However, the maximal stimulation in nigral tissue was only about one-tenth of that in striatal tissue. Penfluridol inhibited the dopamine-sensitive adenylate cyclase in both brain areas in a similar way, inducing a shift of the dose-response-curve to the right.

These results clearly indicate the occurrence of a dopamine-stimulated adenylate cyclase in the substantia nigra of rats. This observation is in good agreement with that published by PHILLIPSON and HORN[9], just when our manuscript was in preparation. The dopamine receptors in both brain regions seem to have a similar affinity for dopamine. The reason for the difference in the efficacy of dopamine might be either a difference in the density of dopamine receptors in both regions or a difference in the transmission from the receptors to the enzyme. If the theory is correct that dopamine, released from dendrites of dopaminergic neurones in the substantia nigra, again reacts with dopaminergic neurones[10-12] (in contrast to the nerve endings, where dopamine-sensitive adenylate cyclase probably reflects the reaction of dopamine with receptors at non-dopaminergic neurones), then the dopamine-sensitive adenylate cyclase seems to play a role in auto-inhibitory actions of dopamine, released from the dendrites and acting on dopaminergic neurones, originating in the substantia nigra. It is tempting to speculate that an adenylate cyclase system might also play a role in dopamine receptors, located presynaptically at the nerve endings in dopaminergic neurones ('autoreceptors'), although the bulk of cycl. AMP, formed after stimulation by dopamine, seems to be located postsynaptically[13] and hence might mask the small amount of cycl. AMP, formed presynaptically.

Penfluridol is apparently a competitive inhibitor of dopamine in both brain regions, since it induces a parallel-shift of the dose-response-curves of dopamine to the right. A Lineweaver-Burk-plot of our results (which is not shown here) clearly supports these conclusions.

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Potentiation by Taurine of the Inotropic Effect of Ouabain and the Content of Intracellular Ca^{++} and Taurine in the Heart

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Summary. Under certain conditions, taurine (3.0 m*M*) potentiated cardiac contractile response to ouabain in the normal medium. The potentiation by taurine was also observed in the low K^+ medium, in which the positive inotropic effect of ouabain increased. The potentiation as seen in both media was, at least in part, due to the increase by taurine of Ca^{++} content in the heart. Taurine in the heart was not directly related to this potentiation.

Taurine is present in mammalian hearts in large quantities[2-4], and the concentration of myocardial taurine can be altered by some diseases[5-7] and drugs[7]; its function in the heart, however, has long been unknown. At present, taurine is known to possess an antiarrhythmic effect. For instance, READ and WELTY[8] reported that i.v. taurine depressed the development of epinephrine-induced ventricular premature contraction and stopped digoxin-induced arrhythmias in vagotomized dogs. In addition, the present authors showed that taurine prevented the prolongation of P–R intervals caused by acutely-infused ouabain in rats[9], and the T wave-disappearance in the guinea-pig treated chronically with digitoxin[10]. Unlike the effect of taurine in whole animals, in isolated hearts taurine increased contractile response to strophanthin-K[11] and inhibited a decrease of contractile force by Ca^{++}-free media[12].

Ca^{++}, an important ion in an excitation-contraction coupling, was shown to be taken up more extensively in the taurine-treated heart than in the control[12] and with the sarcoplasmic reticulum isolated from rat skeletal muscle, taurine slowed a rate of loss of Ca^{++} transport caused by phospholipase C[13], suggesting that taurine was acting as a membrane stabilizer.

We therefore attempted to find whether or not the potentiation by taurine of the positive inotropic effect of ouabain paralleled changes in intracellular Ca^{++} and taurine contents in isolated heart preparations. In addition, since the inotropic response to ouabain was increased in a low K^+ medium[14], it was also examined whether or not taurine could potentiate further the ouabain-induced inotropism in the medium.

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Materials and methods. Left atrial strips were prepared from male guinea-pigs (250–350 g) and driven by electric stimulation in Tyrode's solution as reported previously in detail[10]. After changes by ouabain in the contraction amplitude were recorded for 15 min, the preparation was subjected to determinations of intracellular contents of Ca^{++} and taurine, according to procedures of DOLARA et al.[12] and GUIDOTTI et al.[11], respectively. In some experiments, taurine was added to an organ bath at final concentrations of 0.5 and 3.0 mM, 10 min prior to ouabain. Isotonicity in the low K^+ (2.0 mM)-medium was adjusted by NaCl. Total and extracellular water was determined by the antipyrine method[15] and the inulin method[16], respectively. Drugs used were taurine (Taisho Pharmaceutical Co., Ltd., Tokyo) and ouabain (E. Merck, Darmstadt).

