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Research Article

THE ACTION OF PITUITARY TARTRATE ON THE HEART OF THE UNANESTHETIZED DOG

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INTRODUCTION

In another paper (Resnik and Geiling (1925)) we have described the effect of extracts of the posterior lobe of the pituitary (Armour's Pituitary Liquid) upon the heart of the unanesthetized dog. It was found that this substance quickly produced a period of acceleration followed by a profound slowing of the heart rate associated with depression of auriculo-ventricular conduction. During the slowing, the electrocardiographic records resembled those described as sino-auricular block. When the drug was given after a full dose of atropine however a different effect was observed. There was a brief phase of acceleration followed by a marked slowing of the heart accompanied by slight depression of conduction. A second period of acceleration followed, during which the auriculo-ventricular conduction was usually greatly impaired and the heart rate often elevated well above the maximum rate attained after complete vagal paralysis. A prolonged period of progressive diminution of cardiac rate then occurred which was independent of the influence of vagal tone. These effects were found to be due to central vagal stimulation and also to a direct action upon the myocardium. The second period of acceleration was apparently due in part to an outpouring of adrenal secretion called forth by the diminution of oxygen supply to the tissues, which occurs according to Kolls and Geiling (1924), after administration of pituitary extract.

Abel, Rouiller and Geiling (Abel, 1924) have investigated the action of pituitary tartrate, which they consider to contain the purified principle of the extract of the posterior lobe of the pituitary gland. They have found that it reproduces exactly the various effects obtained with commercial extracts. Through the kindness of Drs. J. J. Abel and C. A. Rouiller, we have obtained a small amount of pituitary tartrate (oxytocic titer 160 $\times$ β-I phosphate) which we have used in a study of its action upon the heart of the unanesthetized dog.

METHODS

The experiments were performed upon two of the dogs previously used in the study of the action of pituitary extract. The methods

were similar to those employed in the former experiments and need not be given in detail here. Pituitary tartrate was given in doses of 1 mg.

EXPERIMENTAL

Owing to the limited amount of the drug at our disposal we were able to perform but four experiments. Nevertheless these few observations were sufficient to indicate that the purified pituitary tartrate duplicated in every important detail the action of the commercial extract.

Effect upon the animal before atropine

This was studied in two experiments (table 1). About 10 seconds after the start of the injection, the rate rose rather markedly and this rise was associated with a quickening of auriculo-ventricular conduction. These changes were followed rapidly by a retardation of the rate of the whole heart, associated with a definite depression of auriculo-ventricular conduction. Electrocardiographic records showed sino-auricular block during the period of slowing. In table 1 are given protocols of these experiments. Atropine was given after the slowing occurred with the results that are described later.

Effect upon the animal after atropine

In two experiments (table 2), pituitary tartrate was given after full doses of atropine. Shortly after pituitary tartrate was injected, there was an elevation of heart rate above the maximum level previously reached with the use of atropine alone. In one animal, G3, this rise began 10 seconds after the injection, while in the other, G1, it occurred between 10 to 30 seconds after the injection. In this animal there was a simultaneous decrease of the conduction time. There then followed a fall which reached a maximum in 1 to 2 minutes, associated in both experiments with a slight increase in auriculo-ventricular conduction time. The heart rate then rose again. In one instance, G1, the maximum reached was well above that obtained with atropine alone, and during this period there was heart block with the dropping of many ventricular beats. In the other case,

