CSF was drawn on 3 different occasions at about weekly intervals from each of the patients during the pretreatment period. The mean AK value of the 10 patients from the 1st sampling occasion was 0.115 units/l ± 0.027 compared to those of the 2nd and 3rd occasions being 0.111 ± 0.022 and 0.115 ± 0.032 units/l, respectively. Thus, the fact that the mean values of the 10 patients were practically the same on 3 different occasions during the 1st month without treatment contradicted the idea that there might be a spontaneous cyclic variation within the time-frame of a month of the AK activities in CSF of these patients.

Discussion. We have shown that a substantial release of AK occurs during ingestion of Hydergin by patients suffering from cerebral arteriosclerosis. The tendency towards increased activities during the treatment period compared to the pretreatment period was discernible in 8 out of 10 patients although this difference was not statistically significant. This lack of significance might be due to the limited number of patients involved in this study. When comparing the treatment period with the post-treatment period, either alone or taken together with the pre-treatment period, a statistically significant increase in AK activity exists during Hydergin treatment. This difference is of interest and indicates an increased leakage of AK through the plasma membranes of the brain cells into the extracellular fluid as represented by CSF during treatment. The explanation for this is unclear. However, it could be anticipated that the manifest presence of AK in the CSF of patients with cerebral arteriosclerosis is due to a lowered adenylate charge potential in the brain cells leading to a diminished electrochemical potential[2-5]. The effect of Hydergin might then be a further lowering of the electrochemical potential in the brain cells. This effect is most probably not exerted indirectly by a further influence on the adenylate charge potential. Instead we propose a direct action by Hydergin on the Na^+- and K^+-dependent ATPase system in the plasma membranes of the brain cells which, working in synergism with the aforementioned mechanism, results in increased leakage through the plasma membrane.

It has been reported that norepinephrine exerts activating effects on this ATPase system of brain cells[6] and the concentration of this substance in CSF was found to be increased in ischaemic brain patients[7]. This catecholamine-stimulated Na^+- and K^+-dependent ATPase activity was intensively inhibited by dihydroergot alkaloids and the inhibitory effect could be observed at as low a concentration as 1×10^{-7} M of several substances of this class including Hydergin as demonstrated in an in vitro experimental system[8,9]. Therefore, there are reasons to believe that the molecular basis for the action of Hydergin might be the same under in vivo-conditions as well. The significant lowering of the AK activity in the CSF (also in comparison with the pretreatment period) on discontinuation of the treatment with Hydergin might be explained by a rebound effect exerted by the catecholamines no longer being restrained in their action on the Na^+- and K^+-dependent ATPase system.

Thus, it seems to us that the direct action by Hydergin on the Na^+- and K^+-dependent ATPase system results in the maintenance of the intracellular ATP pool on a somewhat higher level although the resultant effect was increased leakage through the plasma membrane due to a lowered electrochemical potential.

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The effect of β-adrenergic stimulation and blockade on the efflux of PGE_1-like material from the isolated perfused rabbit heart

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Summary. Prostaglandin (PG) release was measured from the isolated perfused rabbit heart. The effects of β-adrenergic stimulation and blockade suggest that PG synthesis is regulated in part by adrenergic mechanisms.

Several authors have suggested that PGs act as modulators of hormone action and neurotransmission[2,3] Aiken and Vane[4] concluded that there was continuous PG release in the kidney which contributed to the local regulation of vascular tone. The existance of PGs in cardiac tissue is well established; however, their physiological role, and the precise mechanism underlying their effects, have received little attention. Hedqvist[3] reported that the release of catecholamines from adrenergic nerve terminals was modulated by PGE_1. The present study is concerned with the role of β-adrenergic mechanisms in the release of PGE_1 from the rabbit heart.

The rabbit heart was mounted according to Langendorff's technique and perfused with oxygenated Krebs' solution maintained at 37 °C. The hearts were allowed to stabilize for 10 min before drugs were given. The perfusate was collected during this period for 7 min to determine the resting out-put of PGE_1-like activity. The drugs adrenaline (9.5×10^{-6} M) or sotalol (7.2×10^{-2} M) were then perfused for 7 min. During this period the perfusate was collected separately and assayed for PGE_1-like activity. There was an interval of 10 min before administration of the next drug.

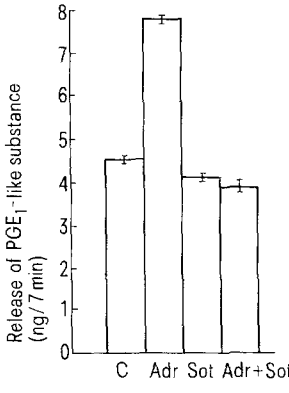
The PGE_1-like activity was assayed against standard PGE_1 on an isolated rat stomach strip, as described by Vane[5].

