food were offered every 15th day and water was provided ad libitum.

The cages were placed in plexiglas chambers which were perfused with controlled gas mixtures, 50% of the animals (CO_2 hamsters) were exposed to 5% CO_2, 21% O_2, 74% N_2; the control hamsters were breathing air (0.03% CO_2).

Torpor cycles were monitored by continuous measurement of body temperature by means of radio telemetry.

The U-test of Wilcoxon, Mann and Whitney was used for statistical analysis as the data did not follow normal distribution.

Results. The data on the onset of hibernation, i.e. the time from the start of the experiment to the first hibernation bout, showed a high individual variability. On average, however, the CO_2 hamsters started torpor cycles earlier (191 ± 149 h) than the control-hamsters (293 ± 194 h) (fig.). Furthermore, the periods of homoiothermy between two hibernation bouts were shorter in the CO_2 hamsters. The mean duration of these inter-torpor cycles was significantly ($p < 0.001$) shorter in the CO_2 hamsters (26 ± 27 h) than in the control hamsters (35 ± 31 h) (fig.).

A summary of the data obtained during the 5 experimental months shows that the mean duration of torpor cycles was significantly ($p < 0.0001$) shorter in CO_2 hamsters (23 ± 24 h) than in the control hamsters (41 ± 25 h) (fig.). In the CO_2 hamsters 67% (control 29%) of the hibernation bouts were shorter than 20 h and 25% (control 64%) of the torpor cycles had a duration of 30–80 h. Thus, the mean frequency of torpor cycles in the CO_2 hamsters (8.4 cycles per month, SD 3.2) was significantly ($p < 0.05$) higher than in the control hamsters (5.9 cycles per month, SD 2.0) (fig.).

The mean percentage of time spent in hibernation was dependent on the season, with the highest value during January. In every month the control hamsters spent more time in hibernation than the CO_2 hamsters. On average, the CO_2 hamsters spent 14.5% (SD 18.3) of the experimental time in hibernation and the control hamsters 25.1% (SD 20.8) (fig.).

The CO_2 concentration used in the present study did not influence the daily distribution of entrance into and arousal from hibernation. The CO_2 hamsters and the control hamsters did not differ in the duration of entrance- and arousal-time.

Discussion. The finding that the CO_2 hamsters started hibernation earlier than the control-animals and showed significantly shorter inter-torpor cycles indicates that a high CO_2 concentration in the respiratory air favors entry into hibernation. This effect might be related to the observation that in golden hamsters neurons of the thermosensitive preoptic region are inhibited during acute hypercapnia[3]. Additionally, hypercapnia might modify enzymatic pathways, which could lead to a decrease of metabolic rate[5] and thus favor the entry into hibernation.

The results of the present study further show that the torpor cycles of the CO_2 hamsters are significantly shorter than in the control hamsters, i.e. a high CO_2 content in the respiratory air favors arousal. Similar results were reported by Lyman who found that short exposure to CO_2 concentrations above 5% induces the waking process[6]. It seems unlikely, however, that this effect plays a role in the induction of arousal under natural conditions. In the natural burrow of a hibernator the CO_2 concentration will decrease during the torpor bout, since CO_2 loss by diffusion exceeds CO_2 production when the metabolic rate of the hibernating animal is low.

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Adenosine activates a potassium conductance in guinea-pig atrial heart muscle

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Summary. Adenosine shortens the action potential and diminishes the force of contraction in guinea-pig left atria. These effects may be brought about by the activation of a potassium conductance. This assumption is supported by voltage clamp and ^{42}K release experiments.

Adenosine and related compounds exert pronounced effects on the heart; pacemaker activity, force of contraction in the atrium and atrioventricular conduction are depressed (for review, see Burnstock[1]). The effects of adenosine on the heart are very similar to those of acetylcholine, however, they are not blocked by atropine[2]. Studies with adenosine covalently linked to an oligosaccharide have indicated the existence of specific adenosine receptors outside on the cell surface[3]. The subcellular events underlying the actions of adenosine are still poorly understood. Direct membrane effects[4-9] as well as interactions with the sarcolemmal adenylate cyclase[10-12] have been postulated. We report here that adenosine activates a potassium conductance in guinea-pig atrial heart muscle. The evidence for this is derived from electrophysiological experiments and tracer studies with ^{42}K.

Methods and results. Hearts were taken from guinea-pigs and myocardial preparations were mounted for the measurement of the force of contraction (F_c), transmembrane potential and currents, and ^{42}K efflux as described earlier[13-15]. Figure 1a shows the effects of acetylcholine and adenosine on the action potential and F_c in a guinea-pig atrium at maximally effective concentrations. The duration of the action potential was extremely shortened and F_c was almost completely abolished by both substances. In partially depolarized preparations, acetylcholine and adenosine induced large increases in the resting potential. Figure 1b shows the original record of a partially depolarized prep-

aration which was electrically driven at 1 Hz and, in addition, developed irregular spontaneous activity. Upon the addition of adenosine, the resting potential was increased by about 15 mV and the spontaneous activity was abolished.

