course of ACTH activation is more or less uniform and shows a latency of 1–10 sec after the start of microelectrophoretic application; the recovery time is in the same order. Figure 1C demonstrates a biphasic effect of ACTH microelectrophoresis on neuronal activity. Initially a clear activation is recorded, which is followed by an inhibition of neuronal activity. When dopamine and ACTH were administered simultaneously to neurones activated by ACTH alone, the strong inhibitory effect of dopamine prevailed over the excitatory effect of ACTH (3 cells). Dexamethasone-phosphate insensitive neurones were never influenced by ACTH. Dopamine on the other hand inhibited the discharge rate of 7 out of 16 steroid insensitive neurones tested in the hypothalamus.

With the fast green method the position of the steroid sensitive and insensitive neurones was microscopically identified. All steroid sensitive neurones investigated in this series were situated in the medial basal hypothalamus, such as DMH (nucleus dorsomedialis hypothalami), VMH (nucleus ventromedialis hypothalami) and ARH (nucleus arcuatus hypothalami) and in the anterior hypothalamus (AHA — anterior hypothalamic area).

These experiments may demonstrate the dual sensitivity of certain hypothalamic nerve cells (Figure 2): (1) Neurohumoral sensitivity (dopamine): Experimental stimulation with dopamine might simulate the effect of dopamine containing nerve terminals. Dopamine could by inhibition regulate the trigger mechanism for the neurones producing the corticotropin releasing factor (CRF). (2) Hormonal sensitivity (ACTH, corticosteroid): Stimulation with these substances might simulate hormonal effects normally mediated by the blood. This mode of action of ACTH could represent a positive feedback mechanism[10] while the corticosteroid (dexamethasone-phosphate[11]) effect may represent a negative feedback mechanism in the regulation of ACTH production.

Zusammenfassung. Mit Hilfe der Mikroelektrophorese wurde die Wirkung von Dexamethasonphosphat, Dopamin und ACTH lokal an Einzelneuronen des Hypothalamus der Ratte geprüft. Dexamethason-phosphat (ein synthetisches Corticosteroid) hemmte mehrheitlich die Aktivität der steroidempfindlichen Zellen im Hypothalamus, einige wenige dieser Zellen wurden aktiviert. Dopamin hemmte die Aktivität dieser steroidempfindlichen Neuronen sehr stark. ACTH dagegen aktivierte diese Zellen. Diese Resultate werden in Zusammenhang mit einem negativen und einem positiven «Feedback»-Mechanismus, der die ACTH-Bildung steuert, diskutiert.

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The Effect of Prolonged Sympathetic Stimulation on Conduit Vessel Diameter

The disability of smooth muscle of resistance vascular bed to maintain sustained contraction at sympathetic stimulation, has been repeatedly reported[1–3]. Although the interpretations of the mechanisms underlying this phenomenon may vary, there seems to be little controversy in admitting the more or less pronounced role of accumulated tissue metabolites as a consequence of an impaired blood flow[4,5].

Thus it seems reasonable to presume that smooth muscle of vessels with no nutritional function, e.g. conduit vessels, should exhibit sustained contraction for any duration of stimulation and hence 'autoregulatory escape' should not be expected.

To investigate this problem, experiments were performed on 16 dogs, anaesthetized with thiopental sodium 60–70 mg/kg body weight. The peripheral end of the cut sympathetic trunk at the level of L_3–L_4 was stimulated with unipolar rectangular impulses of 5 msec duration, supramaximal amplitude and graded frequencies; each stimulation lasting 10 min. The diameter of the femoral artery (inductive transformer[6]) and pressure (electromanometer Elema) were recorded simultaneously.

As Figure 1A shows, at low frequency stimulation 1 imp/sec) the diameter of the femoral artery keeps contracting throughout the whole stimulation period. In contrast, at high frequency stimulation (15 imp/sec, Figure 1B) the diameter, after having reached minimum values (i.e. maximum response), tends to return to initial values in spite of continued stimulation.

The changes of diameter during stimulation at various frequencies, as related to the time axis of stimulation, were quantified and expressed as percentages of the maximum response of the respective series of stimulation. It is apparent in Figure 2 that at stimulation frequencies 1–2–4–8 imp/sec the diameter, having reached minimum values within 3–4 min of stimulation, varies insignificantly until the end of the stimulation. However, a gradual relaxation of the femoral artery occurred at 15 imp/sec stimulation, after contraction had reached its maximum within 4 min.

In view of existing discrepancies relative to release of the transmitter with prolonged sympathetic stimulation[7,8], it seemed less likely that the failure to maintain sustained contraction should be attributed solely to gradually decreasing amount of the transmitter at the site of its action. Thus, other mechanisms responsible for the revealed gradual decay of contraction had to be considered.