The results are summarized in the figure. The resting output was found to be 4.5 ± 0.33 ng per 7 min (n = 5). Adrenaline increased the output of PGE_1 to 7.9 ± 0.33 ng (n = 5) which was significantly different from the control

($p < 0.001$). Sotalol decreased ($p < 0.001$) the PGE_1-like activity slightly but significantly to 4.1 ± 0.36 ng ($n = 5$). Administration of adrenaline and sotalol in combination did not produce any significant alteration in the PGE_1 content in the effluent as compared to the control value ($p > 0.05$).

These results thus suggest that there was a basal efflux of PGE_1-like material which increased after the administration of adrenaline. There was a decrease in the efflux of PGE_1 after sotalol, a β-adrenoceptor blocking agent. In the presence of sotalol, adrenaline was unable to augment the PGE_1 content.

The present results extend the previous studies of Botting[6] who suggested that the PGE_1-like activity released from the isolated guinea-pig ileum during field stimulation was caused by the release of noradrenaline from intramural sympathetic nerves which acted on α- and β-adrenoceptors. Our finding that adrenaline increased the release of PGs suggests that β-adrenoceptor stimulation participates in PG release. Shaw and Ramwell[7] also postulated an interrelationship between sympathetic neurohumoral transmitter and PGs on the basis of findings that noradrenaline-stimulated lipolysis is associated with increased release of PGE_1-like substances. The increased amount of PGs released from rabbit heart by adrenaline can be regarded as an overflow resulting from an increase in PG production or from a decreased inactivation of PG. PG release in the heart may have an inhibitory regulatory function on sympathetic influence on the heart[3,8,9]. It is known that tissue damage of various kinds leads to PG formation[10]; this suggests that at least part of the continuous basal release of PGs is due to tissue damage. Sotalol decreased slightly the spontaneous efflux of PGE_1-like activity suggesting that endogenous noradrenaline accounted for only a small fraction of PG release in the non-stimulated heart.



The effect of β-adrenoceptor agonist and antagonist drugs on the output of prostaglandin (assayed against standard PGE_1) from perfusate of the isolated heart of rabbit. C, Control; Adr, adrenaline; Sot, sotalol; Adr, + Sot, adrenaline + sotalol.

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Effects of prostaglandin E_1 on $^{45}Ca^{++}$-incorporation and spike activity in longitudinal smooth muscle of cat jejunum

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Summary. Prostaglandin E_1 (0.3 µM) decreased both the $^{45}Ca^{++}$-incorporation and the spike activity in isolated longitudinal smooth muscle preparations of the cat jejunum probably by an inhibition on the Ca^{++} influx.

Several studies have linked the effects of prostaglandins of the E group with transmembrane calcium transport and intracellular calcium mobilization, leading to an increased or decreased Ca^{++} availability[1-3]. Our earlier investigations[4,5] have shown that the inhibitory effect of prostaglandin E_1 on smooth muscles of the cat jejunum depends on the Na^+/Ca^{++} ratio and the Ca^{++} concentration.

In this study we compared the effects of prostaglandin E_1 (PGE_1) on the $^{45}Ca^{++}$ incorporation with the PGE_1 effects on the calcium-dependent[6] generation of spike potentials in longitudinal smooth muscle of the cat jejunum.

Materials and methods. Strips from the proximal jejunum of male cats anaesthetized with chloralose (80 mg/kg) were used. The preparations were suspended in Krebs solution bubbled with O_2 at 36 °C. A radioautographic method was used for semiquantitative evaluation of the $^{45}Ca^{++}$ incorporation by the smooth muscle cells[7]. The electrical activity was recorded by pressure electrodes[8] and the mechanical activity by a strain gauge at initial tension of 1 g.

The effects of PGE_1 (0.3 µM) were observed under the following experimental conditions: A) in normal Krebs solution containing 2.5 mM calcium; B) in Krebs solution with increased calcium, 3.5 mM; C) in Krebs solution with decreased sodium (normal content of $Na^+ = 135.4$ mM), as 35% of sodium was substituted by sucrose; and D) on preparations pretreated with caffeine (0.5 mM) in normal Krebs solution. $^{45}Ca^{++}$ was added as a label (2 µCi/ml; 10 nM/ml) and after 5 min exposure the smooth muscle tissue was prefixed in glutaraldehyde (2.25% in 0.1 M cacodylate buffer, pH 7.2, 4 °C, for 4 h) and postfixed in osmium tetroxide (2% in 0.1 M cacodylate buffer, for 2 h). The silver grains (s.g.) in the radioautograms were counted in an area of 1000 µm² for assessment of the $^{45}Ca^{++}$ incorporation. The changes in the number of silver grains as well as slow waves with spike potentials (s.w.) per min were followed before and at the 5th min of the PGE_1 treatment. The data from groups B, C and D were compared statistically with the data from group A using Student's t-test.