What is the reason for the hyperpolarizing effect of adenosine? To answer this, we voltage-clamped atrial trabeculae using the single sucrose gap voltage clamp method. Under voltage clamp conditions, at most potentials, large changes in the steady state holding current were induced by adenosine. Figure 2a shows the original current trace of a preparation held at −60 mV. On the addition of adenosine, a large increase in outward current was observed. In response to a voltage clamp range from −100 mV up to 0 mV within 20 sec, complete current-voltage relationships were obtained both under control conditions and in the presence of adenosine (fig. 2b). The control current-voltage relationship displayed anomalous rectification which was virtually abolished in the presence of adenosine. The adenosine-induced current was outward at potentials smaller and inward at potentials greater than −90 mV. The reversal potential of the adenosine-induced extra current almost exactly corresponds to the predicted equilibrium potential for potassium ions ($E_K = -89$ mV at extracellular and intracellular K^+ concentrations of 5.4 mmoles/l and 150 mmoles/l, respectively). This suggests that the adenosine-induced current is a pure potassium current. The most direct way of testing this hypothesis is to follow the efflux of radioactively labeled potassium. We have therefore determined the rate constants of ^{42}K efflux both under control conditions and in the presence of adenosine, in beating as well as in resting preparations. Figure 3 summarizes the results which were obtained in resting preparations. The preparations were first loaded with ^{42}K for 90 min. The release of ^{42}K into non-radioactive solution was then followed a) under control conditions and b) in the

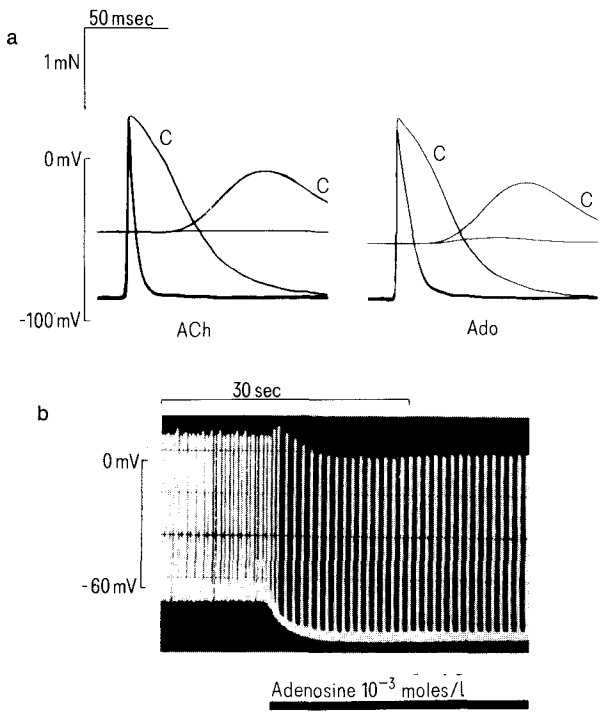

Figure 1. *a* Effects of acetylcholine 10^{-6} moles/l (ACh) and adenosine 10^{-3} moles/l (Ado) on the action potential and force of contraction in a guinea-pig left atrium. Original records under control conditions and 5 min after the addition of the drugs were superimposed. C denotes the original records (action potential and force of contraction) under control conditions. The effects of acetylcholine and, after washout, of adenosine were observed in the same preparation. Stable microelectrode impalement throughout the experiment. Frequency of stimulation: 1 Hz. Concentration-dependent effects of adenosine were observed between 10^{-7} moles/l and 10^{-3} moles/l; the EC_{50} was 1.6×10^{-5} moles/l. *b* Effects of adenosine 10^{-3} moles/l on the resting potential and spontaneous activity in a partially depolarized preparation driven at 1 Hz. Each dash represents one action potential. The same result was obtained with acetylcholine 10^{-6} moles/l.

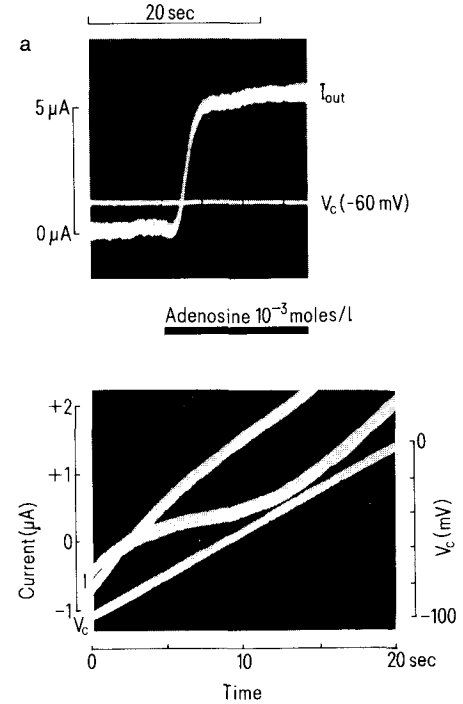

Figure 2. *a* Effect of adenosine 10^{-3} moles/l on the steady state outward current (I_{out}) of a preparation held at −60 mV (V_c) under voltage clamp conditions. Original record. *b* Voltage clamp ramp (V_c) and resulting membrane currents (I) under control conditions (N-shaped) and in the presence of adenosine were superimposed. Stable microelectrode impalement throughout the experiment. The effects of adenosine shown in a) and b) were fully reversible within 5 min after washout. The same results as shown for adenosine were also seen with acetylcholine (n = 7 for adenosine and n = 4 for acetylcholine).

