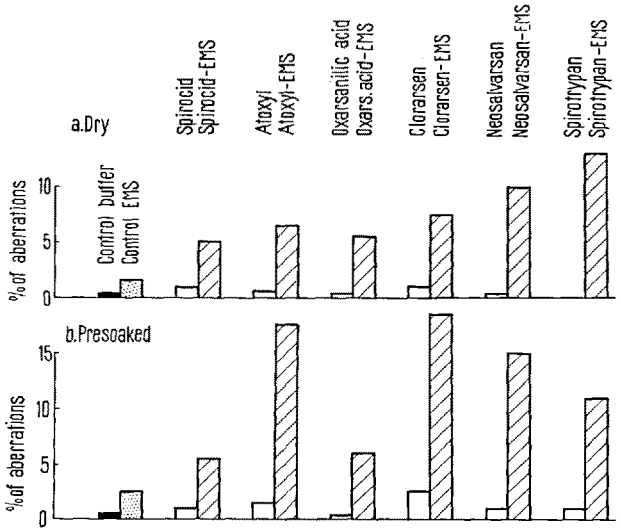

Fig. 1. % of aberrations recorded at metaphase (200 metaphases analysed in each case). Concentrations: arsenical $1 \cdot 10^{-3} M$, EMS 0.3 g/100 ml. a, Dry seeds treated. b, 30 h presoaked seeds. Striped: combined treatment.

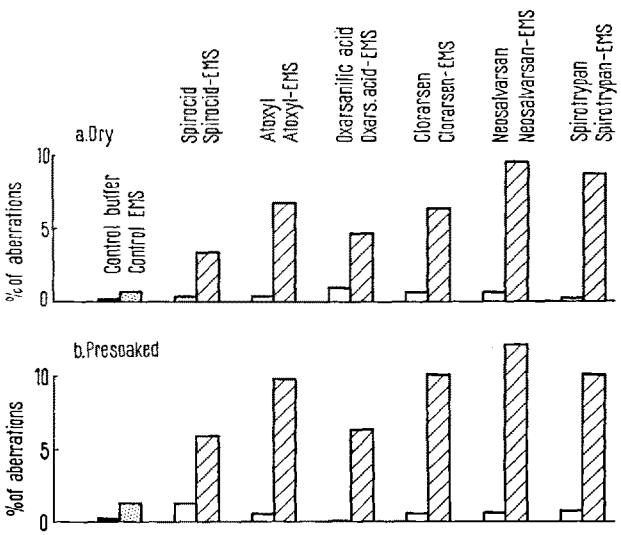

Fig. 2. % of aberrations recorded at anaphase (600 anaphases analysed in each case). Concentrations: arsenical $1 \cdot 10^{-3} M$, EMS 0.3 g/100 ml. a, Dry seeds treated. b, 30 h presoaked seeds. Striped: combined treatment.

The exception can probably be imputed to sampling errors. The increased effect can be attributed to the appearance of aberrations of the subchromatid class.

From the comparative efficiency of the arsenicals, and considering all the criteria together, viz. metaphase and anaphase effects and increased effects after presoaking, the following conclusions can be drawn: (a) the pentavalent compounds (Spirocid, Atoxyl and Oxarsarnilic acid) are less efficient; (b) the efficiency of the double bond compounds (Neoarsphenamine and Spirotrypan) is higher and also seems to be more regular than the effects of pentavalents; (c) the efficiency of the trivalent compound (Clorarsen) can in some respects be compared with the double bond compounds.

These findings give strong indications that the behaviour of the arsenicals in plant tissues is in many respects similar to that in higher animal tissues[4]. However, all the substances tested are definitely less toxic for plant tissues.

The extension of previous experiments with thiol-inhibiting substances has proved the implication of specific –SH enzymes in chromosome rejoining processes.

The possible implication of other enzymatic systems is under investigation[5].

Résumé. Des semences d'orge ont été traitées par 6 arsénoxydes (3 pentavalents, 1 trivalent, 2 molécules à doubles liaisons) avant d'être traitées par une solution de méthane sulfonate d'éthyl (EMS) à 0,3 g par 100 ml/3 h. Ces substances accroissent considérablement les taux d'aberrations des chromosomes normalement produits par l'EMS. Il s'agit principalement d'aberrations de types chromosomique et subchromatidique. Les dérivés trivalent et à double liaison sont les plus actifs. Le problème de l'inhibition d'enzymes à fonction –SH intervenant dans la genèse de ces aberrations est discuté.

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[4] J. F. Danielli, *Cell Physiology and Pharmacology* (Elsevier Publ. Co., New York 1950).

[5] This work was financially aided by the 'Centre National belge d'Etude des Mutations'. – The authors wish to thank Socothera SA for providing a large amount of arsenicals, and Dr. M. K. Jana for reviewing the manuscript.

Effect of Angiotensin on the Cardiac Arrhythmias Induced by g-Strophanthin

Recently a number of papers have been published concerning the antiarrhythmic activity of some biologically active polypeptides. Panisset and Beaulnes[1], and Brodeur and Beaulnes[2] have shown that oxytocin and lysyl[8]-vasopressin prevent cardiac arrhythmias in anaesthetized dog, induced by chloroform and adrenalin. Beaulnes et al.[3,4] have observed the same effect with angiotensin. These authors have shown that in vitro

