THESIS

Cardiovascular Effects of Intravenous Cocaine Hydrochloride on an Anesthetized Dog, *Canis familiaris*

Submitted by

John D. Wagstaff

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By

John D. Wagstaff

Committee in Charge:

Darrell J. Graff, Chairman

Carl D. Marti

Samuel Zeveloff

The thesis is approved and acceptable in quality and form.

Darrell J. Graff

Carl D. Marti

Samuel Zeveloff

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Abstract

Different doses of cocaine were given intravenously to an anesthetized dog. Blood pressure, respiratory rate, and heart rate were measured before and after each dose. Low, medium, and high doses of 0.05, 0.2, and 0.4 grams were given to explore the cardiovascular effects of varying doses. With the first dose, blood pressure and heart rate rapidly rose, and respiration dropped slightly. The second dose caused a drop in blood pressure and heart rate while respiration rate rose. The final dose caused a rapid drop in blood pressure, resulting in death of the subject. It was concluded that at low dose, cocaine's sympathomimetic effects cause a rapid elevation of blood pressure. At high dose these effects result in hypotension possibly caused by arrhythmia, and coronary vasospasm.

In recent years, recreational use of cocaine in the United States has been increasing in many socioeconomic and age groups. Since the late 1970s, for reasons that remain less than clear, but are undoubtedly related to a marked drop in its price, the prevalence of cocaine has increased. Cocaine use has now reached epidemic levels, affecting over twenty-two million people from all strata of society (Gold et al. 1986).

The recent introduction of "crack" has provided a readily-available, inexpensive, highly addictive, smokable form of cocaine. "Crack" is cocaine base extracted from the hydrochloride by adding a basic solution, such as sodium bicarbonate, and evaporating the mixture leaving a crystallized rock. Because it is smoked, the drug goes directly from the lungs to the brain, producing a higher dose, and leading to a high usually in less than ten seconds (Chatlos 1987). However, this high is very short lived and the subsequent intense crash normally leads the user to seek another dose. Through this continuous cycle a user may become rapidly addicted to this drug.

Cocaine affects the sympathetic nervous system by blocking the reuptake of catecholamines at adrenergic nerve endings, having a stimulatory effect on this part of the nervous system (Dackis et al. 1987).

This sensitizes tissues to the actions of exogenous and endogenous catecholamines (Howard et al. 1985, Hueter 1987, Woods et al. 1987). Cocaine increases the synthesis of epinephrine, norepinephrine, and dopamine (the catecholamines) at presynaptic terminals, and binds the reuptake sites at which they are removed from the synaptic cleft (Taylor et al. 1979) (Fig. 1). By doing this, the synaptic cleft is flooded with catecholamines. Since reuptake sites are bound by cocaine, the catecholamines remain, and consequently their effects are augmented (Woods et al. 1987). Ironically, this also causes catecholamine depletion in these nerves; after ceasing cocaine use the user "crashes." Due to these effects, cocaine has been implicated in many cardiovascular problems such as tachycardia, hypertension, ectopic heart beats, strokes, coronary vasoconstriction, aortic rupture, pulmonary edema, and sudden death (Cantwell and Rose 1986, Cregler and Mark1986, Gay and Loper 1988). Besides the drug's sympathomimetic effects of raising systemic blood pressure, it is also thought to inhibit the parasympathetic nervous system, which normally acts to slow a rapidly beating heart (Cowen 1988).

The objective of this study was to develop the methodology for determining the effects of intravenously injected cocaine on systemic

blood pressure, heart rate, and respiration rate using variable doses of cocaine hydrochloride dissolved in isotonic saline solution using a canine model. "Crack" would have been used in this experiment for evaluation of its short-term effects, but it is not water soluble therefore could not be injected. No other route of administration could better simulate the effects of smoking "crack" than intravenous injection. Because of budgeting limitations and difficulty in obtaining suitable animals, we were limited to one subject and one gram of cocaine hydrochloride.

Methods

The subject, obtained from the Davis County animal shelter, was a condemned springer spaniel weighing 13.6 kg. It was anesthetized by intraperitoneal injection of 8.1 cc. of a 50 mg./cc. solution of sodium pentobarbital (30mg/kg.). Dosage was determined by multiplying13.6 kg. by 30 mg./kg. resulting in 408 mg. This was divided by the concentration of the stock solution of sodium pentobarbital of 50 mg./cc. giving the maximal anesthetizing dose of 8.1 cc. (Geddes and Hoff 1967).

