30-sec-periods of illumination and the mesopic level stimulus. The histogram (Figure 2) indicates some clustering of interspike intervals around values of 0.048 sec, 0.096 sec, 0.144 sec and 0.192 sec. This indicates a regular firing pattern.

In many cases the electrode recorded activity from a number of cells in which the rhythmic activity appeared on bursts of spikes. The duration of the burst was examined. The mean burst duration was 0.047 ± 0.002 sec. The silent period between bursts was found to be 0.028 ± 0.006 sec. The average burst frequency of 12.8 ± 0.3 bursts/sec was observed for the mesopic stimulus of 30 sec duration. When a slightly brighter stimulus was used (3.2 N.D.) with a 30-sec-duration, these values were observed to change. The first duration was found to be 0.032 ± 0.002 sec with a silent period of 0.031 ± 0.003 sec. The average bursting frequency was found to be 15.6 ± 0.5 bursts/sec.

Discussion. The rhythmic activity was found to be identical when recorded from either the optic tectum or retina. Since the activity was recorded from unanaesthetized frogs, it is unlikely that the activity was the result of anaesthetic influences. Hypoxia was reduced by keeping the frog moist and the presentation of an enriched O_2 atmosphere. The activity recorded in the frog is similar to that observed in the cat. In both, bursts of spikes were separated by silent periods of inactivity. One difference was observed. In the cat, the bursting frequency was constant and did not depend on the stimulus intensity[5]. In the frog, the bursting frequency was observed to change with a slight change in stimulus intensity. Steinberg[4] studied the oscillatory potentials in the cat retina, and concluded that this type of ganglion cell discharge was probably related to a process of neural light adaptation. Other workers[3] speculate that efferent fibers may be involved in regulating the rhythmic firing of the ganglion cells. Experiments are presently under way to determine if efferent fibres in the frog optic nerve may be involved in the genention of the rhythm bursting firing pattern.

Zusammenfassung. Nachweis, dass die Netzhaut-Ganglienzellen dritter Klasse bei *Rana pipiens* auf Beleuchtungsperiodenausgleich reaktiv rhythmische Potentialfolgen von «bursts» und «firing» erzeugen. Als wirksamste Beleuchtungsperioden erwiesen sich solche im mesopischen Bereich bei Mindestdauer von 15 sec. Weder skotopische noch photopische Belichtungen führten zu rhythmischer Aktivität.

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Changed Chronotropic Sensitivity to Sympathomimetic Amines in Isolated Atria from Rats Following Cold Acclimation

It has been established that cold acclimation sensitizes the animals to the metabolic effect of noradrenaline (NA) and of isoprenaline (ISO), which effect is mediated by the β-adrenoreceptors[1,2]. Some authors have also observed an increase in cardiovascular sensitivity to NA and to ISO[1,3–5], whereas some have found a decreased sensitivity[6]. Moreover, Himms-Hagen and Mazurkievicz-Kwilecki[7] did not find any change in the sensitivity to NA in isolated tissues from cold-acclimated rats.

A possible reason for the variability in the cardiovascular responses may be the variable extent of reflex adjustment. In addition, the cardiac responses to sympathomimetic amines in vivo are dependent on the duration of cold exposure[8]. Therefore the problem of the changes in response to sympathomimetic amines was studied in isolated cardiac tissues by measuring the chronotropic

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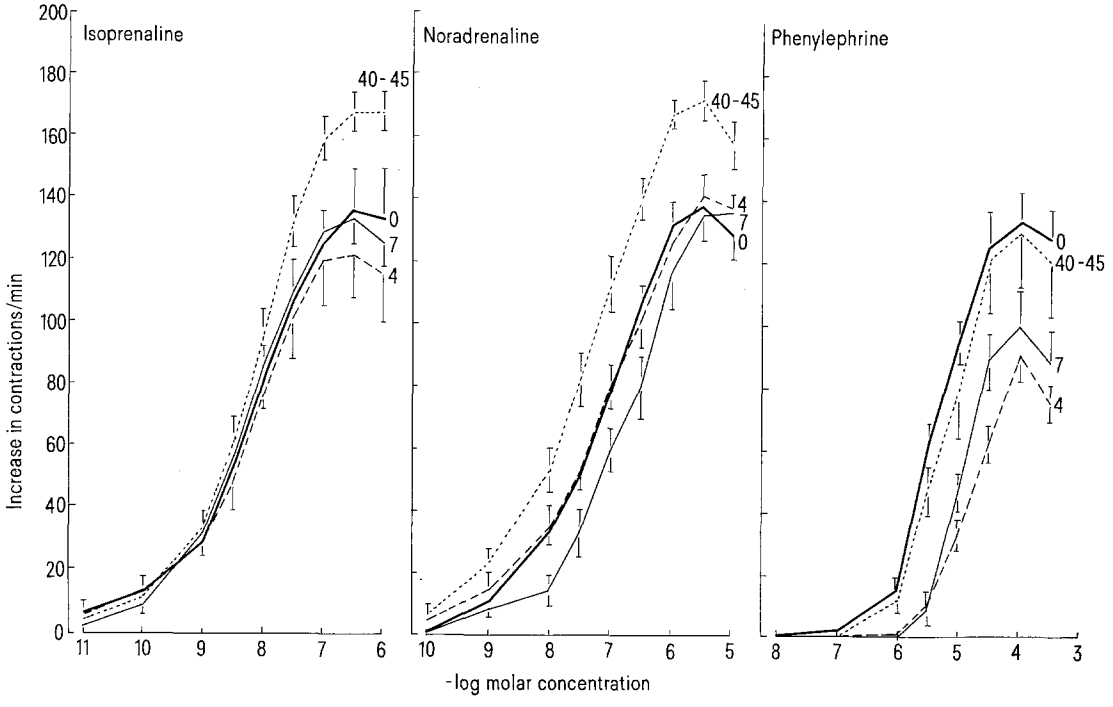
The basic contraction rates, the pD_2-values (-log molar ED_{50}) and the maximum responses (± SE) to isoprenaline, noradrenaline and phenylephrine in isolated atria from control rats (kept at 23 °C) and from animals transferred to 5 °C for different lengths of time