At first, the possibility was examined whether the gradual relaxation in spite of continued stimulation might

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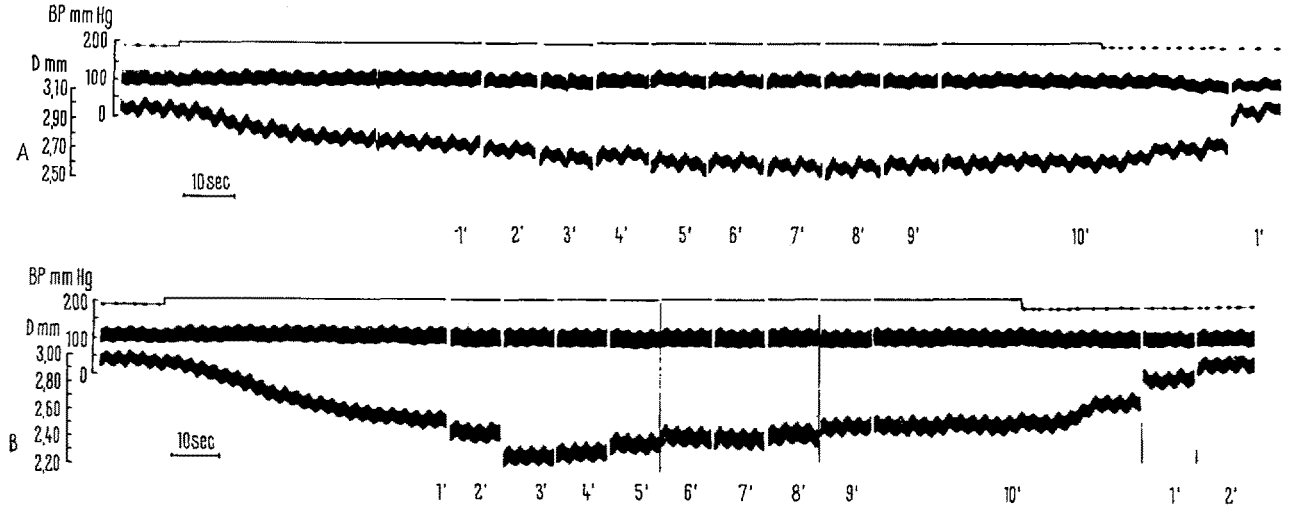

Fig. 1. Effect of prolonged stimulation (signal upward) of the sympathetic trunk at the L_3–L_4 level, with rectangular impulses of 5 msec duration, supramaximal voltage on blood pressure (BP) and diameter (D) of the femoral artery. Bottom numerals: time in min.

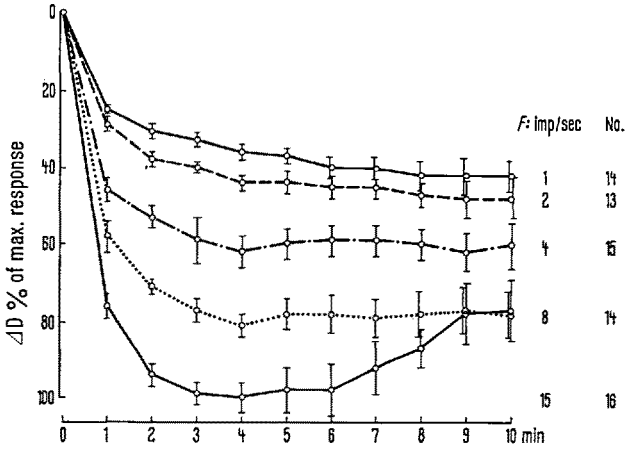

Fig. 2. Time course of diameter changes of the femoral artery (Δ D) in percentages of maximal response at prolonged stimulation of the lumbar sympathetic chain at various frequencies (see righthand numerals). Circles: mean values, vertical bars: S.E.M. No., number of experiments at the respective stimulation frequency.

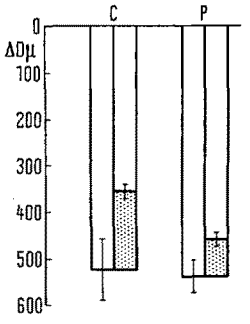

Fig. 3. Differences (black column) between maximal (left) and partially subsided diameter changes (Δ D in μ) at the tenth min of stimulation (right); C before (N = 23), P after i.v. propranolol application (N = 30). Lumbar sympathetic chain (L_3–L_4) stimulated with rectangular impulses, 5 msec duration, supramaximal voltage, 15 imp/sec.

be accounted for by spreading of dilation from the more distal parts of the vascular bed by conduction [9,10]. On 4 dogs the femoral artery was transsected distally to the diameter recording site and, taking care not to derange the longitudinal dimension, recanulated by a plastic tube. Repeated stimulation, however, failed to bring either qualitative or significant quantitative differences.

Thus, in a further group of experiments on 3 dogs propranolol (1.0–2.5 mg/kg body weight) was applied i.v. to explore whether the possible activation of β-receptors in the course of prolonged and high frequent stimulation contributes to gradual relaxation. It appears from Figure 3 that β-receptor blockade significantly reduced relaxation; the difference between the minimum diameter (maximum contraction) and diameter values to the end of stimulation decreasing from $167.2 \pm 13.2\ \mu$ (control) to $77.9 \pm 10.2\ \mu$ (after β-receptor blockade) ($P < 0.001$).

Conclusion. Within a limit of up to 8 imp/sec, the conduit artery – in contrast to resistance vessels – keeps contracting; it does not relax during 10 min of sympathetic stimulation. Over the above limit (15 imp/sec) however, after maximum constriction, the conduit artery tends to relax in spite of continued stimulation. β-Receptor activations seem to contribute to the relaxation.

Zusammenfassung. Wird die Reizfrequenz 8 imp/sec nicht überschritten, vermögen mittelgrosse Arterien – ungleich den Resistenzgefässen – während 10 min andauernder Sympathicusreizung ohne Erschlaffung in anhaltender Kontraktion zu verharren. Bei Anwendung höherer Reizfrequenzen ist eine Tendenz zur Erschlaffung der Gefässmuskeln trotz andauernder Stimulation bemerkbar. β-Rezeptoren-Erregung scheint zur Erschlaffung quantitativ beizutragen.

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