Once anesthetized, the ventral surface of the neck was shaved and a midline incision was made through the skin to the underlying muscle layer.

The muscles were separated bluntly by tearing them longitudinally with hemostats exposing the trachea. Blunt dissection was necessary to decrease the amount of bleeding and to facilitate clotting. A length of suture was passed under the trachea and an incision was made between two tracheal cartilage rings. A t-tube cannula was then inserted with the tip directed toward the lungs, and tied in place with the suture (Geddes and Hoff 1967).

Following the procedure outlined by Geddes and Hoff (1967), the carotid artery running along the trachea was next isolated for use in monitoring arterial blood pressure. A five cm. length was exposed, ligated cranially, and clamped with a hemostat proximally. The artery was then snipped approximately halfway through the vessel on the cranial side. Using a pair of forceps, the cut was enlarged, and an arterial cannula was inserted, tied in place, and the hemostat removed (Geddes and Hoff 1967). The cannula was connected to a E&M Physiograph (Houston, Texas) model P-1000 linear core pressure transducer used to record systemic blood pressure in conjunction with a polygraph. Warm, heparinized saline was flushed through the cannula from time to time to prevent blood from clotting there.

To facilitate the injections of cocaine, the femoral vein was exposed and cannulated by use of a butterfly needle. A length of rubber tubing was attached. Through this cannula, injections were made and flushed with 5 ml. of warm, heparinized isotonic saline solution.

One gram of cocaine hydrochloride was obtained from James Gaskill, Director of the Weber State College Crime Lab. This cocaine was used for evaluating confiscated cocaine, and was virtually 100% pure. The results herein can thus, in all likelihood, be attributed to the drug itself and not to any impurity. One-half gram of this sample was dissolved in 1.1 ml of isotonic saline. In this form, it was injected intravenously. Dosages of 0.1 cc., 0.2 cc., and 0.8 cc. were chosen to explore the difference in effects of low, medium, and high doses on blood pressure. Between the medium and high dose injections, several other drugs, not pertaining to this study, were injected as part of a class project. After each of these drugs were administered, parameters were allowed to return to baseline conditions before the final, high dose injection was made.

An E & M Instrument impedance pneumograph, in conjunction with the polygraph, was used to measure respiratory rate. Needle electrodes were introduced, one on either side of the subject's chest and attached to

the pneumograph. A record of basal respiratory rate was taken in order to calibrate the respirator (Table 1). An E & M Instrument model V100KG respirator was used and set for 15 to 17 breaths/minute with its pressure set between 20 and 30 cm. of water. Opening the chest wall, in order to observe the heart, produced pneumothorax so the respirator was needed to assist the subject's breathing. A midline incision was made from the base of the throat to just below the xiphoid process. The musculature was separated bluntly, and a pair of bone shears used to cut through the ribs on one side of the sternum. Intercostal bleeding was stopped with compress sponges. Major bleeders were clamped with hemostats. Once accomplished, the rib cage was opened exposing the heart and lungs. The pericardium was removed to expose the myocardium.

Results

Before opening the chest, baseline measurements of blood pressure and respiration rate were recorded (Table 1). The first injection consisted of 0.1 cc. (0.05 g) of a 0.5 gm/ml solution of cocaine hydrochloride. After 45 seconds, blood pressure began to rise from 140/80 mm. Hg. to a peak at 160/98 mm. Hg., heart rate rose from 170 to 191 beats/minute, and

respiration dropped from 15 to 12 breaths/minute (Fig. 2).

After five minutes baseline conditions had returned; 0.2cc. (0.1 g) of the cocaine solution was then injected. Blood pressure rapidly dropped from 136/90 mm. Hg. to a low of 110/85 mm. Hg., heart rate fell slightly from 176 to 168 beats/minute, and respiration rose from 15 breaths/minute to 17 breaths/minute (Fig. 3). When the final dose of 0.8 cc. (0.4 g) of the cocaine solution was given, blood pressure rapidly dropped from 136/94 mm. Hg. to 0. Similarly, heartrate and respiration stopped (Fig. 4). These results are summarized in Table 2. In an effort to revive the subject, 1cc of epinephrine was injected intracardially. Within a minute, blood pressure rose erratically from 0 to 220/140.

