occurred especially at low frequencies of stimulation. These results indicate that corticosteroids can enhance the responsiveness of normal striated muscle to electrical stimulation of the motor nerves. The mechanisms underlying this effect are unknown but may involve either presynaptic changes or perhaps, more likely, postsynaptic changes.

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The action of metiamide in anaphylaxis *in vivo* in the guinea-pig

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Bartosch, Feldberg & Nagel (1932) first produced evidence that histamine was released from guinea-pig lungs after anaphylactic shock. Although histamine has been shown to interact with at least two types of receptor (Ash & Schild, 1966), most investigations of the role of histamine in anaphylaxis have studied only H_1-receptors. However, recent work has shown that H_2-receptors may be involved in immune reactions in basophil leucocytes and in the heart (Capurro & Levi, 1973; Chand & Eyre, 1975). In this study the effect of the H_2-receptor antagonist, metiamide (Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973) in anaphylaxis in the guinea-pig was investigated.

Guinea-pigs were sensitized to egg albumen by its injection (100 mg i.p. and 100 mg s.c.) 3 weeks before challenge. Exposure to an aerosol of 1% egg albumen produced an anaphylactic reaction characterized by dyspnoea and cough. The onset times of anaphylactic symptoms in animals pretreated with metiamide (10 mg/kg and 100 mg/kg s.c.) were 144.3 ± 51.0 s and 78.8 ± 13.3 s respectively and were not significantly different from those of control animals ($P < 0.05$). Mepyramine (1 mg/kg i.p.) extended the time of onset of anaphylactic symptoms (551.9 ± 88.7 s) and the protection was not significantly altered by addition of 10 mg/kg metiamide (541.3 ± 94.0 s, $P < 0.05$).

The aerosol method of studying anaphylaxis is very subjective and only gross effects are seen. Therefore, guinea-pigs anaesthetized with 60 mg/kg pentobarbitone sodium were prepared for the recording of respiratory overflow volume by the method of Konzett & Rössler (1940) as modified by Lessin & Kramer (1969). Heart rate and blood pressure were also monitored by means of a rate meter and pressure transducer. Histamine (0.25 μg–8.0 μg) caused increases in air overflow volume of 8.4–108.4%. The increases were blocked by mepyramine (0.05–5 mg/kg) but unaffected by metiamide (10 μg kg^{-1} min^{-1} i.v.). An increase in heart rate of 8.0 ± 3.1 to 51.1 ± 7.2 bts/min was produced by histamine between doses 2 μg and 16 μg. Mepyramine (5.0 mg/kg) produced a shift to the right of the dose response curve (dose ratio = 2.72) and mepyramine (5 mg/kg) plus metiamide (10 μg kg^{-1} min^{-1}) caused a further shift to the right of the curve. (Dose ratio = 13.34.)

Injection of egg albumen (1 mg i.v.) into sensitized anaesthetized guinea-pig gave maximal increases in air overflow volume accompanied by an increase in heart rate and arterial blood pressure and death followed in 6 to 7 animals within 6 ± 0.83 minutes. Pretreatment with mepyramine (2.5 mg/kg), metiamide (50 μg kg^{-1} min^{-1}) or mepyramine and metiamide in combination increased the number of survivors ($^5/_5$, $^4/_5$, $^5/_5$, respectively). Close inspection of the results suggested that metiamide may have been protecting the guinea-pigs by an action upon the heart. This is consistent with the theory that stimulation of H_2-receptors in the heart plays an important role in anaphylactic death.

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Factors regulating the time-course of the relaxation of rabbit aorta strips after contraction by angiotensin II

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It has been shown (Regoli & St-Louis, 1975) that the myotropic response of rabbit aorta strips (RAS) to angiotensin II is diminished in the absence of Ca^{2+} and restored when Ca^{2+} (1.5 mM) is readmitted to the physiological salt solution (PSS). The effect of Ca^{2+} upon the angiotensin II response is still observed for several minutes after the angiotensin II infusion has been stopped, showing that angiotensin II continues to stimulate the receptors for several minutes after washing. Some factors regulating this continued myotropic response have now been investigated.

Helical RAS 2 cm long were equilibrated for 3 h under 3 g tension in a cascade system and superfused with a tris buffered PSS (van Breeman, Farinas, Gerba & McNaughton, 1972) maintained at 37°C. The drugs were applied by infusion in the PSS and isometric contractions were recorded by a Grass FTO3C force transducer.

A steady submaximal contraction was elicited with angiotensin II (4.5×10^{-9} M) and the rate of relaxation of the subsequent tension decrease was observed when angiotensin II or Ca^{2+} or both were removed from the PSS. RT_{50} values (time for 50% relaxation, Kalsner, 1975) were 7.1 ± 0.3 min following angiotensin II removal; 4.5 ± 0.2 min following Ca^{2+} removal; and 3.8 ± 0.2 min following simultaneous removal of both ($n=8$). Regoli & St-Louis (1975) have shown that changes in calcium concentration do not alter the receptor binding of angiotensin II but interfere with the magnitude of the contraction. The present results therefore show that interference with the contractile mechanism can increase the rate of relaxation.

When a 100-fold excess (5×10^{-7} M) of a potent competitive angiotensin II antagonist (8-Gly-angiotensin II; Regoli, Park & Rioux, 1974) was added during the angiotensin II infusion, there is again a decrease in RT_{50} to 3.8 ± 0.1 min ($n=12$). Hence the RT_{50} value can also be decreased by promoting the dissociation of angiotensin II from its receptor (Rioux, Park & Regoli, 1975).

When the steady contraction was caused by analogues of angiotensin II (Regoli *et al.*, 1974) the RT_{50} value for the relaxation after removing the compound from the PSS was correlated with the pD_2 value of each compound. When the antagonist 8-Gly-angiotensin II was added, the RT_{50} values for these analogues were markedly reduced and were well correlated with the pD_2 value of each compound, $r=0.928$ ($n=6$ to 8 for each compound). The response to Ca^{2+} readmission 30 s and 4 min after interrupting the infusion of these same analogues of angiotensin II in Ca^{2+} free PSS, decreased with decreasing pD_2 value of the compounds. These last results suggest that the relaxation, and the residual contraction observed after adding Ca^{2+} to the PSS, are highly dependent on the rate of dissociation of the agonist compound from the angiotensin II receptor.

The results presented here support the conclusion of Regoli & St-Louis (1975) that angiotensin II continues to stimulate the receptors several minutes after washing, and suggest that the dissociation of angiotensin II from its receptors is a rate-limiting step for the decrease in tension when angiotensin II is removed from the superfusing PSS.

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