFFECT OF ADRENALIN AND SYMPATHOMIMETIC AMINES (EPHEDRINE, AMPHETAMINE) ON BILE SECRETION OF THE LIVER

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The present investigation was undertaken in order to establish the character and special features of the effect of adrenalin, ephedrine and amphetamine on the processes of bile secretion and formation in the liver of cholates as the main component of bile.

The question of the effect of adrenalin on the secretory function of the liver has been studied by many authors [1, 4, etc.] but some of its aspects have remained unsolved. Moreover, the effect of sympathomimetic amines – noradrenalin, neoepinephrine, neosynephrine, ephedrine, amphetamine, etc. – on the bile secreting and bile excreting processes has not been described in the literature. Such data, particularly a comparative study of the action of the substances mentioned on the secretion of bile are necessary for the elucidation of the role of hyperglycemia in this process, of the role of adrenergic systems in tissues, the significance of the state of the central nervous system, etc.

The choice of substances for the present investigation was based on the fact that adrenalin was distinguished by a very strong effect on the adrenergic systems of organs and tissues of the body and produced appreciable hyperglycemia, whereas ephedrine and amphetamine caused excitation of the central nervous system (particularly amphetamine) with less marked peripheral effect. Comparison of these pharmacodynamic features in the substances mentioned with the results obtained in our experiments permitted a new interpretation of some aspects of the problem of the physiology of the secretory function of the liver.

EXPERIMENTAL METHODS

Long-term experiments were performed on five dogs with permanent Schwann fistulas of the gallbladder. Attention was paid not only to the intensity of the secretory process but also to the chemical composition of the bile: each hourly specimen of bile was subjected to photometric determination of the cholate concentration by the Shire-Kuni method and of bilirubin by the Van den Bergh method. The amount of bile secreted was noted every 30 minutes over a period of four hours. In order to avoid any possible gastrointestinal influences on bile secretion during digestion all the experiments were conducted in the fasting state. Systematic parallel determinations of blood sugar levels were made by the Hagedorn-Jensen method. A total of over 90 experiments was carried out.

EXPERIMENTAL RESULTS

Adrenalin. As can be seen from the table, there is a marked decrease in the total amount of bile under the influence of 0.05 mg/kg adrenalin given subcutaneously or intravenously (average decrease by 42.4-26.2% in the dog Lokhmatyi, by 6.8% in the dog Tsezar and by 15.5% in the dog Dunai). In isolated experiments the decrease of bile secretion was even more marked. It must be emphasized that in the majority of experiments the diminu-

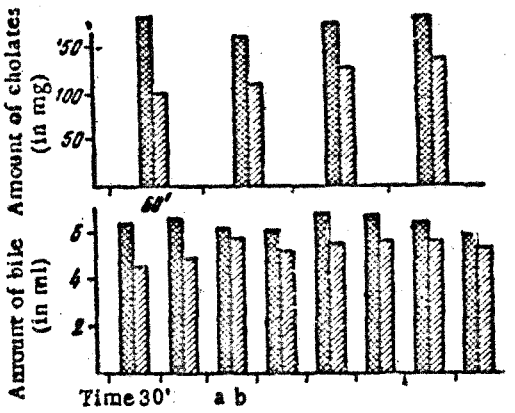

Fig. 1. Effect of adrenalin on bile secretion and process of cholate excretion in the dog Dunai (average values): a) control; b) adrenalin, 0.05 mg per 1 kg body weight, intravenously.

tion of bile secretion under the influence of adrenalin was observed chiefly during the first two hours of experiment, i.e., when the blood sugar level was raised. During the remaining time of experiment bile secretion was less markedly diminished or not diminished at all (Figure 1).

The concentration of cholates and of bilirubin in the bile also underwent a change. A close connection was noted between the level of bile secretion and concentration of bilirubin in the bile, expressed in the fact that the content of this pigment in the bile increased considerably in those intervals of time during the experiment when bile secretion was relatively low and decreased to the initial level as the normal level of bile secretion was restored. The cholate concentration in the bile, on the other hand, was below the control value throughout the experiment in the majority of cases; in some experiments this decrease was greater, in others smaller; only in isolated observations on the dog Lokhmatyi during experiments with marked depression of bile secretion did the concentration of cholates remain unchanged or show a slight rise.