Discussion

Cocaine produced significant, dose-dependent changes in blood pressure. Yet because of limited availability of drugs and experimental subjects, the effects of the intermediate dosages could not be adequately studied. Cocaine is known to be a potent vasoconstricter. This, combined with its effects on the sympathetic nervous system, should have resulted in increased blood pressure. This would be consistent with the results

from the first injection of a low (0.05 g) dose in which blood pressure rapidly rose after its injection. However, the 0.2cc (0.1 g) dose used herein caused blood pressure to drop, which may have resulted from a near overdose. Overdose from the final injection could possibly be attributed to "sudden death," a heart syndrome which may result from increased myocardial oxygen demand, and coronary vasospasm (Waller 1988). This was responsible for the death of Maryland basketball star Len Bias.

These results were consistent with the findings of similar studies. In a study done by Schwartz et al. (1989) using doses very close to those used in the present study, it was found that at low dose (3.7 mg./kg.) systolic blood pressure (SBP) rose from 103 to 175 mm./Hg. At an intermediate dose of 8.4 mg./kg., SBP dropped from 105 to 56. At high dose (37.7 mg./kg.) SBP dropped from 106 to 22. In another study using low, medium, and high doses of 0.4 mg./kg., 2.0mg/kg., and 10.0 mg./kg. respectively, it was found that the low dose raised SBP from 148 to 162. Medium dose lowered SBP from 148 to 130. High dose lowered SBP from 148 to 48 (Friedrichs et al. 1988). Both of these studies were done using different subjects for each dose. While the study herein used only one subject, the reports from previous experiments indicate that our results

are consistent.

It has been shown in dogs that doses as low as 1/1000 of the amount needed to cause a "high" can dramatically raise blood pressure (Hull 1990). This should serve as a clear warning to any user predisposed to hypertension. African-Americans suffer a one-third greater risk of hypertension than whites (Raloff 1990). This group in particular should, therefore, avoid using cocaine. According to a series of research surveys of callers to the "800-COCAINE" National Hotline, however, the proportion of black callers more than doubled from 1983 to 1985 (Washton and Gold 1987).

Cocaine has evolved into a major public health threat in part because of the myths that it is benign, nonaddicting, and an aphrodisiac (Clayton 1985, Cregler and Mark 1986, Waller 1988). Not until the overdose death of comedian John Belushi, and the serious burning injury to Richard Pryor while "freebasing" cocaine in the early 1980's did much of the public opinion view cocaine as a dangerous drug, with hazardous side effects (Byck 1987). This was reinforced by the1986 deaths of Len Bias and pro football player Don Rogers. Their untimely demises also illustrated the drug's ability to precipitate serious cardiovascular events,

even to those in peak physical condition. Finally, these deaths revealed to the general public just how dangerous cocaine can be, and stimulated much needed research into the mechanism by which it acts.

Cocaine produces a profound euphorogenic effect, resulting in a great potential for abuse. Laboratory studies have demonstrated that animals will self-administer cocaine, favoring it to food or sex, even with a greater than 90% mortality rate (Bozarth and Wise 1985, Gay and Loper 1988). Cocaine has also been associated with the elite, rich, and famous, making it attractive to many, especially the youth of this country. Twenty years ago, there were about 10,000 cocaine users in the United States. Ten years ago, there were about 100,000. Recent estimates range from five to over twenty million (Gottheil 1987). With the availability of "crack," a cheap, smokable form of cocaine, this number is expected to increase (Cantwell and Rose 1986). With increasing use, more frequent reports of cocaine related deaths have appeared. Between 1982 and 1983, as reported by the National Institute in Drug Abuse, there was a 91% increase in cocaine-related deaths (Gold et al. 1987). Because of this, more study is needed to fully understand the scope of the drug's effects and the mechanisms by which they occur. Only through this understanding

and further education can effective methods of treating abuse and addiction be established.

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Literature Cited

Byck, R. 1987. Cocaine use and research:three histories. pp. 24-46 'Cocaine: clinical and biobehavioral aspects', ed S. Fisher, A. Raskin, E. Uhlenhuth. Oxford University Press, New York.

Bozarth, M.A., and R.A. Wise. 1985. Toxicity associated with long-term intravenous heroin and cocaine administration in the rat. J. Amer. Med. Assoc. 254:81-83.

