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Effect of Yeast Extracts on Local Anesthetic Activity of Cocaine.

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In connection with studies of the effects of yeast and tissue extracts on the metabolism of microörganisms and tissues we have observed that yeast extracts having the property of increasing respiration offset the toxicity of germicides for molds,[1] rat skin,[2] and yeast.[3] Yeast and tissue extracts also exert antisulfanilamide effects, presumably largely due to the content of *p*-aminobenzoic acid[4] and other substances.[5] Exploratory experiments are being conducted on the possible antagonism of yeast extracts for other physiologically active compounds and the present note reports preliminary work on such antagonism for cocaine.

For this work an aqueous-alcoholic extract of Fleischmann's bakers' yeast was prepared as described previously[6] and corresponded to Fraction A of the earlier work.[6] The local anesthetic activity of 0.05 M (1.7%) cocaine hydrochloride with or without yeast extract was determined on the rabbit cornea after 1-minute instillation of the solution according to the usual technic.[7] Four rabbits were used after first standardizing them with cocaine. At least a week elapsed between successive experiments on the same rabbit to allow complete recovery and prevent any tolerance effects. The experiments are summarized in Table I.

Discussion. The 30-minute duration of anesthesia of the rabbit cornea caused by a 1-minute instillation of 0.05 M cocaine hydrochloride compares satisfactorily with other values reported in the literature.[7,8] Addition of 1% of yeast extract caused a lowering of average duration to 27 minutes, and increasing the concentration of yeast extract to 5% further lowered the average anesthetic duration to 24 minutes.

A reason for the relatively small decrease of activity becomes apparent when it is observed that the addition of the yeast extract raised the pH of the cocaine hydrochloride from 4.8 to 6.1 or 6.2. It is well known that alkalinization of cocaine salt solutions increases their anesthetic activity, presumably due to the release of the free base. Régnier has published data on the effect of pH on the local anesthetic activity of cocaine hydrochloride[9] using a rabbit cornea method which differs from ours in technic[10] but which can be used satisfactorily for comparison. Computations based on Régnier's data indicate that an increase in the pH of cocaine solutions from 4.8 to 6.2 should increase the duration of anesthesia by 24%. This would give a theoretical duration of 37 minutes for 0.05 M cocaine hydrochloride at a pH of 6.2. Since 0.05 M cocaine hydrochloride plus 5% of yeast extract at a pH of 6.2 gave a duration of 24 minutes, this decrease would amount to

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9 Régnier, J., *Compt. rend.*, 1924, **179**, 354; *Bull. sci. Pharmacol.*, 1924, **31**, 513.

10 Régnier, J., *Méthodes de Mesure de l'Activité des Anesthésiques Locaux*, Andre Brulliard, Saint Dizier, 1929.

TABLE I.
Effects of Yeast Extract on Cocaine Anesthesia of Rabbit Cornea (0.05 M Cocaine · HCl).

Yeast extr. conc., %	pH	Avg duration of anesthesia, min.	No. of detns.	% decrease in duration of anesthesia
0	4.8	30.0	16	
1	6.1	27.0	8	10
5	6.2	24.0	8	20
5	4.8	13.5	14	55

35% of the theoretical value. When the 0.05 M cocaine hydrochloride solution containing 5% of yeast extract was adjusted to a pH of 4.8 with hydrochloric acid, an average anesthetic duration of 13.5 minutes was obtained, a decrease over the control of 55%. It is evident that the yeast extract lowers the corneal anesthetic activity of cocaine and that this lowering becomes striking when compensation is made for pH changes.

Experiments, too few for a detailed report, indicated that the yeast extract lowered the subcutaneous LD_{50} of cocaine for rats by about 20% when cocaine and yeast extract were injected simultaneously in equal dosage on opposite sides of the abdomen. Further work is being undertaken on local anesthetics and on other physiologically active compounds.

Summary. Addition of a yeast extract to cocaine hydrochloride solution reduces the corneal anesthetic potency, this reduction being especially notable when the pH of the treated solution is lowered to the level of the control solution. There is evidence that the subcutaneous toxicity of cocaine is also decreased by the extract.

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Angiotonin Myotropism

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Page and Helmer[1] stated that angiotonin exhibited smooth-muscle stimulating properties since it constricted blood vessels of the perfused rabbit ear, caused contraction of isolated segments of rabbit ileum and elevated arterial tension in the pithed cat. Apparently no effort was made in their vascular experiments to determine if angiotonin acted myotropically or by way of sympathetic vasoconstrictor components. Another approach to this problem is afforded by the technic employed in our experiments involving sympatholysis.*

Method. Ten cats and 2 dogs were anesthetized either with urethane gastrically or pentobarbital intravenously and then prepared for the insertion of cannulæ into the trachea, femoral vein and carotid artery. In 4 experiments Wharton's duct was also cannulated to determine the effect of angiotonin upon submaxillary salivation. Salivary flow was recorded manometrically. Blood pressure was recorded from the carotid artery with a mercury manometer (Gorrell's plastic tube type) and all drugs were infused intravenously in physiologic saline solution.

Drugs were administered in the following order and usually in the following dosage in mg or cc per kg: Epinephrine HCl, 0.015 mg;

[1] Page, I. H., and Helmer, O. M., *J. Exp. Med.*, 1939, **71**, 29.

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