Calculation of the total amount of cholates secreted with the bile as indication of the intensity of the process of their synthesis in the liver enabled us to establish that under the influence of adrenalin the absolute cholate content of bile showed a considerable decrease (in the case of Lokhmatyi by an average of 16.2-37.3% in the case of Tsezar and Dunai by 31.6 and 30.9% respectively). The most marked decrease in cholate secretion was observed during the first hour of the experiment after which it rose gradually but remained considerably below the corresponding values throughout the experiment (Figure 1).

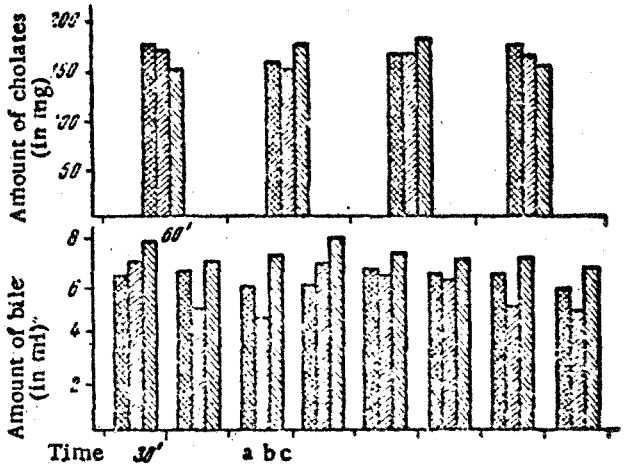

Fig. 2. Effect of ephedrine on bile secretion and cholate secretion in the dog Dunai (average values): a) control; b) ephedrine in dose 2 mg per 1 kg body weight; c) ephedrine in dose 4 mg per 1 kg body weight (intravenous injection.

Adrenalin thus evokes marked depression of bile excretion and cholate synthesis in the liver; this preparation does not exert any appreciable effect on the process of bilirubin secretion.

Ephedrine. Less marked changes were observed following intravenous administration of 1-5 mg/kg ephedrine.

Doses of 1-2 mg/kg gave rise to slight depression of bile secretion in isolated cases and no changes in others while doses of 3-5 mg/kg caused no change in bile secretion in a number of cases or caused an average rise of 5-15% (Figure 2); changes in the chemical composition of bile were more consistent. The concentration of bile bilirubin increased markedly in those experiments in which the secretion of bile was below the initial level and dropped to some extent in those cases in which bile secretion was greater than in the control series of experiments. Thus, in the case of the dog Lokhmatyi administration of 1 mg/kg ephedrine caused an average drop in the total amount of bile from 40.9 to 29.8 ml, the bilirubin concentration rising from 38.8-44.5 to 60.8-77.8 mg%. When the same dog received 6 mg/kg of ephedrine the total amount of bile secreted during four hours increased up to 63.4 ml, the concentration of the pigment falling to 34.3-23.8 mg%. In this case the changes resembled in character those observed on administration of adrenalin.

The concentration of cholates in the bile was noticeably lower in all the experiments with ephedrine than in the control ones. The total amount of cholates secreted with bile was also lower than the initial value in the majority of experiments. This decrease was marked in the case of Lokhmatyi somewhat more than in the case of Dunai. Only in one experiment (Lokhmatyi) was there an increase in the absolute cholate content of the bile after administration of 5 mg/kg ephedrine; the increase was from 786.8 to 1149 mg. The consistent reaction of the organism from the point of view of bile secretion is thus dilution of the bile, the level of secretion and the process of cholate synthesis in the liver depending on the dose of the preparation: as the dose increases these processes rise to the normal level and in some cases (especially with respect to bile secretion) exceed the latter.

