In salt loaded animals, antinatriuretic doses of 0.00005 and 0.0005 μg/kg/min had no effect on mean arterial pressure and doses of 0.005 μg/kg/min caused slight increases of 3% and 6% in only 2 out of 5 animals. The log dose response of arterial pressure and sodium excretion in salt loaded animals is compared in Figure 2. It will be seen that the threshold of the antinatriuretic effect of angiotensin is less than 1% of the lowest pressor dose.

The influence of sodium status on the renal response to infused angiotensin may well be mediated by the rate of endogenous production of the hormone. In salt depletion the local renal concentration of angiotensin may be at optimal antinatriuretic levels; infusion of additional angiotensin would then be either without effect, or by summation cause the natriuresis seen with large pressor doses. Most studies of the renal action of angiotensin have used such large doses and the physiological relevance of the resulting natriuresis may be questioned. Much smaller doses, less than 1% of that required to raise arterial pressure, are shown here to reduce sodium excretion in the salt loaded animal. It is likely that angiotensin acts normally as a sodium retaining hormone, an action mediated by small amounts which have no direct pressor action.

Résumé. Chez les lapins auxquels on a administré du sel, l'angiotensine en doses de 0.005–0.00005 μg/kg/min a réduit l'excrétion urinaire de sodium à une quantité correspondant au logarithme de la dose, tandis que des doses inférieures à 0.005 μg/kg/min n'ont eu aucun effet sur la tension artérielle. Chez les mêmes lapins lors d'une déplétion de sel, de telles doses n'ont eu aucun effet sur l'excrétion de sodium. Des doses fortes (> 0.05 μg/kg/min) qui élevaient toujours la pression sanguine, provoquèrent souvent une augmentation lente de l'excrétion de sodium, beaucoup plus marquée quand l'animal était exempt de sel que lors qu'il en était pourvu. On suggère que l'angiotensine agit normalement comme une hormone qui retient le sodium, action produite par de petites quantités sans effet sur la tension artérielle.

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The Participation of Kinins in the Pathogenesis of Early Disturbances in the Skin Capillary Permeability in Local β-Ray Irradiation

Jolles and Harrison[1,2] showed that, in rabbits pretreated with soya bean trypsin inhibitor or ε-aminocaproic acid (EAC), the early increase of capillary permeability of skin locally irradiated by X-rays was abolished. Antihistamines and antiserotonin proved to have no effect on the degree of leakage of the dye. The results indicated the participation of protease system liberating substances active on capillary endothelium in early phase of X-ray inflammation and did not prove that histamine and serotonin are involved.

The experiments to be reported here were designed to investigate this problem further. Albino and pigmented rabbits of either sex weighing 2.5–4.0 kg were used in all experiments. Inflammation was evoked by β-ray (Sr^{90}-Y^{90}) irradiation of 3 areas (diameter, 1 cm) of shaved abdominal skin in doses 1660, 4750 and 9500 rad (270 rad/min). The increase in blood vessel permeability was controlled with Evans blue (20 mg/kg) and Na-fluorescein[3] (5 mg/kg) given i.v. Evans blue was administered immediately after the irradiation for the revelation of early changes of capillary permeability. Na-fluorescein was used for the evaluation of capillary permeability in various terms following the irradiation. The diffuse blueing of the skin resulting from the Evans blue administration did not prevent the visualization of the injured skin fluorescence by 360 nm.

Antihistamines. Dimedrol (Benadryl) and Dimebolin hydrochloride (the derivative of gammacarbolin series) were administered i.m. (10 mg/kg) 30 min before the irradiation. EAC was given i.v. (200 mg/kg) and Trasylol (Bayer, Leverkusen) i.p. (2000 KIE/kg) 1 h before the irradiation.

The results were evaluated according to the method of Litchfield and Wilcoxon modified by Roth[4].

The most pronounced inhibitory action was obtained with Trasylol and the least with Dimebolin. The results proved the significant role played by kinins in the development of early manifestations of the radiation-induced inflammation, in the pathogenesis of the derangement of the skin vessel permeability, in particular. This can be concluded from the protective action of Trasylol and EAC. Trasylol (proteolytic inhibitor obtained from parathyroid glands) inactivates kallikrein and hence inhibits formation of the kinins[5]. EAC, as an antifibrino-

Effect of antiproteolytic and antihistaminic preparations on the development of capillary permeability disturbances caused by β-ray irradiation of rabbits' skin

Preparation	Doses (rad) 1660	4750	9500
None	5/8	6/8	7/8
Dimedrol	1/8	2/8	4/8
Dimebolin	2/8	2/8	5/8
EAC	1/8	1/8	4/8
Trasylol	0/8	1/8	2/8

The numerator: number of rabbits with increased skin vessel permeability, the denominator: total number of rabbits in group.

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litic, inhibits formation of plasmin which promotes development of kinins by means of activation of kallikreinogen[6] or acting directly on kininogen[7]. This mechanism of protective activity of EAC seems to be most probable. EAC, as is shown in the experiments on rabbits, is deprived of antihistaminic or antiserotoninic activity[8]. As was shown in our experiments, EAC does not affect the permeability response of rabbit's skin vessels to synthetic bradykinin[9].