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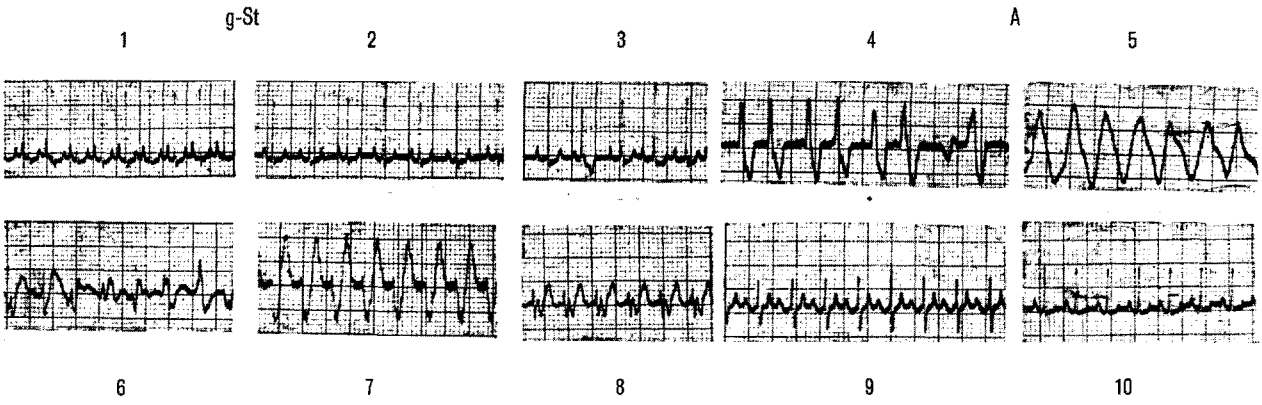
[2] J. Brodeur and A. Beaulnes, Rev. Canad. Biol. *23*, 37 (1964).

[3] A. Beaulnes, G. Gariepy, J. Brodeur, and E. Beltrami, Fed. Proc. (Abstr.) *23*, 121 (1964).

[4] A. Beaulnes, J.-C. Panisset, J. Brodeur, E. Beltrami, and G. Gariepy, Circulation Res. *14*, 11 (1964).



Guinea-pig, 750 g weight, anaesthetized with urethan 2 g/kg. 1, Initial; g-ST, g-Strophanthin 1.4 γ/kg/min; 2, after 5 min; 3, after 10 min; 4, after 20 min; A, g-Strophanthin perfusion is stopped and angiotensin perfusion is started, 3 γ/kg/min; 5, after 2 min; 6, after 5 min; 7, after 10 min; 8, after 15 min; 9, after 20 min; 10, after 30 min.

angiotensin (10^{-10} g/ml) produced a 25% lengthening of the refractory period of isolated rabbit atria. This effect is dose dependent. They also have observed an antiarrhythmic effect of angiotensin on isolated perfused rabbit heart and on anaesthetized dog heart induced by electrical stimulation, $CaCl_2$, and epinephrine-chloroform. VARMA, MELVILLE and SILVER[5] showed that oxytocin had a protective effect on chloroform-epinephrine-induced fibrillation, but had no effect on ouabain induced fibrillation.

During our experiments on the influence of polypeptides on isolated heart preparation of warm blooded animals (guinea-pig, cat), it was observed that angiotensin had antiarrhythmic properties. Rhythm irregularities produced by g-Strophanthin intoxication reverted back to normal when 1–5 μg of angiotensin was given. This was especially obvious in extrasystoles secondary to digitalis effect. It was then decided to check the effect of angiotensin in vivo.

For this investigation two separate groups of animals were used. Each group contained six (600–750 g) guinea-pigs. The animals were anaesthetized with intraperitoneal urethane (25% solution, 2 g/kg). One jugular vein from each animal was cannulated and connected to a perfusion system. Their initial ECG's were taken once every 5 min.

In the first group of animals the perfusion rate of g-Strophanthin was 1.39 ± 0.08 (S.E.) μg/kg/min. Of these six animals, four developed ventricular tachycardia, one ventricular fibrillation, and the last, multifocal ventricular extrasystolies. All these arrhythmias developed within 20–30 min, at which time g-Strophanthin perfusion was stopped and angiotensin perfusion was started. In each instance angiotensin effectively restored sinus rhythm within 17 to 30 min. The dose of angiotensin necessary to do this varied from 1–10 μg/kg/min from one animal to another, with total doses ranging between 16.6 and 140 μg. There was no relation between the dose of g-Strophanthin which induced the arrythmias and the dose of angiotensin necessary to cause reversion to normal sinus rhythm. When sinus rhythm was restored, angiotensin perfusion was stopped and the animals were kept anaesthetized for an additional 1.5–4 h. No arrhythmias were observed during this time. The Figure shows the ECG changes in one of the experiments.

In the six control animals, g-Strophanthin perfusion rate was 1.2 ± 0.09 (S.E.) μg/kg/min. The perfusion time of g-Strophanthin varied between 17 and 30 min, at which time perfusion was stopped (as above) with the appearance of an arrhythmia. All of these animals developed ventricular tachycardia and died of ventricular fibrillation 5–20 min after perfusion was stopped (i.e. 35–50 min after the beginning of perfusion).

In two guinea-pigs angiotensin was perfused at a rate of 10 μg/kg/min for 20 min. Neither guinea-pig died, although bradycardia and some ventricular extrasystolies were observed. These abnormalities reverted back to normal with cessation of the perfusion.

Our results suggest that angiotensin has antiarrhythmic properties on digitalis arrhythmias. According to BEAULNES et al.[3,4] this is a direct effect of angiotensin on the myocardium by a quinidine-like mechanism. The systemic physiological action of angiotensin is very short, because this polypeptide is easily metabolized in blood. However, our results indicate that the antiarrhythmic activity of angiotensin continues for a long time. One possible explanation is that some metabolite of angiotensin has this property, or else that angiotensin acts indirectly by means of altered ionic environment[6].

Résumé. On démontre que l'angiotensin-II a, chez les cobayes anesthésiés, une action antiarythmique provoquée par la g-strophanthine.

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June 8, 1965.

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