The difference between $E_{r_{epp}}$ and $E_{r_{ACh}}$ that amounted to 23 mv cannot be explained by supposing that AS, methylatropine and tropacine influence the liberation of ACh from the nerve terminals, because E_r of the postsynaptic membrane is independent of the amount of mediator. Moreover, it is known that AS does not affect the quantum content of epp[1]. Also the existence of 2 cholinoreceptor types on the frog end-plate (muscarinic type connected with K^+ permeability, the inhibition of which by AS might cause a shift of $E_{r_{epp}}$, and the nicotinic type) was not confirmed[5]. Although it seems improbable, it is necessary to consider the possibility that apart from ACh, another different substance is liberated from the nerve terminal and that the action of this substance is affected selectively by AS, inducing a change in $E_{r_{epp}}$, whereas $E_{r_{ACh}}$ remains unchanged. However all present knowledge speaks against this hypothesis, including the fact, that the same concentration of AS lowers the epp and ACh potential in the same extent[1]. If we should assume, that AS hinders in some way the diffusion of K^+ from the synaptic gap, then we must expect according to TAKEUCHI[6,7] that the concentration of K^+ is approximately 50 mM in the gap, when E_r is shifted to + 9 mv. This is also improbable, because no depolarization of the presynaptic membrane (resulting in higher frequency of the miniature epp's) or decrease of the resting potential does not occur under AS. On the other hand, if we assume that Na^+/K^+ concentration in the synaptic gap does not change due to AS, then at $E_{r_{epp}}$ equal to + 9 mv (according to the formula presented by TAKEUCHI) $\Delta gNa/\Delta gK$ should give 2.6, which means it increases approximately twice. Such a change of the $\Delta gNa/\Delta gK$ ratio under the effect of atropine could explain not only its ability to block cholinoreceptors but also selectively block the potassium channel. However, even in this case it is difficult to explain the difference in the effect on the epp and the ACh-potential. It is of interest that the quaternary analogue of atropine, methylatropine, the molecule of which is fully ionized and therefore cannot easily enter the cell, has a similar effect to that of atropine[8]. The site of action of atropine and its analogues is apparently localized on the external surface of the muscle fibre membrane.

Changes in the shape of epp may also be the result of some postsynaptic processes, as can be concluded from our finding concerning the alteration of the shape of epp during artificial changes of the membrane potential. The epp thus reversed are distinctly 'faster' than normal epp (Figure 3). It is not possible to elucidate the change of shape of the epp by passive electric properties of the postsynaptic membrane, because the form of the postsynaptic current is influenced by atropine[9]. Moreover, a direct relationship between the form of transmembrane current and the corresponding course of the membrane potential was recently demonstrated[10].

Further analysis of the effect of atropine and its analogues on the postsynaptic membrane of the muscle fibre may throw light on the mechanism by which the interaction of the mediator with the specific receptor of the postsynaptic membrane gives rise to current flow across the membrane[11].

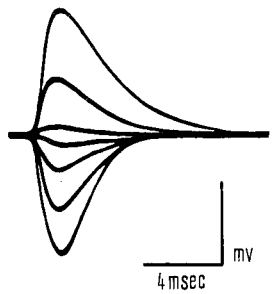

Fig. 3. Changes of the shape of epp at different values of MP (from − 40 to + 25 mv). The reversed epp's are markedly shortened. No drugs are present. Temperature 21 °C.

Zusammenfassung. Mittels intrazellulärer Mikroelektroden wurde der Einfluss von 7 Tropinestern auf Amplitude und Umkehrpunkt (E_r) der Endplattenpotentiale am M. sartorius des Frosches untersucht. Alle Substanzen erniedrigen die Amplitude und verändern die Form der Endplattenpotentiale, während 3 von ihnen den Umkehrpunkt (E_r) in der Richtung zum Na-Gleichgewicht verschieben.

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Potentiation of Cutaneous Inhibition by Alcohol

Cutaneous nerves conducting corticopetal tactile sensibility from the body surface first synapse in the cuneate and gracile nuclei. Transmission across these nuclei shows a remarkable safety factor but is subject to strong presynaptic inhibition from cutaneous as well as contralateral cortical regions[1,2]. This inhibition functions as an important negative feedback mechanism controlling tactile sensory input at the level of the first central synapse. Central nervous system depressants, including

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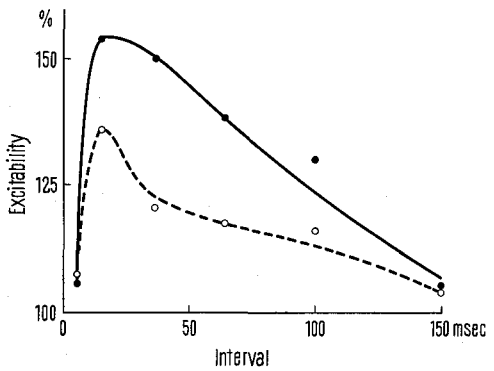
ethyl alcohol, have been reported to increase presynaptic inhibition of muscle afferents in the spinal cord[3]. In view of the importance of tactile sensory input to the organism, a study was made of the effects of ethyl alcohol on cuneate and gracile presynaptic inhibition. In the following experiments this form of inhibition was displayed by surface records, by excitability testing of presynaptic terminals, and by plots of the time course of depression of the post-synaptic discharge in the medial lemniscus after conditioning cutaneous volleys.