Results and discussion. Lowering the K^+ concentration to 2.0 mM from 5.6 mM in the external medium resulted in a significant increase in the positive inotropic effect of ouabain at doses ranging 10^{-8} to 10^{-6} M (Figure 1). Taurine at a dose of 3.0 mM (but not 0.5 mM) increased the cardiac response to ouabain in either the normal or low K^+ medium. Since taurine has been shown to be positively-inotropic in the guinea-pig heart preparation[17], myocardial taurine concentrations were determined, and it was found that taurine was taken up by the heart (Table). That the uptake was not significantly promoted

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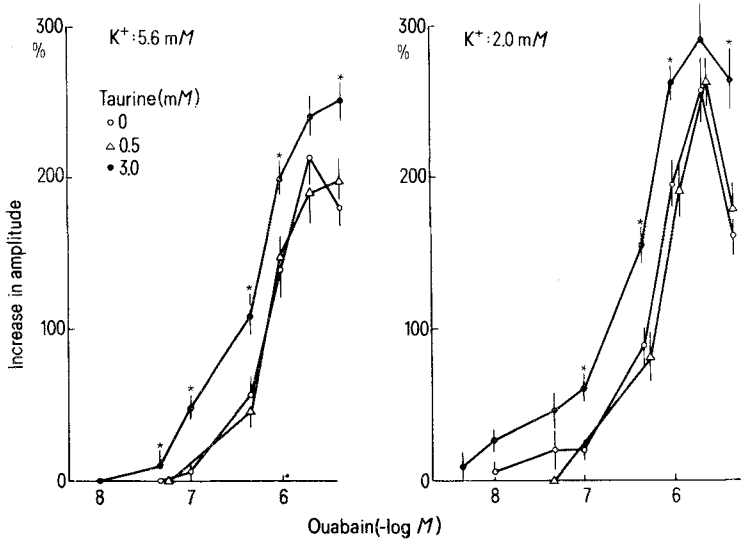

Fig. 1. Effect of ouabain on the contraction amplitude in the normal (left) and the low K^+ (right) media in the absence (○) or the presence of taurine at doses of 0.5 (△) and 3.0 mM (●). Ordinate, % change in the amplitude, abscissa, molar concentration of ouabain (–log scale). Bars represent S. E. M. in 15–20 instances. * Significant ($p<0.05$) when compared with the control in each medium.

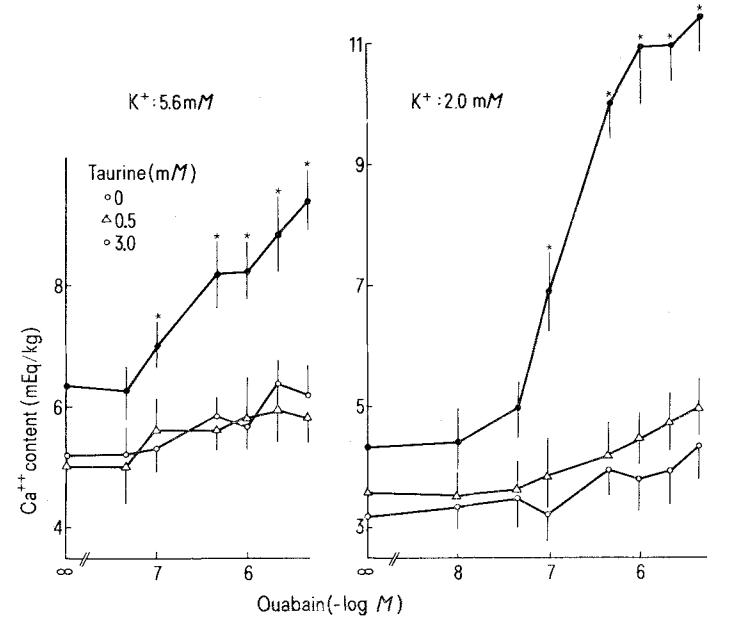

Fig. 2. Effect of ouabain on the intracellular Ca^{++} concentration. Ordinate, Ca^{++} content expressed as mEq/kg wet tissue corrected for extracellular space. Same legends as in Figure 1.