Days at 5 °C	Basic atrial rate/min	Isoprenaline		Noradrenaline		Phenylephrine	
		pD_2	Maximum response/min	pD_2	Maximum response/min	pD_2	Maximum response/min
Control	228 ± 8 (29)	8.23 ± 0.12 (6)	137 ± 14	7.10 ± 0.08 (7)	138 ± 7	5.39 ± 0.08 (7)	134 ± 10
4	220 ± 10 (21)	8.22 ± 0.09 (8)	124 ± 15	7.08 ± 0.15 (6)	142 ± 6	4.76 ± 0.06[c] (6)	91 ± 8[b]
7	196 ± 6[c] (26)	8.30 ± 0.11 (6)	133 ± 8	6.60 ± 0.13[b] (7)	136 ± 10	4.96 ± 0.04[c] (6)	101 ± 12[a]
12	204 ± 13 (6)			7.06 ± 0.11 (6)	139 ± 16		
40–45	228 ± 9 (17)	8.12 ± 0.12 (6)	167 ± 6[a]	7.38 ± 0.10 (6)	172 ± 7[b]	5.29 ± 0.06 (5)	130 ± 17

Significant difference from the control: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$. Figures in parentheses indicate number of rats in the groups.



Log concentration-response curves for the chronotropic responses to isoprenaline, noradrenaline and phenylephrine in isolated atria from control rats (0, kept at 23 °C) and from animals transferred to 5 °C for 4, 7 and 40–45 days. Vertical bars indicate ± SE. Numbers of experiments are identical with those given in the Table.

sensitivity to NA in isolated atria from rats acclimated to cold for different lengths of time. In addition to NA, ISO and phenylephrine (PHE) were used as selective β- and α-receptor stimulants, respectively, in an attempt to relate the possible changes in response to different adrenoreceptors.

Material and method. Adult male Sprague-Dawley rats weighing on average 312 g (range 192–490 g) were acclimated to 5 °C for 4, 7, 12, and 40–45 days. The control animals were kept at 23 °C. The animals were decapitated. The atria were dissected from the heart and suspended in 30 ml of Tyrode's solution at 37 °C. The solution was aerated with 95% O_2-5% CO_2. The atria were held horizontally with a tension of 600 mg, and the rate of spontaneous contractions was recorded by means of a suction electrode connected to a Mingograph 24B jet recorder. After a stabilization period of 40–60 min, the cumulative concentration-response relationships were determined by the addition of agonist at 120 sec intervals in molar concentration steps of 0.5 log units until the maximum chronotropic response to that agonist had developed[9,10]. A single concentration-response relationship curve was determined with each atrial preparation. The molar concentration of agonist required to produce 50% of the maximum response (ED_{50}) was determined from the log concentration-response curve obtained. The results are given as pD_2-values, which means -log molar ED_{50}[9]. Statistical significances were calculated by means of the analysis of variance.

Results. The results in the Table show that the basic contraction frequency of rat atria was reduced after transferring the control rats to 5 °C for 7 days. After 40–45 days of cold acclimation, however, the atrial rate returned to the initial level. The results in the Figure and in the Table show that cold acclimation did not change the sensitivity of isolated atria to ISO. However, cold acclimation for a longer period (40–45 days) resulted in a significant increase in the maximum response to ISO.