TABLE 1

The effect of pituitary tartrate in animals before atropine

G1					G3				
	Time after pituitary tartrate	Rate		Auriculo-ventricular conduction time		Time after pituitary tartrate	Rate		Auriculo-ventricular conduction time
		Auricular	Ventricular				Auricular	Ventricular	
Resting		80	80	0.14–0.16	Resting		84	84	0.11–0.12
1 mg. pituitary tartrate					1 mg. pituitary tartrate				
	12 seconds	107	107	0.14–0.15		15 seconds	178	178	0.10
	45 seconds	55	55	0.16–0.20		45 seconds	74	74	0.12–0.14
	4 minutes	35	35	0.16		4 minutes	63	63	0.14–0.16
	10 minutes	42	42	0.14–0.20		10 minutes	60	60	0.14–0.17
	30 minutes	62	62	0.15–0.16	1 mg. atropine	11 minutes			
1 mg. atropine	31 minutes					11 minutes and 30 seconds	140	67*	0.13–0.16
	32 minutes	224	224	0.14		13 minutes	252	252	0.16
	37 minutes	240	240	0.14		25 minutes	202	202	0.12
					1 mg. atropine	27 minutes			
						27 minutes and 30 seconds	252	252	0.12
						49 minutes	160	160	0.11
					1 mg. atropine	49 minutes and 15 seconds			
						50 minutes	250	250	0.10

* A-V block with varying 1:1, 2:1, 3:1 ventricular response.

TABLE 2

The effect of pituitary tartrate in animals after atropine

G1					G3				
	Time after pituitary tartrate	Rate		Auriculo-ventricular conduction time		Time after pituitary tartrate	Rate		Auriculo-ventricular conduction time
		Auricular	Ventricular				Auricular	Ventricular	
Resting		104	104	0.16	Resting		100	100	0.11–0.12
1 mg. atropine		226	226	0.14	1 mg. atropine		261	261	0.08
1 mg. pituitary tartrate					1 mg. pituitary tartrate				
	30 seconds	238	238	0.13+		10 seconds	282	282	0.08
	1 minute	204	204	0.14		2 minutes	218	218	0.12
	2 minutes and 30 seconds	252	228	0.18–0.22*		3 minutes	254	254	0.16
	7 minutes and 15 seconds	200	200	0.18		14 minutes and 20 seconds	224	224	0.12
1 mg. atropine	9 minutes				1 mg. atropine	15 minutes			
	10 minutes	242	242	0.17		17 minutes	230	230	0.13–0.14
	38 minutes	188	188	0.15		24 minutes	215	215	0.12
1 mg. atropine	40 minutes				1 mg. atropine	26 minutes			
	41 minutes	208	208	0.15		27 minutes	210	210	0.12
	48 minutes	192	192	0.14*		31 minutes	205	205	0.11

* The conduction time could not be measured accurately.

