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-

istered β-blocking agents (propranolol or practolol) was shown by us and reported elsewhere[6]. These observations supported our previous claim for a sympathetic mechanism, and implicated catecholamine mediation peripherally and/or centrally.

Searching for another avenue for the investigation of the phenomenon and for development of possible protective agents against its pathologic consequences, we selected oxytocin for the following reasons: Firstly, this endogenous octapeptide hormone is biosynthesized in the hypothalamus, in regions of the periventricular and of the supra-optic nuclei, which are different from the one under consideration, and is secreted and stored in the posterior lobe of the hypophysis[7]. Because it is also present in males, oxytocin is suspected to have a more general function than its well-known oxytocic role in females. This additional role has not yet been elucidated. However, it has been reported that exogenously administered oxytocin antagonizes vasopressin-induced angina-like ECG disturbances similar to the phenomena under consideration[8]. Furthermore, an increasing amount of evidence shows that oxytocin plays important modulatory roles in synaptic neurotransmission especially in relation to catecholamines[9]. It seems to have a general homeostatic role peripherally[7], and a central modulatory role in neuronal pathways[8], which deserve clarification.

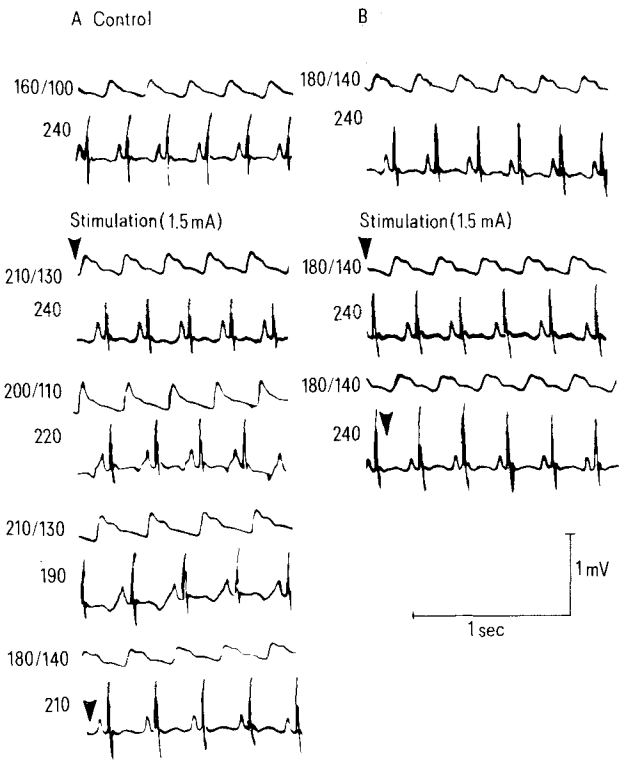

Figure 1. ECG and BP records of a cat. *A* Top strip-sample ECG and BP control records. The strips that follow are representative samples of changes induced by LH stimulation. Beginning and end of stimulation are marked by 1st and 2nd arrows, respectively. Note that the 1st change to appear is a pressor effect (2nd strip), followed by T-wave inversion, ST-segment prolongation and slight bradycardia (sample records in 3rd and 4th strips). The last strip is a sample record taken during the recovery period. *B* The blockade of these changes by ocytocin, 10 units administered i.v. 15 min prior to stimulation. Top strip-control records under oxytocin. Note that oxytocin per se does not modify the ECG and causes only a slight pressor effect, but completely blocks both the ECG and BP changes induced by LH stimulation.

Experiments were conducted on 20 cats. The animals were anesthetized with ether followed by 70–80 mg/kg, i.v. α-chloralose. They were then placed in the stereotaxic instrument. Stimulation electrodes were introduced into the lateral hypothalamus bilaterally at targets frontal 9.5–10, lateral 3 and depth-3 of the Horsley-Clark (HC) coordinates[3,10], the targets selected to be in the vicinity of, but well outside, the posterior hypothalamus. Bipolar stainless steel electrodes with 1 mm inter-electrode distance were used: threshold intensities varied from animal to animal but ranged between 0.5 and 2.0 mA, 100 Hz frequency, 0.5 msec pulse duration, 15 sec trains. Systemic blood pressure was recorded from the femoral artery by means of a Grass pressure transducer and displayed together with ECG in lead II on a Grass polygraph. In most of the experiments the animals were artificially ventilated. Automatic heat control of the animals was provided. At the end of the experiments, the position of the stimulation electrode was confirmed histologically.

Records of BP and of ECG in lead II were taken prior to, during and for a few min after cessation of stimulation. 2–3 such runs at 15 min intervals were carried out prior to drug administration. As previously shown[3], lateral hypothalamic stimulation at the sites under consideration induced 2 types of ECG changes together with pressor responses. These are illustrated in figures 1 and 2. a) T-wave inversion with prolongation of the ST-segment observed in 60% (12/20) of the animals (fig. 1A), and b) tall T-wave observed in 40% (8/20) of the animals (fig. 2A). Bolus intravenous administration of 10 units oxytocin about 15 min prior to lateral hypothalamic stimulation in 10 animals that showed T-