Taurine uptake[a] by the isolated guinea-pig heart

Taurine concentration in media (mM)	Normal medium	Low K^+ medium
0	21.3 ± 2.6[b]	29.0 ± 4.4
0.5	25.3 ± 3.1	34.9 ± 6.0
3.0	44.2 ± 3.8	63.2 ± 13.6

[a] μmoles/g of intracellular water; [b] mean ± S.E.M. in 8–12 instances.

by the decrease in K^+ contents in the medium (table) and was not changed by ouabain at the doses used in both media (data not shown) would suggest that the potentiation by taurine of ouabain-induced inotropism was not explained by the change in myocardial contents of taurine. On the other hand, DOLARA et al.[12] suggested that taurine would increase amounts of Ca^{++} available for contraction. This may explain the potentiation by taurine of the inotropism of digitalis. In the present experiment, in which intracellular Ca^{++} contents were indeed measured in the presence of taurine, ouabain did not change total Ca^{++} content in the control heart but increased significantly the Ca^{++} content in the taurine (3.0 mM)-loaded heart in both media (Figure 2). The increase in the Ca^{++} content, which was greater in the low K^+ medium than the control, paralleled the positive inotropic response to ouabain. The potentiation by taurine of the positive inotropic effect of ouabain would be, at least in part, due to the increased content of Ca^{++} in the heart. Although neither taurine nor ouabain alone changed the Ca^{++} content in the present experiment, taurine in the presence of ouabain might be, to some extent, concerned in the myocardial uptake of Ca^{++}, because it has already been reported that taurine inhibited the loss of intracellular Ca^{++} in some way[6,12,13]. The accumulation of Ca^{++} in the taurine-loaded heart might result in the increase of Ca^{++} used for activating contractions and consequently in the potentiation of myocardial response to ouabain. Increase by taurine of the response to ouabain at a dose of 5×10^{-6} M remained unexplained in this paper.

Mikroskopische Untersuchungen zur «gefässabdichtenden» Wirkung der Kalziumionen

Microscopical investigations on the 'vessel sealing' effect of calcium ions

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Summary. The effect of locally applied calcium on the vascular permeability is studied under the conditions of an acute inflammatory reaction. Using the Sephadex-inflammation, local elevated calcium concentration neither inhibited oedema formation, nor were reduction of inflammatory signs at all observed on the microscopical level.

Kalzium gilt seit langem als entzündungshemmendes Mittel. Durch direkte Einwirkung auf eine interzelluläre «Zementsubstanz» und auch auf das Bindegewebe sollen Ca^{2+} «gefässabdichtend» und somit gegen Ödembildung und Leukozytenemigration wirken. Die Befunde von CHAMBERS und ZWEIFACH[1,2], dass bei Perfusion der Kapillaren mit Ca^{2+}-freier Lösung die Permeabilität zunimmt, stützen diese Vorstellung. Allerdings ist nicht erwiesen, ob auch dann, wenn kein Kalziummangel besteht, durch Steigerung der Ca^{2+}-Konzentration die Gefässpermeabilität beeinflusst wird.

Zellzahl, Granulozyten und Mastzellen, 6 Stunden nach Injektion von $CaCl_2$-Sephadex

	Kontrolle	$CaCl_2$-Sephadex		
		4,5 mmol	7,5 mmol	30 mmol
Gesamtzellzahl	1990±300	2870±1400	2410±470	1200±300
% Granulozyten	83±6	82±1	83±4	77±5
Mastzellen	3,2±0,54	3,0±0,91	2,9±0,85	2,5±0,94
% intakter Mastzellen	35	36	35	23

Es erschien aussichtsreich, diese Frage an der Sephadex-Entzündung[3] zu studieren, weil sich diese entzündungserregende Substanz leicht mit Ca^{2+} beladen lässt. Somit könnte sich am Ort der Entzündung ein hemmender Einfluss der gleichzeitig anwesenden Ca^{2+} bemerkbar machen. Dabei ist es von Vorteil, dass Ca^{2+} aus dem subkutan injizierten Sephadexdepot entsprechend der Diffusionsbedingungen allmählich und über einen längeren Zeitraum in das umgebende Gewebe abgegeben werden.

Material und Methoden. 1 ml Sephadex G 200, welches in $CaCl_2$-Lösungen (4,5, 7,5, 30 mmol/l Ca^{2+}) gequollen war, wurde Ratten vom Wistar-Stamm 150 g ± 10% subkutan unter die Rückenhaut injiziert. In 0,9% NaCl gequollenes Sephadex diente als Kontrolle.

Histologische Untersuchung. Nach 6 bzw. 24 Stunden wurden die Injektionsstellen mit dem umgebenden Gewebe entnommen, Gefrierschnitte angefertigt (Färbung Hämatoxyl-Eosin Van Gieson und Toluidinblau) und darin die Anzahl der Mastzellen in einem Gesichtsfeld (Vergr. 10 × 40) gezählt, das vom Sephadexdepot und vom Hauptmuskel begrenzt war. Ausserdem wurde der Prozentsatz der intaktgebliebenen Mastzellen bestimmt.

Zählung der Exsudatzellen. Eine abgewogene Menge Sephadex aus dem Entzündungsherd wird mit 0,1 m Zitronensäure mit 0,1% Kristallviolett für 30 Minuten

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