Cantwell, C.D., and F.D. Rose. 1986. Cocaine and cardiovascular events. Phys. Sport. Med. 14: 77-83.

Chatlos, C. 1987. "Crack": what you should know about the cocaine epidemic. The Putnam Publishing Group, New York.

Clayton, R.R. 1985. Cocaine use in the United States: in a blizzard or just being snowed? Natl. Inst. Drug Abuse Res. Monogr. Ser. 61:8-34.

Cowen, R. 1987. Cocaine and the nervous system. Sci. News 137: 238.

Cregler, L.L., and H. Mark. 1986. Medical complications of cocaine abuse. N. Engl. J. Med. 315:1495-1500.

Dackis, C.A., M.S. Gold, and A.L.C. Pottash. 1987. Central stimulant abuse: neurochemistry and pharmacotherapy. pp 7-21 'Cocaine: pharmacology, addiction, and therapy', ed B. Stimmel. The Haworth Press, New York.

Friedrichs, G.S., H. Wei, and G.F. Merrill. 1988. Coronary vasodilation caused by intravenous cocaine in the anesthetized beagle. Presented at the1988 annual meeting of the American Physiological Society, Montreal.

Gay, G.R., and K.A. Loper. 1988. The use of labetalol in the management of cocaine crisis. Ann. Emerg. Med. 17:282-283.

Geddes, L.A., and H.E. Hoff. 1967. Experimental physiology. Baylor School of Medicine, Houston, Texas.

Gold, M.S., M. Galanter, and B. Stimmel. 1987. Cocaine: a new epidemic. pp 1-5 'Cocaine: pharmacology, addiction, and therapy', ed B. Stimmel. The Haworth Press, New York.

Gottheil, E. 1987. Cocaine abuse and dependence: the scope of the problem. pp 23-30 'Cocaine:pharmacology, addiction, and therapy', ed B. Stimmel. The Haworth Press, New York.

Howard, R.E., D.C.Hueter, and G.J. Davis. 1985. Acute myocardial infarction following cocaine abuse in a young woman with normal coronary arteries. J. Amer. Med. Assoc. 254: 95-96.

Hueter, D.C. 1987. Cardiovascular effects of cocaine. J. Amer. Med. Assoc. 257: 979-980.

Hull, S.S. 1990. Cocaine's harmful effects. Presented at The Federation of American Societies for Experimental Biology annual meeting. Washington D.C. Apr.1-5.

Raloff, J. 1990. Lead heightens hypertension risk in blacks. Sci. News 135:261.

Schwartz, A.B., S.D. Janzen, R.T. Jones, and W. Boyle. 1989. Electrocardiographic and hemodynamic effects of intravenous cocaine in awake and anesthetized dogs. J. Electrocardiol. 22:159-166.

Taylor, D., B.T. Ho, and J.D. Fagen. 1979. Increased dopamine receptor binding in rat brain by repeated cocaine injections. Commun. Psychopharmacol. 3:137-143.

Waller, B.F. 1988. Cocaine and the heart. Indiana Med. 81: 956-959.

Washton, A.M., and M.S. Gold. 1987. Recent trends in cocaine abuse: a view from the national hotline, "800-COCAINE". pp 31-47 'Cocaine: pharmacology, addiction, and therapy', ed B. Stimmel. The Haworth Press, New York.

Woods, J.H., G.D.Winger, and C.P.France. 1987. Reinforcing and discriminitive stimulus effects of cocaine: analysis of