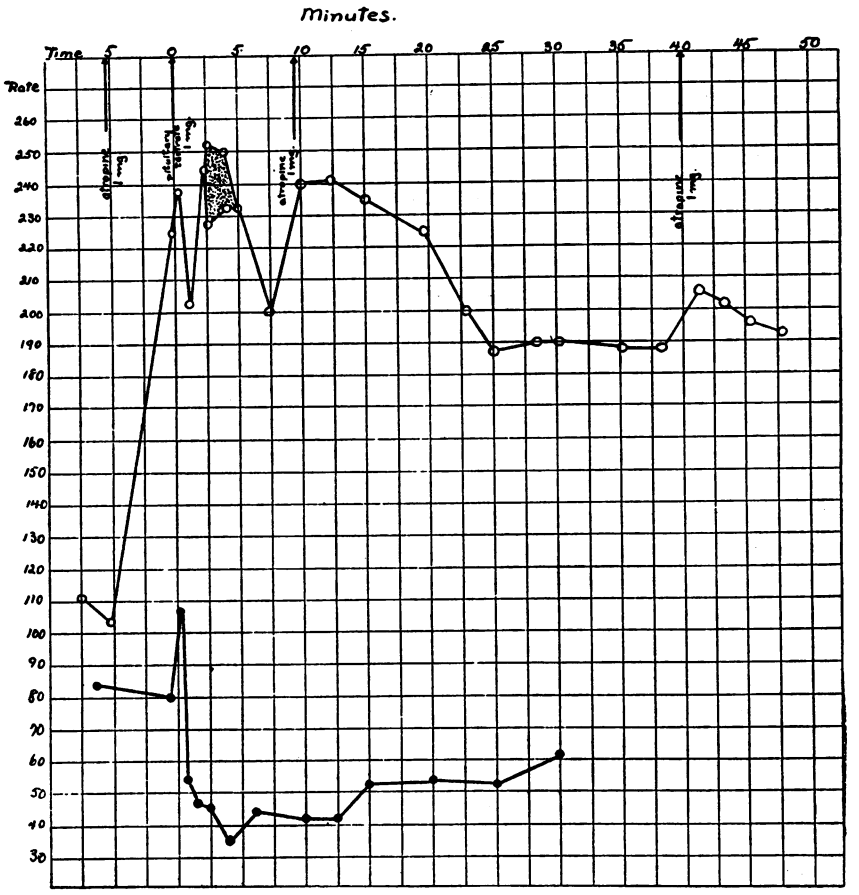

FIG. 1. A chart showing the effect of the intravenous administration of 1 mgm. pituitary tartrate before (lower curve) and after (upper curve) atropine (G1).

The shaded area in the upper curve represents auriculo-ventricular block and shows the difference between auricular and ventricular rates. In the lower curve, there is seen the early acceleration and the later period of retardation of rate. In the upper curve, there is shown successively (1) the primary rise, followed by (2) a brief period of slowing, (3) a secondary rise succeeded by (4) a gradual fall during which period the effect of the third dose of atropine (40 minutes) is distinctly less than that of the second (9 minutes). Compare with figures 1 and 2 of the preceding paper.

G3, the rate rose to a level slightly below that with atropine, and the conduction time increased definitely, but no auricular beats were blocked. The heart rate gradually fell again. This fall results partly from recovery of vagal tone, but not wholly, for subsequent injections of atropine had less and less influence in effecting an increase in ventricular rate. During this period the conduction time gradually diminished. Table 2 gives the essential data of these experiments. Figure 1 illustrates graphically the results in one animal, G1.

DISCUSSION

In those experiments in which atropine was given after pituitary tartrate, the results indicate definitely that central stimulation of the vagi was the chief factor in the slowing produced by pituitary tartrate. In G1 there was no conclusive evidence that the drug exerted a direct action on the myocardium. It is possible that such an action had been present but had passed off by the time atropine was given, although when pituitary tartrate was given to the same animal after atropine, the direct effect on the heart muscle was still evident after 41 minutes. In G3 the heart rate was slightly lower after atropine than that obtained in other experiments. More definite evidence of a direct action is seen in the increased conduction time. Following the use of atropine, the conduction time on several occasions was 0.08 to 0.10 second. In this experiment it was as high as 0.16 second. It is apparent, however, that the action of pituitary tartrate upon the heart muscle is more pronounced when the drug is given after atropine. Whether this holds for commercial preparations of pituitary extract we have not determined.

The effect of pituitary tartrate upon the heart of the unanesthetized dog is exactly similar to that of the commercial preparation which we had previously studied. The interpretation of the various phases of the effect has been given in the preceeding paper. The differences between the actions of the two are merely quantitative, as was to be expected, as 1 mg. of pituitary tartrate of the particular titer which was available had been found in other experiments to be slightly less effective than 1 cc. of pituitary extract (Armour). These results offer further evidence that pituitary tartrate contains the active principle of the extract of the posterior lobe of the pituitary.

CONCLUSIONS

Pituitary tartrate produces exactly the same changes in the heart of the unanesthetized dog that have been found to occur after the administration of pituitary extract.

BIBLIOGRAPHY

Abel, J. J. Bull. Johns Hopkins Hosp. 1924, xxxv, 305. Physiological, Chemical and Clinical Studies on Pituitary Principles.

Kolls, A. C., and Geiling, E. M. K. Jour. Pharm. and Exp. Therap., 1924, xxiv, 67. Contributions to the Pharmacology of Extracts of the Posterior Lobe of the Pituitary Gland.

Resnik, W. H., and Geiling, E. M. K. Jour. Clin. Invest., 1925, i, 217. The Action of Pituitary Extract upon the Heart of the Unanesthetized Dog.