Cats were lightly anaesthetized with pentobarbital sodium (35 mg/kg) or decerebrated under ether, immobilized with a muscle relaxant (gallamine triethiodide) and placed under artificial respiration. The dorsal column nuclei were exposed for recording gross potentials (silver surface electrode) after electrical stimulation of the ipsilateral forepaw or hindpaw. In other experiments a glass microelectrode, filled with $4M$ sodium chloride, was inserted to a depth of about 1 mm into the cuneate nucleus and used to deliver strong brief electrical stimuli. The antidromic potentials were recorded with platinum hook electrodes placed on a severed cutaneous nerve (superficial radial), whereas the synaptically induced lemniscal discharge was recorded with a steel electrode placed stereotaxically in the contralateral medial lemniscus. The position of the latter electrode was ascertained by the usual techniques. A conditioning pulse of 0.1 msec duration was delivered to the ipsilateral forepaw pad at various intervals before the test stimulus, and a master unit drove all stimulating channels at the rate of 1 c/4 sec. Femoral blood pressure was continuously monitored, and the esophageal temperature was maintained around 37 °C by a heating pad placed under the cat. A 20% v/v solution of 95% ethyl alcohol in 0.9% saline was prepared and administered slowly through the anticubital vein. It produced a mild drop in blood pressure.

Upon stimulation of the ipsilateral forepaw, the brief negative wave (N wave) recorded at the surface of the cuneate nucleus is followed by a prolonged positive wave (P wave). This P wave reflects the depolarization of the synaptic terminals of cuneate tract fibers[1]. Alcohol (3–5 ml of 20% solution/kg) produced a prompt increase in the depth of the P wave averaging 30%, but little or no effect on the N wave. The time of rise to summit of the P wave, but not its duration, was decreased by about 5 msec. Larger doses of alcohol (up to 8–10 ml of 40% solution/kg) sometimes resulted in an increase in duration of this wave but did not further increase its size appreciably. The P wave evoked in the gracile nucleus after stimulation of the ipsilateral hindpaw was likewise increased in size. The effects of alcohol were also apparent, though less pronounced, in decerebrate cats.

By stimulating the cuneate nucleus directly and recording the antidromic potentials in the superficial radial nerve, it was possible to assess the excitability of the afferent terminals before and after conditioning stimulation to the ipsilateral forepaw. A plot of the time course of the increase in excitability of cuneate terminals could thus be obtained. This time course is typical of presynaptic inhibition. The antidromic record consists of 2 spike complexes. The second spike complex reflects stimulation of interneurons which impinge upon the presynaptic terminals and thus constitutes the dorsal column reflex[4]. The size of this reflex was increased by alcohol. The increase in the size of the first spike complex by conditioning stimulation was simultaneously facilitated (Figure). At a conditioning-test interval of 20–30 msec, this facilitation averaged 12 $\pm$ S.E. 3.2 in 7 cats. Finally, the effects of alcohol on the time course of inhibition of the lemniscal response by conditioning cutaneous volleys was also investigated. Alcohol increased the inhibition of the postsynaptic discharge at intervals between 5 and 150 msec, but this effect was not as pronounced and reproducible as the increase in excitability. Chloral hydrate (100 mg/kg) showed similar effects.

All of these results demonstrate the ability of usual doses of alcohol to increase presynaptic inhibition of cutaneous transmission at the level of the cuneate and gracile nuclei. This is of interest in relation to appreciation of the spacial and temporal sequence of a series of tactile stimuli. Furthermore, since chloral hydrate, pentobarbital and other general depressants are also capable of increasing presynaptic inhibition, it would appear that this action is rather nonspecific.



The effect of alcohol on the excitability of cuneate afferent terminals. Time course of the increase in excitability of cuneate presynaptic terminals after conditioning stimulation (single pulse) to the ipsilateral forepaw before, and 2 min after, 5 ml of 20% alcohol solution/kg. Excitability was tested by direct stimulation of the cuneate nucleus of a lightly anaesthetized cat (pentobarbital) with a microelectrode, the antidromic response being recorded in the superficial radial nerve. ●—●, after alcohol; ○—○, control.

Résumé. Les effets de l'alcool éthylique sur l'inhibition présynaptique dans le Noyau de Burdach furent étudiés. Il apparut que ce produit intensifie l'accroissement en excitabilité des extrémités afférentes cunéaires et l'inhibition de la réaction lemnisque, ceci en conditionnant les décharges cutanées. L'alcool augmente aussi l'intensité de l'onde de surface positive. En conclusion, l'alcool intensifie l'inhibition présynaptique du stimulus cutané au niveau du Noyau de Burdach.

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