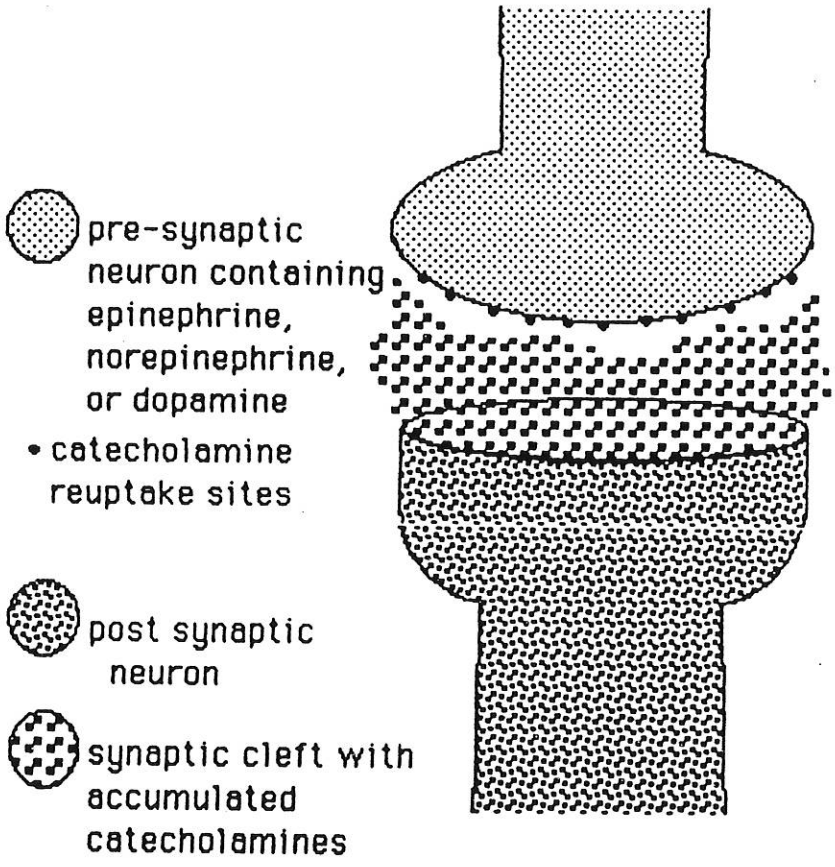
pharmacological mechanisms. pp 21-65 'Cocaine: clinical and biobehavioral aspects', ed S. Fisher, A. Raskin & E. Uhlenhuth. Oxford University Press, New York.

Table 1 Baseline conditions in an anesthetized dog

blood pressure	heart rate	resp. rate
140/80	170	15

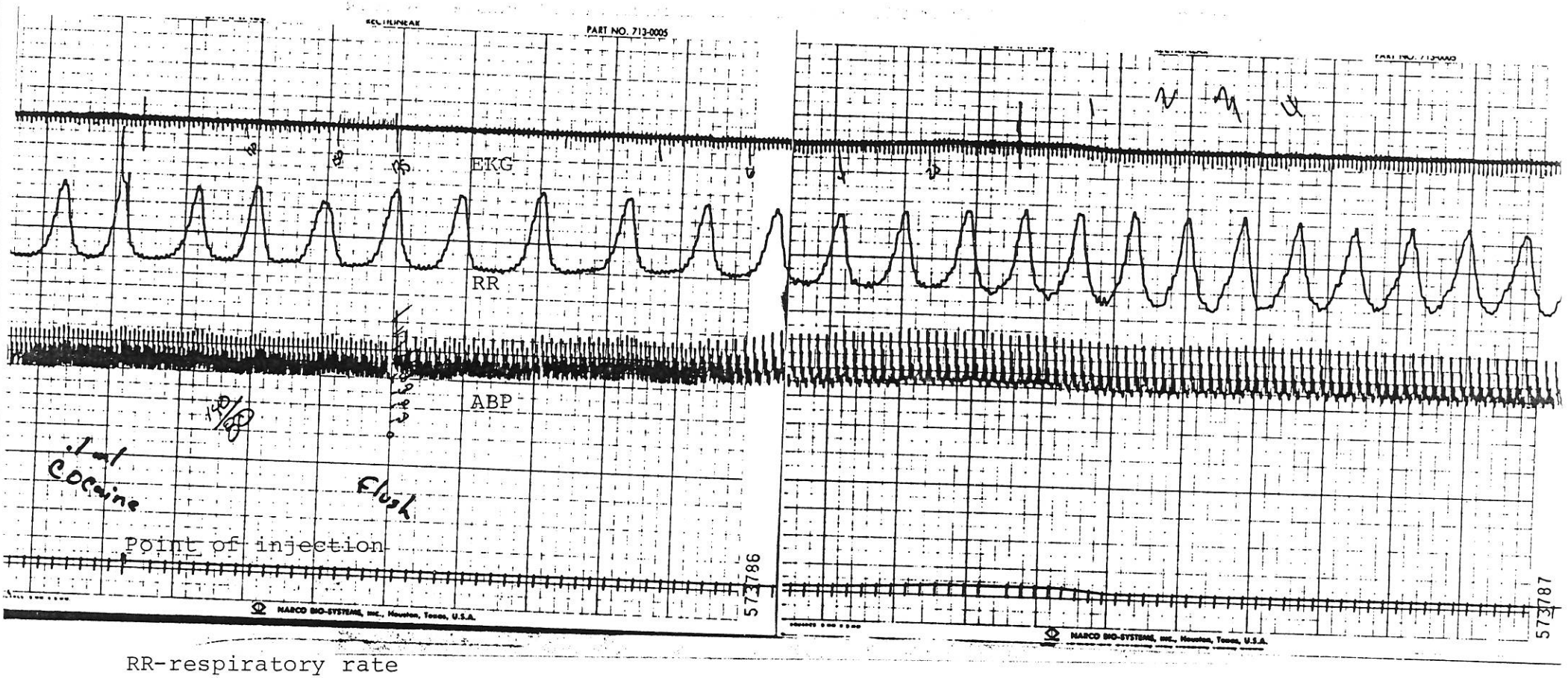
Table 2 Effects of cocaine injections on an anesthetized dog

