A discussion of the results and the significance of these drugs for synaptic transmission will be deferred until this work is reported in detail.

Zusammenfassung. Mikroelektrophoretisch verabreichtes Histamin, Histidin und Imidazolessigsäure hemmen die Aktivität von Neuronen der Medulla oblongata der Katze. Strychnin, welches in reversibler Weise die hemmende Wirkung von Glycin blockiert, zeigt keinen Antagonismus zu Imidazolessigsäure.

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The Origin of Tourniquet Shock-Induced Cardiovascular Failure in Exogenous Hyperthyroidism

It is controversial whether the sudden cardiovascular collaps of hyperthyroid animals in shock is primarily due to myocardial or peripheral failure.

In exogenous hyperthyroidism the enlarged heart ejects more blood and is more efficient than the normal, euthyroid heart under basal conditions and during loading[1]. There are, however, indications that areas of relative hypoxia may exist in the hypertrophied myocardium of hyperthyroid animals. Marked tachycardia and increased oxygen requirement result in a non-uniform distribution of coronary blood flow, myocardial hypoxia and decreased contractile force[2]. This pattern could cause the sudden deaths of exogenous-hyperthyroid animals and may be the primary deteriorating factor in shock since susceptibility to shock is directly related to an increased metabolic rate of most organs[3] including the heart[4].

The following experiments were designed to differentiate between myocardial involvement and peripheral involvement as the primary deteriorating factors in the development of shock. Hyperthyroid animals were pretreated with either reserpine, a norepinephrine depleting agent or phenoxybenzamine, an α-blocking agent. The cardiovascular system was then challenged by unilateral or bilateral tourniquets on the hind limbs.

Material and methods. Male albino rats of the Sprague-Dawley Strain (Holzman) weighing 220 ± 15 g were used. The rats were made hyperthyroid by a daily s.c. injection during 14 days, of 20 µl/100 g of body weight of l-triiodothyronine (Cytomel: Smith, Klein & French Co.). The control animals received injections of solvent in the same volume to body weight ratio. Reserpine pretreatment consisted of a s.c. injection of Serpasil: Reserpine (Ciba Pharmaceutical Products, Inc.), 1 mg/kg body weight, 1 day before the tourniquet was applied. Phenoxybenzamine: Dibenzyline (Smith, Klein and French Lab.) 1 mg/kg of body weight, was given i.p. 1 h before tourniquet application. Tourniquet shock was produced by the ligation of the hind limb(s) of anesthetized animals (pentobarbital – 30 mg/kg i.p.) at the inguinal level, with a double rubber band kept in place for 5 h. Death was confirmed by electrocardiogram. Total body oxygen consumption was measured with a M.O.U.S.E. spirometer (Mod. 160, Custom Eng. & Dev. Co., St. Louis, Mo.). Blood pressure was recorded in the carotid artery by a Statham pressure transducer and the mean arterial blood pressure is expressed as diastolic pressure $+^1/_3$ of pulse pressure. The Student-*t*-test was used to determine the significance of the difference between two means. *P*-values less than 0.01 were accepted as significant.

Results and discussion. 5 h bilateral limb ischemia caused 100% mortality in eurythyroid rats (Table I). The survival time could be increased significantly by pretreatment with phenoxybenzamine but reserpine was completely ineffective. Similar results were seen with hyperthyroid animals having incresed cardiac work load (increased blood viscosity due to extravasation from the ischemic limbs) during the development of tourniquet shock. The animals died within a short time after the release of the tourniquets but again, phenoxybenzamine significantly lengthened the survival time.

Recent studies[5] fail to support the previous concept[6] that hyperthyroid animals are less resistant to shock as a

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Table I. Bilateral limb ischemia: The effect of drugs on euthyroid and hyperthyroid rats

Treatment	Euthyroid			Hyperthyroid			
	No. of rats	Survival time (h)	Mortality (%)	No. of rats	Survival time (h)	Mortality (%)	Significant difference between Euthyroid-Hyperthyroid
Saline	11	11.2 ± 1.61	100	15	0.92 ± 0.24	100	$P < 0.01$
Reserpine	10	11.64 ± 1.24	100	14	0.85 ± 0.18	100	$P < 0.01$
Phenoxybenzamine	12	19.32 ± 2.84	83*	15	2.48 ± 0.45	100	$P < 0.01$

*2 of 12 animals lived 7 days and were sacrificed.