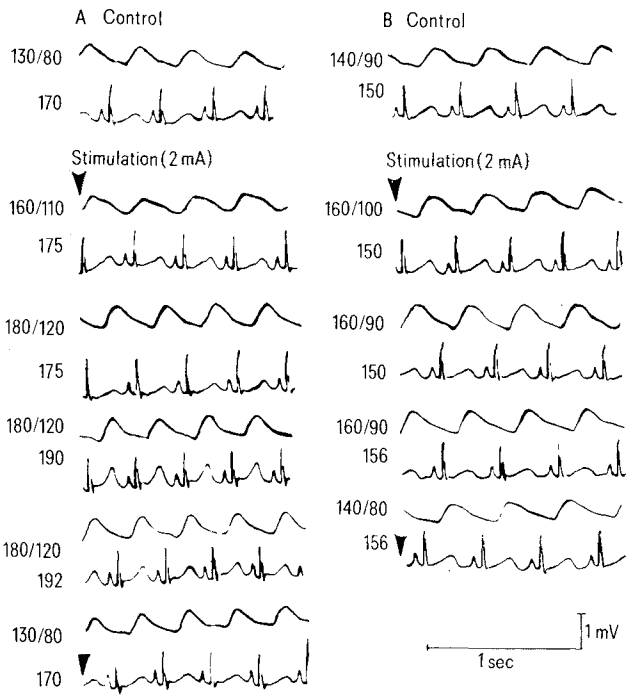

Figure 2. Representative sample records of ECG and BP from another cat. *A* Top strip-control. The strips that follow are representative sample records of the changes induced by LH stimulation: a pressor effect (2nd strip) appears first, followed by tall T-waves, tachycardia and further increase in BP (2nd, 3rd, 4th and 5th strips); the last strip is a record taken during the recovery period. *B* Complete blockade by oxytocin of the ECG and HR changes and partial block of the BP alterations induced by the LH stimulation. Note that oxytocin itself did not modify the ECG and caused a slight pressor effect.

wave inversion prevented in 9/10 animals both the T-wave inversion and the BP rise (fig. 1B), both protective effects lasting 2–3 h.

In a 2nd group of 6 cats in which stimulation, presumably of the same site[8] resulted in the appearance of tall T-waves and in a 50 ± 10 mm Hg increase in BP (fig. 2A), the same treatment with 10 units of oxytocin prevented both the ECG and BP changes in 3 out of 6 animals (fig. 2B). These protective effects also lasted about 2–3 h. The hemodynamic effects of the oxytocin administration per se were a small increase in BP in about 50% of the animals, with no effect on ECG or heart rate. In all cases the time-course of the protection against the ECG changes paralleled that of the protection against the pressor effect; the effects on both lasted 2–3 h.

Control animals (4 animals) that did not receive oxytocin protection did not show such a reduction of the effects upon receiving the same number of stimulations. We conclude therefore that the protection against the above-mentioned autonomic disturbances of central etiology was due to oxytocin.

In previous work we showed that the ECG changes and BP alterations could be induced independently of one another by LH stimulation. By varying the stimulus conditions we were able to discriminate between the two effects. Yet the protective effects of oxytocin on ECG and on the BP changes ran in parallel and were equally potent against parameters. This contrasted with the effects of the β-adrenoceptor blocking agents which blocked the ECG changes at half the dosage necessary to prevent BP changes[6]. Oxytocin is known to have peripheral actions on the heart and on blood vessels[11], as well as central actions[7]. However, we have no evidence for exogenous oxytocin gaining access to the hypothalamus or to related CNS regions, which would support the argument for a central mechanism of action.

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Effects of submandibularectomy and castration on thymus and spleen weights in male mice

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Summary. Submandibular-sublingualectomy of male mice did not result in thymic hyperplasia or potentiate the thymic hyperplasia which occurs after castration. Hemagglutination titers to sheep red blood cells were similar in immunized sham operated and submandibular-sublingualectomized mice but significantly less than titers in castrated mice.

Submandibularectomy of male mice is reported to result in significant thymic hyperplasia 28–40 days later[2,3]. In the present study, the effect of submandibularectomy on the thymic hyperplasia which normally follows castration of mice[4] was investigated. Additionally, the effects of submandibularectomy and castration on the antibody response to sheep red blood cells were evaluated.

Materials and methods. Male Swiss mice were purchased from Southern Animal Farms, Prattville, Alabama, USA. Mice were housed in shoebox plastic cages on hardwood bedding under controlled temperature, humidity, and light cycles and offered Purina rodent chow and tap water ad libitum.

Operations were performed under ether anesthesia and consisted of extirpation of submandibular-sublingual glands (SMX) through a ventral neck incision, gonadectomy (GX) through a mid-scrotal incision, or blunt neck dissection as a sham operation (SH). Vascular supply was not ligated prior to organ excission; bleeding occurred, but was well tolerated. Four Series of mice, consisting of 4 groups each, received the operations described. All remained untreated except for Series 2 which was injected with 1×10^8 sheep red blood cells (SRBC) i.p. on day 28 after surgery. Mice were sacrificed 30–42 days after surgery by cardiac puncture under ether anesthesia. Serum was collected and stored at −20 °C.

The thymus and spleen were removed at sacrifice, fixed in 10% formalin, cleaned of fascia and fat, weighed to the nearest 0.1 mg on a Mettler balance, and expressed as a percent of body weight. For antibody titration, sera was heated to inactivate complement, then diluted with saline 1:10 initially, and 1:2 thereafter. 100 µl of 2% 4 times washed SRBC suspension was added to 100 µl of diluted sera, incubated for 30 min in a 37 degree water bath, centrifuged, and gently agitated to determine if the cells went freely into suspension. The highest dilution giving visible agglutination was taken as titer and expressed as $\log_{10}$.

Results. Gonadectomized (GX) and submandibularectomized-gonadectomized (SMXGX) mice of all 4 Series had significant thymic hyperplasia compared to non-castrates (table). In Series 1, the combined operation (SMXGX) resulted in a potentiation of the thymic hyperplasia which occurred after only castration. However, this effect was not