dose	blood pressure		heart rate		resp. rate	
grams	before	after	before	after	before	after
0.05g	140/80	134/86	170	191	15	1
0.1g	136/90	110/85	176	168	15	17
0.4g	136/94	0	168	0	16	0



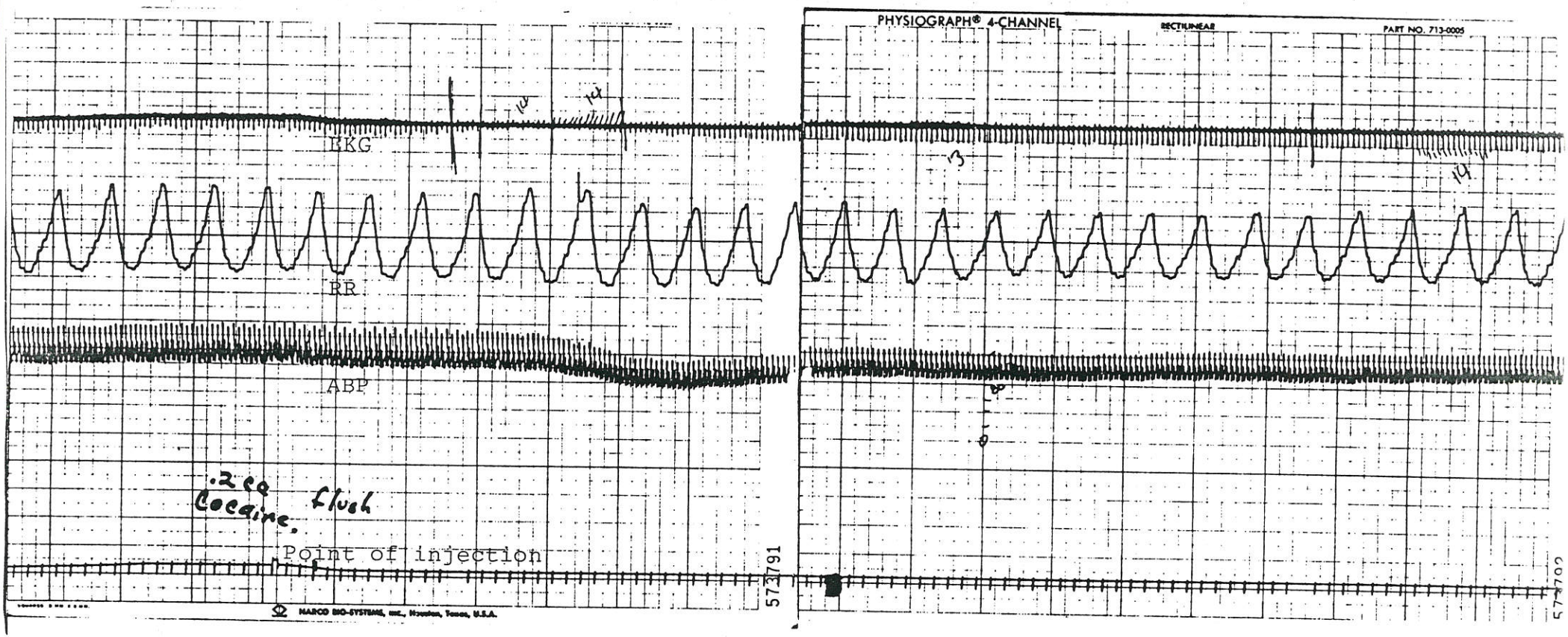
Cocaine increases synthesis of catecholamines, but binds their reuptake sites thus flooding the synaptic cleft causing increased firing of the post-synaptic neuron.