Table II. Unilateral limb ischemia: The effect of drugs on euthyroid and hyperthyroid rats

Treatment	Euthyroid			Hyperthyroid			
	No. of rats	Survival time (h)	Mortality (%)	No. of rats	Survival time (h)	Mortality (%)	Significance
Saline	14	[a]	0	11	1.88 ± 0.41	100	
Reserpine	12	[a]	0	13	1.56 ± 0.36	100	$P > 0.01$
Phenoxybenzamine	12	[a]	0	15	5.82 ± 1.12	80[b]	$P < 0.01$

[a] Lived 7 days, then were sacrificed. [b] 3 of 15 lived 7 days and were sacrificed.

Table III. Parameters obtained (with the exception of heart weight) just prior to tourniquet application

Groups	No. of rats	Total body oxygen consumption (ml/h/100 g body wt.)	Heart weight (mg/100 g body wt.)	Heart rate (min)	Mean blood pressure (mm Hg)
1. Intact (euthyroid)	10	238 ± 21	362 ± 28	322 ± 46	112 ± 14
2. Intact and reserpine	8	222 ± 24	358 ± 36	304 ± 38	119 ± 18
3. Intact and phenoxybenzamine	8	202 ± 32	365 ± 23	316 ± 28	116 ± 11
4. Hyperthyroid	10	530 ± 64	602 ± 83	596 ± 88	228 ± 38
5. Hyperthyroid and reserpine	9	521 ± 49	638 ± 65	518 ± 72	184 ± 28
6. Hyperthyroid and phenoxybenzamine	10	436 ± 56[a]	618 ± 76	564 ± 76	206 ± 38

[a] $p < 0.05$ between groups 4 and 5.

thyroid hormone sensitizing the tissues to endogenous or catecholamines. If this were true we would observe some beneficial effect in tourniquet subjected hyperthyroid animals after reserpinization when the noradrenalin content of the heart was depleted. But, in fact, reserpine pretreatment does not change the survival time at all. Therefore, neither by increasing nor decreasing the endogenous catecholamine content are we able to alter the animals' susceptibility to shock.

Although the tachycardia of hyperthyroidism appears to be mediated by a hyperactive sympathetic system, metabolic effects do not seem to be so related; reserpinization of hyperthyroid animals does not change oxygen consumption (Table III) or cardiac output[7].

The use of a unilaterial tourniquet (Table II) which is not lethal to euthyroid rats[8], kills hyperthyroid rats within 2 h. Reserpine pretreatment again had no effect, however phenoxybenzamine not only increased the overall survival time but some of the rats survived as long as seven days, at which time they were killed.

The main beneficial effects of phenoxybenzamine is due to the blocking of peripheral constriction of circulating sympathomimetics thus enhancing peripheral blood flow[9]. We also observed a decreased total body oxygen consumption (Table III). Because the reflexes involving the heart are intact after α-adrenergic blockade[10], the lengthened survival time was due to improved peripheral blood flow and possibly a less demanding tissue oxygen utilization.

We conclude therefore, that the critical factor in the development of tourniquet shock of hyperthyroid rats is decreased peripheral efficiency rather than myocardial failure.

Zusammenfassung. Die Veränderung des endogenen Catecholamin-Gehaltes des Herzens hyperthyroider Ratten hebt die Schockempfindlichkeit der Tiere nicht auf.

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Effect of Phenformin and Chlorpropamide on Renin Activity in the Rat

Several drugs have been added during the last decade to the treatment of diabetes insipidus (DI), in addition to the substitution treatment with vasopressin. Chlorothiazide and other diuretics were introduced with considerable clinical success[1,2]. However, no satisfactory explanation for the mechanism of action of the benzothiadiazines in DI has been suggested. We have previously reported that thiazides had an antidipsic effect when applied to nephrectomized rats or following implantation in the hypothalamus[3,4]. The introduction of antihyperglycemic drugs, chlorpropamide and metformin, to the treatment of diabetes insipidus[5,6] presented another challenge as to the mechanism of action of the various unrelated drugs in this disease.

Recently BROWN et al.[7] have suggested a new and interesting hypothesis for the antidiuretic effect of thiazides in DI. The crucial factor according to this hypothesis is an increase in plasma renin activity and hence – angiotensin. This would then reduce urine volume and, secondarily, reduce the thirst, a remarkable feature in this disease.