

gall bladder distended, the stomach full with erosion of the mucous membranes, and with a few small petechial hemorrhages in the intestines. The kidney was the only tissue showing definite microscopic abnormalities. Dr. Stacy Mettier noted numerous areas of focal necrosis, with extensive hyaline degeneration of the epithelial cells lining the tubules, and with some desquamation of these cells. All 3 compounds in crystalline form are irritating to the mucous membranes of the eyes of rabbits, causing a marked pan-ophthalmitis within 24 to 48 hours after application of a single small flake. Octylresorcinol is very irritating to the skin and mucous membranes of the face and hands of one of us, producing a vesicular dermatitis on parts of the skin coming in contact with the agent.

5449

Comparative Actions of Sympathomimetic Compounds: Responses of Cocainized Rabbit's Intestine.

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The extensive use by Tainter and others of the cocaine sensitization-desensitization phenomena in studies of the circulatory actions of sympathomimetic compounds, made it desirable to determine whether the same phenomena could be elicited with intestinal muscle. Some data were available in papers by Tainter and Chang¹ and Thienes and Hockett.² In no case, however, had the study of excised intestine been sufficiently extensive to indicate the range of spontaneous variation in the responses to successive administrations of the amines. We, therefore, investigated the influence of cocaine upon the responses of excised rabbit duodenum to epinephrine, tyramine, ephedrine and barium, controlling the results by observations of the responses to repeated applications of the same drug in the absence of cocaine. The changes in tonus, amplitude, and rhythmic activity were correlated as much as possible.

The tissues were fresh and active, the majority being taken from recently killed rabbits. Some tissues, however, were kept on ice for 24 hours; this procedure has been found by Burn and Tain-

¹ Tainter, M. L., and Chang, D. K., *J. Pharm. Exp. Therap.*, 1927, **30**, 193.

² Thienes, C. H., and Hockett, A. J., *PROC. SOC. EXP. BIOL. AND MED.*, 1928, **25**, 793.

ter³ to increase the augmentor action of tyramine. The Magnus technic with longitudinal strips and Tyrode's solution were used. The pH of the bath was 7.6, and was not altered by the aeration, nor by the drugs added. A given amount of the drug was put in the organ-bath, and, after the response had been recorded, was washed out with fresh Tyrode. Before the next application, time was allowed for complete recovery of the tissue to its initial activity. A second application of the same amount of the drug was then made, and the 2 responses were compared. In the cocaine experiments the required amounts of cocaine to give concentrations between 1:15,000 and 1:2,500,000 were added to the bath before the second application of the drug being studied, so that the second response was obtained in the presence of the cocaine. The effects of barium were studied in 66 strips, tyramine in 34, epinephrine in 42, and ephedrine in 15, the data being sufficient to give reliable averages. Analysis of the results showed that the initial tonus level, the amplitude of contractions, or the concentrations of the drugs (if submaximal) did not condition the type of response obtained after cocaine. Hence these factors need not be considered in detail. The significant results may be briefly summarized with reference to tonus changes.

Barium: Two successive applications of barium (1:1,700 to 1:50,000) to uncocainized strips produced equal increases of tonus, but, if the intestines were cocainized before the second application, the barium response was diminished by 37%. Using atropinized and uncocainized strips, a striking difference was seen: 2 successive applications of barium no longer produced equal responses, the second response being 193% (average) greater than the first. When such strips were cocainized before the second application of barium, the response was still increased, but to a lesser degree (43%). Under both conditions, therefore, cocaine decreased the degree of the barium-response as compared with the controls. The mechanism of the sensitization of barium to barium by atropine has not been gone into further, but would seem to merit investigation.

Epinephrine: When concentrations of epinephrine were used (1:500,000 to 1:50,000,000) giving small responses (up to 1 cm. inhibition), the second application, to both the cocainized and uncocainized strips, gave a slightly smaller (14%) fall of tonus. With concentrations of epinephrine causing inhibitions of tonus greater than 1 cm., in uncocainized strips, the second response was 46% smaller, and 48% smaller in the presence of cocaine. The higher concentrations of epinephrine apparently depressed the responsive-

³ Burn, J. H., and Tainter, M. L., in press.

ness of the intestines to the subsequent application of the drug. However, cocaine did not modify either the large or small responses to epinephrine, when the differences between the first and second doses were taken into consideration. This result was in contrast to the results of Burn and Tainter³ using the cat intestine, where cocaine desensitized to epinephrine, but was in agreement with those of Thienes and Hockett² on rabbit and guinea pig intestines, which showed no sensitization and apparently only occasional desensitization.

Tyramine: Tyramine augmented 28 strips of intestine and inhibited 6 in concentrations from 1:2,500 to 1:100,000. The augmentation was not as marked as that of barium, but was definite (6 mm., average) and constant. This predominance of muscular stimulation of the rabbit's intestine by tyramine confirmed the earlier results of Tainter.⁴ The second response to tyramine was only about one-third the first, in both cocainized and uncocainized strips. Hence, cocaine did not alter the response to tyramine. In 5 strips which were atropinized, but not cocainized, the second response to tyramine was double the first. This unusual sensitization to successive doses of the same drug in atropinized strips resembled the responses to the muscular stimulant barium, and hence, might be interpreted as further evidence of the muscular origin of the augmentor response to tyramine. Cocaine was used on only 2 such atropinized strips, but both responded with desensitization, *i. e.*, decreased response to the second application. This was also in keeping with the effects of barium on such strips.

Ephedrine: This drug was rather unsatisfactory because of extreme variability of response. With concentrations ranging between 1:10,000 and 1:25,000, in 11 strips, the first response was inhibitory, and in 4 it was augmentory. The second application of ephedrine produced only one-fourth the initial response, and cocainization between the 2 applications did not definitely alter this ratio.

Conclusions: Cocaine desensitizes excised strips of rabbit's intestine to barium, but not to epinephrine, tyramine and ephedrine. With atropinized but uncocainized strips, the second application of barium or tyramine results in marked sensitization. This sensitization is antagonized by cocainization before the second application of barium or tyramine. The failure to demonstrate the same kind of cocaine-sensitization and desensitization to these drugs in rabbit's intestinal muscle, as is seen in the muscles of the circulatory system, suggests that the mechanisms of the responses after cocaine may vary with different tissues.

⁴ Tainter, M. L., *J. Pharm. Exp. Therap.*, 1926, **30**, 163.