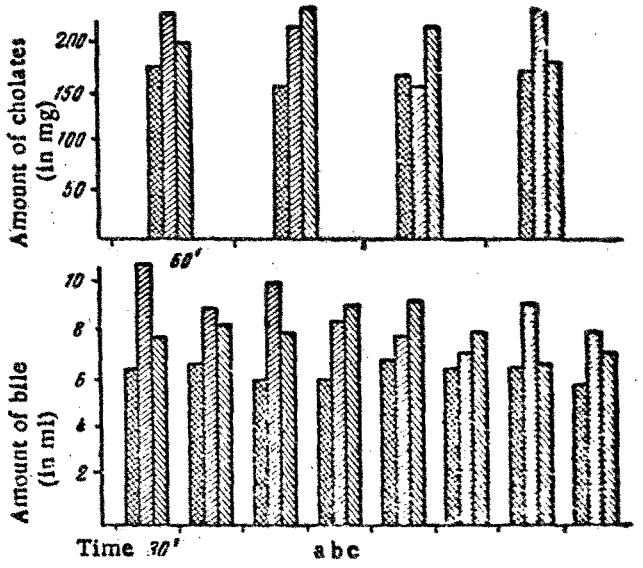

Fig. 3. Effect of amphetamine on bile secretion and process of cholate secretion in the dog Dunai (average values): a) control; b) amphetamine in dose 0.5 mg per 1 kg body weight; c) amphetamine in dose 1 mg per 1 kg body weight (intravenous injection).

Amphetamine. The effect of amphetamine in doses of 0.5-2 mg/kg on the bile-secreting function of the liver was studied in experiments on four dogs. The preparation was given subcutaneously and intravenously. As can be seen from the data given in the table, bile secretion was markedly increased in all experiments with slight exception (absence of reaction in Lokhmatyi upon parenteral administration of 1 mg/kg of amphetamine). This effect of amphetamine was most pronounced on intravenous injection: the bile-secreting action increased as the dose rose from 0.5 to 1 mg/kg and decreased on further increase of the dose. Thus, in the case of the dog Aza the average increase of bile secretion following administration of 0.5 mg/kg amphetamine was 37.3% and 73.4% when the dose was increased to 1 mg/kg; when the dose was further increased to 2 mg/kg, however, there was no increase in bile secretion. It was also noted that when amphetamine was given parenterally the increase in bile secretion occurred from the second to third hour onwards, whereas when the preparation was given intravenously bile secretion was raised throughout the experiment (Figure 3).

Effect of Adrenalin, Ephedrine and Amphetamine on Bile Secretion and Chemical Composition of Bile in Dogs (Mean values)

Dog's name	Before administration of preparation				Dose of preparation in mg/kg and mode of administration		After administration of preparation			
	amount of bile in 4 hours (ml)	concentration in mg%		total amount of cholates in 4 hrs (mg)			amount of bile in 4 hours (ml)	concentration in mg%		total amount of cholates in 4 hours (mg)
		cholates	bilirubin					cholates	bilirubin	
Adrenalin										
Lokhmatyi	40.9	2280-1860	44.5-38.8	786.8	0.05	Subcutaneously	23.6	2320-2020	–	659.0
	40.9	2280-1860	44.5-38.8	786.8	0.05	Intravenously	35.3	1630-1210	50.0-39.0	493.5
Tsezar	32.4	1850-1730	–	550.5	0.05	Subcutaneously	30.2	2000-1040	–	376.6
Dunai	50.1	1520-1480	73.0-60.2	686.1	0.05	Intravenously	43.0	1180-1030	70.9-57.4	474.4
Ephedrine										
Lokhmatyi	40.9	2280-1860	44.5-38.8	786.8	1.0	Intravenously	29.8-42.0	1620-980	77.8-60.8	370.4-492.0
	40.9	2280-1860	44.5-38.8	786.8	3.0	"	40.8-45.2	1180-860	47.6-29.7	387.1-479.8
	40.9	2280-1860	44.5-38.8	786.8	5.0	"	39.8-63.4	1680-1160	34.3-23.8	402.4-1149.0
Dunai	50.1	1520-1480	73.0-60.2	686.1	2.0	"	46.3	1690-1320	77.1-56.8	664.4
	50.1	1520-1480	73.0-60.2	686.1	4.0	"	58.3	1320-1050	72.6-50.8	669.0
Amphetamine										
Lokhmatyi	40.9	2280-1860	44.5-38.8	786.8	1.0	Parenterally	38.0	1820-1110	45.3-39.7	543.0
	40.9	2280-1860	44.5-38.8	786.8	2.0	"	45.3	1320-1120	40.8-33.6	572.2
Amur	44.1	2660-2000	62.1-52.1	1026.3	0.5	"	56.1	2020-1440	–	1046.6
	44.1	2660-2000	62.1-52.1	1026.3	1.0	"	63.2	1850-1490	44.8-30.8	1020.5
	44.1	2660-2000	62.1-52.1	1026.3	2.0	"	52.8	2130-1250	68.3-37.2	851.5
Aza	56.8	–	–	–	0.5	Intravenously	78.0	–	–	–
	56.8	–	–	–	1.0	"	98.5	–	–	–
	56.8	–	–	–	2.0	"	57.9	–	–	–
Dunai	50.1	1520-1480	73.0-60.2	686.1	0.5	"	69.3	1370-1090	61.9-50.7	842.7
	50.1	1520-1480	73.0-60.2	686.1	1.0	"	64.2	1400-1260	48.9-38.0	849.0