Figure 1 Mechanism by which cocaine sensitizes tissues to catecholamines



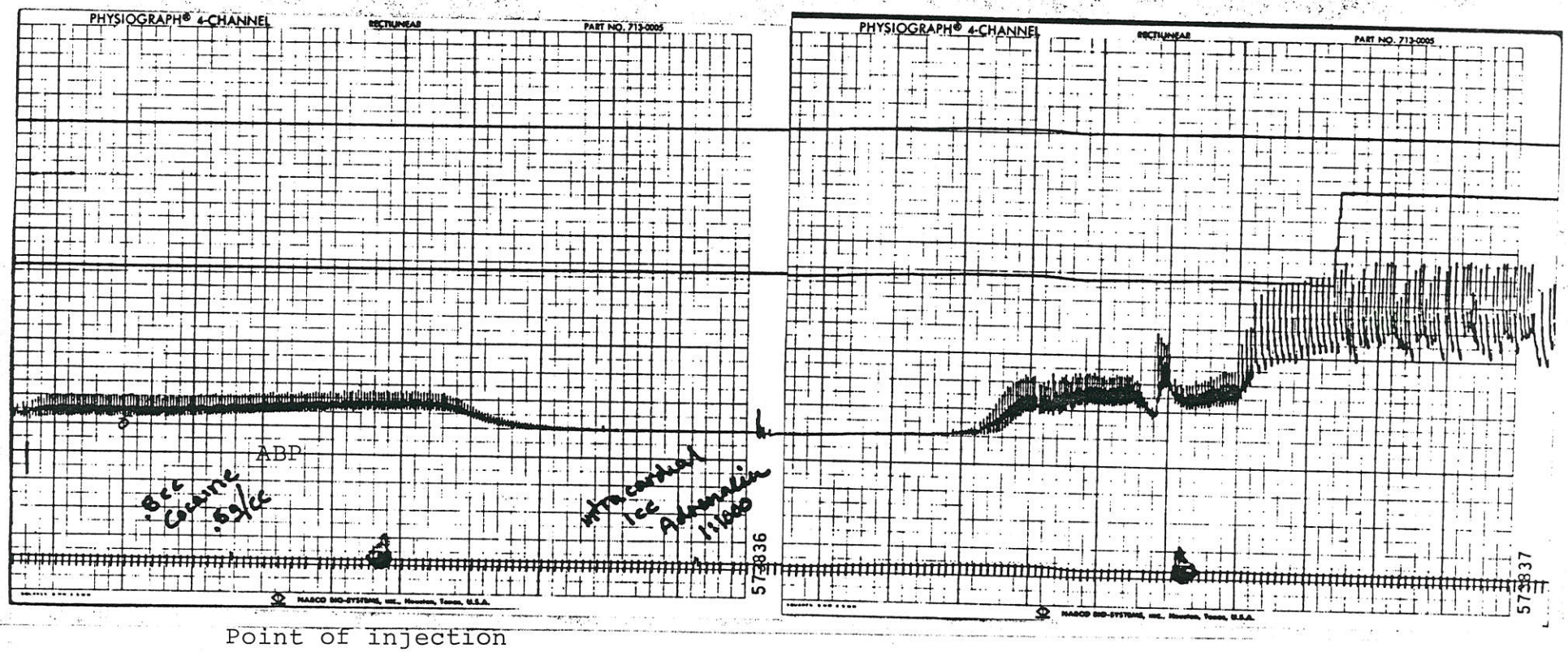
RR-respiratory rate
ABP-arterial blood pressure

Figure 2 Effects of 0.05 g. cocaine hydrochloride injected intravenously



RR-respiratory rate
ABP-arterial blood pressure

Figure 3 Effects of 0.1 g. cocaine hydrochloride injected intravenously



Point of injection
ABP-arterial blood pressure

Figure 4 Effects of 0.4 g. cocaine hydrochloride injected intravenously