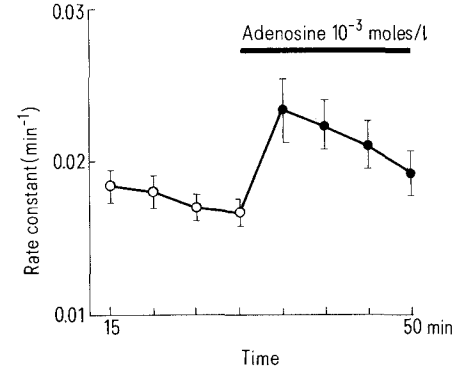

Figure 3. Effect of adenosine 10^{-3} moles/l on the rate constant of ^{42}K efflux in resting guinea-pig left atria. ○, Control; ●, adenosine 10^{-3} moles/l. Symbols represent means ± SE of 6 preparations.

presence of adenosine. The rate constants (k) of ^{42}K efflux were obtained from plots of log concentration of ^{42}K in the tissue against time according to $A = A_0 e^{-kt}$. After a control period of 15 min, k reached a fairly stable level and was observed for a further 15 min. Upon the addition of adenosine, k was significantly increased at all sampling intervals. Similar results were also obtained in beating preparations.

The relatively high concentrations of adenosine required to produce the effects are obviously due to a rapid inactivation process, either due to uptake or to degradation to inosine. Inosine 10^{-3} moles/l was completely ineffective. Adenosine was about 30 times more potent in the presence of dipyridamole 10^{-6} moles/l, which inhibits the inactivation of adenosine. Phenylisopropyladenosine, which cannot be inactivated, was about 1000 times more potent than adenosine.

Discussion. We have shown that adenosine increases the steady state outward current and the ^{42}K efflux in atrial heart muscle. The adenosine-induced current drives the membrane potential to more negative values during excitation and at rest. Identical effects have been described earlier for acetylcholine[15]. Acetylcholine and adenosine, therefore, induce a hyperpolarization which can easily be demonstrated at a low level of the maximum diastolic potential. Our results are in line with the study of Hartzell[16] who was the first to describe a pronounced hyperpolarization of the frog sinus venosus in response to adenosine. The hyperpolarizing effect of acetylcholine and adenosine contributes to the abbreviation of the action potential and, indirectly, by inhibiting the influx of calcium during excitation, to the negative inotropic effect. Additional effects on the calcium conductance are not excluded.

The physiological effects of adenosine are indistinguishable from those of acetylcholine except that the effects of acetylcholine are blocked by atropine and those of adenosine by theophylline. The similarity between the actions of adenosine and acetylcholine justifies the proposal that both substances may activate the same potassium conductance via stimulation of different receptors. A common post-receptor pathway could therefore mediate the cardiac effects of both acetylcholine and adenosine. We suggest that both adenosine and acetylcholine play a role in the regulation of excitation-contraction coupling in atrial heart muscle, involving the same post-receptor pathway. In contrast to the atrium, ventricular heart muscle is not responsive either to acetylcholine or to adenosine although receptors for acetylcholine[17] and adenosine[18] have been demonstrated also in ventricular myocardium. This discrepancy may be due to the lack of a receptor-controlled potassium conductance in ventricular heart muscle.

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Oxytocin antagonism of hypothalamic-induced angina-like ECG changes and pressor effects in the cat

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Summary. Electrical stimulation of a specific site in the lateral hypothalamus of the cat, in a region posterior to Hess' defense area, results in pressor effects and angina-like ECG changes which consist either of T-wave inversion and ST-segment prolongation or in the appearance of tall T-waves. Oxytocin (10 U, i.v.) administered 15 min prior to stimulation, prevents the former ECG changes and BP rise in 90%, and the latter ECG changes and BP rise in 50% of the animals.

Electrical stimulation of specific sites within the cat lateral hypothalamic area (LH), which lie just caudally of Hess' perifornical zone of the defense region, induced angina-like ECG changes often accompanied by blood pressure changes[2]. We have previously shown that these are mediated through the sympathetic nervous system[2,3]. We have proposed[3] a relationship between this phenomenon and clinical cases of cerebral trauma that result in similar symptoms[4,5]. This latter assumption is supported by our observations that repetition, 6–20 times, of the hypothalamic stimulations that result in the above-mentioned phenomena, does not lead in most cases to hyposensitivity but rather to an increasing effect and even to a permanent myocardial pathology[3]. We have, therefore, suggested that this cardiac pathology may have a clinical pathognomic significance analogous to Cushing's ulcer.

Protection against these autonomic disturbances in heart function and in blood pressure by prophylactically admin-