In those experiments in which enhancement of bile secretion was absent or slight the bile bilirubin concentration was unchanged; it decreased substantially in experiments in which there was definite stimulating effect of the preparation on bile secretion. The concentration of cholates in the bile, regardless of the level of bile secretion, was noticeably lowered including those experiments in which the level of bile secretion was unchanged. The absolute cholate content of bile increased by an average of 22.8-23.7% in Dunai, remained almost unchanged in Amur and decreased by an average of 31-27.2% in Lokhmatyi.

Thus, unlike adrenalin and ephedrine, amphetamine exerts a stimulating effect on bile secretion which resembles in its character the action of the majority of cholagogues (salts of bile acids, cholosas, flaminum, etc.).

Data obtained under long-term experimental conditions on dogs with permanent Schwann gallbladder fistulas show that adrenalin and sympathomimetic amines (ephedrine and amphetamine) possess a number of properties with respect to the bile-secreting function of the liver which are characteristic for each preparation individually. Adrenalin produces marked lowering of bile secretion, ephedrine produces small fluctuations towards both diminution and enhancement of bile secretion (especially on increasing the dose of the preparation) while amphetamine is distinguished by a typical cholagogic action. Changes in the chemical composition of bile, on the other hand, were uniform: concentration of bile bilirubin was in close relation to the degree of the bile-secreting reaction, while the concentration of cholates was lowered in the majority of the experiments.

Taking into account the distinctive features of the pharmacodynamics of adrenalin, ephedrine and amphetamine provides a basis for suggesting that the character of the effect of these substances on the processes of bile secretion and synthesis of cholates in the liver is in definite relationship with the ability of the preparations mentioned to elicit stimulation of the central nervous system on the one hand, and on the other to influence the adrenergic systems in tissues. In this series of substances the central action increases with decline of the peripheral effect. Therefore, evidently, the bile-secreting effect and the process of cholate formation in the liver depend on the degree of peripheral and central action of substances such as adrenalin, ephedrine and amphetamine. Predominance of peripheral over central effect (adrenalin) leads to depression of bile secretion and cholate synthesis, whereas predominance of central effect over peripheral (amphetamine) is accompanied by definite cholagogic action with increase of cholate formation in the liver seen in a number of experiments. Ephedrine occupies an intermediate position with relation to the central nervous system and with respect to effect on bile secretion.

It is also essential to point out that hyperglycemia which develops under the influence of adrenalin plays a definite part in the depression of bile secretion associated with administration of adrenalin. Our earlier work [6, 7] and data of A.F. Platonova-Petrovskaia [2, 3], R.V. Rudoi [5] and others suggest close connection between the process of bile secretion and carbohydrate metabolism expressed in the fact that in the presence of hypoglycemia the level of bile secretion shows a sharp rise, while considerable hyperglycemia is accompanied by marked inhibition of this process. As indicated previously [6], this connection is based on a neurohumoral mechanism.

SUMMARY

Long-term experiments were performed on five dogs with a permanent Schwann fistula of the gallbladder. The effect of adrenalin, ephedrine and amphetamine on bile production by the liver and on the chemical content of the bile was studied. It was established that adrenalin inhibited the bile secretion and promoted decrease of the absolute content of cholates in the bile. Amphetamine, on the other hand, has a promoting effect on bile production. The effect of ephedrine on production of bile is less characteristic and is unstable. Changes in the chemical content of the bile showed that the concentration of bilirubin in the bile depended on the degree of bile production. As to the concentration of the cholates – in the majority of experiments they showed considerable decrease. The mechanism of action of the preparations referred to above is discussed in this paper.

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