Dimebolin protects guinea-pigs from 2416 lethal doses of histamine and its antihistaminic activity is 74 times greater than that of Dimedrol[10]. Our experiments with histamine injections in rabbit's skin has shown that Dimebolin is 95 times more active than Dimedrol. Dimebolin, in spite of its pronounced antihistaminic activity, is less potent as a protector in β-ray inflammation. This confirms the insignificant role of histamine in the pathogenesis of early manifestations of radiation-induced inflammation. The protective action of Dimedrol and Dimebolin in the inflammation depends probably on antibradykininic properties of these preparations. Dimedrol as a protector is 1.5 times stronger than Dimebolin. The more pronounced protective action of Dimedrol can be explained by its antibradykininic activity. We were able to demonstrate in the experiments on rabbits with i.c. injections of bradykinin that a premedication with Dimedrol was also 1.5 times more effective than in the case of Dimebolin.

In conclusion, it is possible to explain the protective action of Trasylol and EAC in β-ray inflammation of the skin by the inhibition of kinins formation, and the activity of Dimedrol and Dimebolin by the inactivation of kinins which have already been formed.

From the practical point of view it was interesting to investigate the influence of the inhibition of the early manifestations of the inflammation of the subsequent development of skin injury. Observations of pretreated and non-pretreated rabbits during 30 days showed that the skin injury and the derangement on vessel permeability were less pronounced in rabbits pretreated with Trasylol and Dimedrol. It seems likely that the rupture of some links in the pathogenesis of early phase of inflammation, inhibition of kinin system, in particular may be beneficial to the subsequent development of skin inflammation.

Выводы. Развитие воспаления кожи кроликов, облученной β-лучами источника $Sr^{90} + Y^{90}$, наиболее эффективно тормозится тразилолом, а наименее при применении димеболина. Димедрол и Σ-аминокапроновая кислота (ЕАКК) по антивоспалительной активности занимает промежуточное место. Защитное действие тразилола и ЕАКК, повидимому, объясняется торможением образования кининов а активность димедрола и димеболина-инактивацией уже образованных кининов.

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Über die Wirkung von Prostaglandin E_1 auf den Ca-Haushalt isolierter Meerschweinchenherzen

Die Wirkung der Prostaglandine auf das cardiovaskuläre System besteht nach bisherigen Erfahrungen bei in vivo-Anwendung in einer Abnahme des Blutdruckes (z.T. auch des Minutenvolumens) und einer sekundären Zunahme der Herzfrequenz (Übersichten[1-3]). In Versuchen mit isolierten Herzpräparaten konnten jedoch auch Hinweise auf eine direkte Herzwirkung erhalten werden: Unter geeigneten Bedingungen verursacht Prostaglandin E_1 (PGE_1) am isolierten Meerschweinchenherzen eine Zunahme des Coronardurchflusses, der Schlagfrequenz und der Kontraktionskraft[4]. Diese Effekte lassen sich durch Blockade der β-Rezeptoren oder durch Reserpinisierung nicht beeinflussen, können somit nicht über eine direkte oder indirekte adrenerge Wirkung erklärt werden. Die positiv inotrope Wirkung ist vor allem bei erniedrigter Ca-Konzentration im Perfusionsmedium gut ausgeprägt[4]. PGE_1 vermag auch eine Phosphorylase des Herzens in ähnlicher Weise zu aktivieren wie Ca (oder Adrenalin), allerdings nur an intakten Zellen, nicht im Homogenat[5].

Diese Beobachtungen lassen einen Zusammenhang zwischen der positiv inotropen Herzwirkung dieser Substanz und dem myocardialen Ca-Haushalt vermuten. Es wurden deshalb Messungen des cellulären Ca-Umsatzes im Meerschweinchenherzen bei Infusion von PGE_1 vorgenommen.

Methode. Meerschweinchenherzen wurden nach der Langendorffmethode mit Tyrodelösung (30 °C, carbogengesättigt) durchströmt, bis sich konstante Werte für die Kontraktionskraft und den Durchfluss eingestellt hatten (30–60 min). Dann wurde die Perfusion mit ^{45}Ca-haltiger Tyrodelösung fortgeführt, teilweise unter Kontrollbedingungen, teilweise bei gleichzeitiger Infusion von PGE_1 (1 μg/min in 0,1 ml). Nach verschiedenen Zeiten wurde die Ca-Konzentration und die aufgenommene ^{45}Ca-Menge in diesen Präparaten bestimmt und daraus – nach Korrektur des extracellulären Aktivitäts- und Ca-Anteiles – der Markierungsgrad des intracellulären Ca errechnet (Methoden[6-8]).

Ergebnisse. Der Ca-Gehalt des Gewebes war in den einzelnen untersuchten Abschnitten verschieden, blieb jedoch während der gesamten Versuchsdauer konstant und wurde durch PGE_1 nicht beeinflusst (Tabelle). Die Aufnahme von ^{45}Ca erreichte innerhalb von 30–60 min ihr Maximum (Figur). Die Berechnung der intracellulären spezifischen Aktivität im Gleichgewichtszustand des