Cold exposure for 7 days shifted the concentration-response curve for NA to the right (Figure, Table). The ratio of ED_{50} of control rats to ED_{50} of rats acclimated to cold for 7 days was 1 : 3.1. This means that cold exposure for a week decreased the sensitivity of isolated atria to NA by 3.1 times. After the animals had been at 5 °C for 40 days, the concentration-response curve shifted to the left of that of the control rats and all the responses measured to concentrations 10^{-9}–10^{-5} M of NA were significantly greater in cold-acclimated animals ($P < 0.05$–$P < 0.01$). However, at 40–45 days of cold acclimation, owing to a marked increase in the maximum response, the pD_2-value did not differ significantly from that of the controls. Cold exposure for 4 and 7 days decreased the sensitivity of isolated atria to PHE by 4.5 and 2.8 times, respectively, inspite of the significantly decreased maximum responses (Figure, Table). At 40–45 days of prolonged cold acclimation, the concentration-response curve no longer differed from that of the controls.

Discussion. TIRRI et al.[8] found recently that in vivo the cardiac response after a week's cold exposure was decreased more to NA than to ISO. Since PHE failed to increase the heart rate under the conditions used, they suggested that this lowered response was probably mediated by the β-adrenoreceptors. Our present results support these findings in that cold acclimation for a week decreased the sensitivity of isolated rat atria to NA. The response to ISO, however, did not change at all, and in

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in vitro conditions now used, the atria responded markedly to PHE and this response was significantly lowered after a week's cold exposure. It can thus be concluded, supported by the findings from frogs and toads[8,11], that this lowered sensitivity results from a decreased sensitivity of cardiac α-adrenoreceptors. Furthermore, it is reasonable to assume that the enhanced sympathetic activity of cold-exposed rats is responsible for this subsensitivity of α-receptors. This assumption is supported by the findings that the decreased sympathetic activity in rats resulting from decentralization or from 6-hydroxydopamine treatment causes supersensitivity to NA but not to ISO[12,13]. On the other hand, sympathetic hyperinnervation caused by the treatment with nerve growth factor results in subsensitivity to NA when measured in an isolated mouse intestine[14]. Actually, the increase in NA release at the beginning of cold acclimation[15] is related temporally to the subsensitization of the α-adrenoreceptors found in this study. However, it still remains obscure why the sensitivity subsequently returns although the higher NA release still continues.

The present results further show that, after prolonged cold acclimation, the maximum response increased to ISO and to NA but not to PHE. It has been found that cold-acclimated rats show a striking increase in their metabolic response to NA and to ISO, due to an increased capacity of the β-receptors to respond rather than to increased sensitivity[16,17]. It is the higher level of NA in cold-exposed rats which results in this increased β-response[1,2]. Thus the increased maximum response to ISO and to NA found in the present study after prolonged cold acclimation can be regarded as an increased β-response, due to an increased release of NA from the sympathetic nerve endings.

The prolonged cold acclimation also caused another significant change in response to NA. The sensitivity of atria to NA was markedly increased after 40–45 days of cold acclimation. This type of supersensitivity was not found to ISO or to PHE, which probably means that neither β- nor α-receptors are involved. This supersensitivity to NA could be explained by a reduction in NA uptake, because the affinity of NA for the uptake process is much greater than that of either ISO or PHE[18]. This explanation, however, is unsatisfactory on the basis that a higher level of NA (or ISO) in the organism, as produced by repeated injections, did not affect the activity of the uptake process in the rat heart[19]. Thus, the mechanism(s) involved in this sensitization still have to be elucidated in further experiments.

Zusammenfassung. Eine Woche Kälteadaptation vermindert die Frequenz der isolierten Rattenherz-Vorkammern und reduziert ihre chronotrope Empfindlichkeit besonders gegen Phenylephrin, weniger gegen Noradrenalin, und gar nicht gegen Isoprenalin. Hingegen verstärkte eine 6wöchige Kälteadaptation die maximalen Effekte von Isoprenalin und Noradrenalin.

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Bemegride Antagonism to the Development of Physical Dependence on Barbitone in Rodents[1]

The problem of physical dependence on barbiturates and related sedative-hypnotics and minor tranquilizers is one of profound scientific and medical importance, especially in the present social atmosphere where misuse of drugs is so prevalent[2,3]. The present paper reports a study in the rat relating the intensity of phsyical dependence on the hypnotic barbitone to the depth of associated central nervous system (CNS) depression. The degree of CNS depression was modified by administering barbitone together with the analeptic bemergride[4].

Materials and methods. In 3 replicate experiments, groups of 20 female Wistar rats (140–180 g) received barbitone sodium (BARB), bemegride (4-methyl-4-ethylglutarimide, BEM) or a mixture of both drugs (BARB-BEM) by the regimen shown in Table I. The drugs were prepared in a saccharin solution (0.05%, SACC) to mask their taste and administered in the drinking water[5]. A control group of 20 rats received SACC alone (Table I).

Since the 3 drug solutions retained their potency for at least 24 h, they were changed each evening and the volume of fluid ingested by each group was determined. The behaviour of the rats was observed at various times throughout the day and each group was weighed twice

Table I. Oral dose regimen for rats

Drug[a]	Week of treatment				
(mg/kg/day)	1	2	3	4	5
BARB	100	200	300	400	500
BEM	75	100	125	150	150

[a] Given ad libitum in drinking water containing saccharin (0.05%).

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