SAKMANN, B. & ADAMS, P.R. (1976). Fluctuation and relaxation analysis of endplate currents of frog neuromuscular junction induced by different concentrations of bath applied agonists. *Pflügers Archiv.*, **365**, R145.

SHERIDAN, R.E. & LESTER, H.A. (1977). Rates and equilibria at the acetylcholine receptor of *Electrophorus* electroplaques. *J. Gen. Physiol.*, **70**, 187–219.

Effects of glucocorticoids on acetylcholine release at the neuromuscular junction

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It has been shown in our laboratory (Veldsema-Currie, Wolters & Leeuwin, 1976) that glucocorticoids have a direct presynaptic effect on neuromuscular transmission in the rat diaphragm, i.e. a stimulation of the choline uptake in the endplate region. It has been suggested that this direct presynaptic action of the glucocorticoids might contribute to the favourable effect of glucocorticoids in myasthenia gravis. The present study has demonstrated that prednisolone exerts several effects on the miniature endplate potentials (MEPPs), endplate potentials (EPPs) and muscular contraction. Concentrations of 4–32 μmol/l cause an increase in the mean MEPP amplitude, with a maximum of 134% of the control value at 16 μmol/l while concentrations of 260 μmol/l and higher cause a decrease below the control value. The frequency of the spontaneous MEPPs is significantly increased at concentrations of 32 μmol/l and higher, the frequency being twice the control value at 620 μmol/l. Comparable results have been obtained for EPP amplitudes, in preparations treated with a high concentration of Mg^{2+} or with (+)-tubocurarine. The quantum content and resting potential remain unchanged. An effect on muscle contraction becomes apparent after treatment with (+)-tubocurarine. The gradual decrease in twitch amplitude is retarded in presence of low concentrations of prednisolone.

After pretreatment of rats with prednisolone (1 mg/kg, i.m.) the MEPP amplitude and EPP amplitude in the isolated diaphragm are increased with a maximum at 4 h after the injection. The decrease in twitch amplitude after addition of (+)-tubocurarine is also slower than in the diaphragms of untreated rats. Iontophoretic application of acetylcholine has shown that these effects are not due to a postsynaptic effect of prednisolone. These experiments confirm the notion that glucocorticoids have a direct presynaptic effect on neuromuscular transmission and that this effect may contribute to the therapeutic value of glucocorticoids in myasthenia gravis.

Reference

VELDSEMA-CURRIE, R.D., WOLTERS, E.CH.M.J. & LEEUWIN, R.S. (1976). The effect of corticosteroids and hemicholinium-3 on choline uptake and its incorporation into acetylcholine in rat diaphragm. *Eur. J. Pharmac.*, **35**, 399–402.

Direct effects of glucocorticoids at the neuromuscular junction

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There is little doubt at the moment that myasthenia gravis shows a number of features of an auto-immune disease. Circulating antibodies against the acetylcholine receptor protein have been isolated from blood of myasthenic patients and accordingly neuromuscular defects in these patients are considered to be localized postsynaptically (Ito *et al.*, 1978). Glucocorticoids improve muscle function in myasthenic patients, and this effect is attributed to their immunosuppressive action. Work from our laboratory has shown that in addition glucocorticoids have a direct presynaptic effect viz. a stimulation of the choline uptake in nerve endings. The endplates of the rat diaphragm possess a choline carrier system with sigmoidal kinetics, and glucocorticoids are positive cooperative effectors of this system. On the other hand there have been reports of glucocorticoids counteracting the neuromuscular blocking action of curare-like drugs, thus supporting the concept of a post-synaptic effect of glucocorticoids (Arts & Oosterhuis, 1975). We have found that the LD_{50} of (+)-tubocurarine in rats is increased significantly, although not substantially, by dexamethasone. Choline gives some protection against (+)-tubocurarine, and cholinesterase inhibitors give full protection. The blocking effect of (+)-tubocurarine on the phrenic nerve diaphragm

preparation and on the sciatic nerve tibialis anterior muscle preparation were antagonized slightly by glucocorticoids. Our recent work demonstrates that (+)-tubocurarine also effects the choline carrier system in rat diaphragm in a way that is comparable, but not the same as that of the choline structural analogue hemicholinium-3. These experiments indicate that glucocorticoids have direct presynaptic as well as postsynaptic effects on neuromuscular transmission. It is conceivable that part of their beneficial effects in myasthenia gravis may be due to these direct effects.

References

ARTS, W.F. & OOSTERHUIS, H.J. (1975). Effect of prednisolone on neuromuscular blocking in mice *in vivo*. *Neurology (Minneap.)* **25**, 1088–1090.

ITO, Y., MILEDI, R., MOLENAAR, P.C., NEWSOM DAVIS, J., POLAK, R. & VINCENT, A. (1978). Neuromuscular transmission in myasthenia gravis and the significance of anti-acetylcholine receptor antibodies. In: *The biochemistry of myasthenia gravis and muscular dystrophy*. Ed. G.G. Lunt and R.M. Marchbanks, 89–110. London, Academic Press.

Effect of histamine upon core and tail skin temperature of the conscious restrained rat

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The hypothermic effect of systemically administered histamine in the rat is well established (Lomax & Green, 1975). However, the mechanism by which this is achieved has not been fully elucidated. The tail of the rat has been shown to be of major importance in thermoregulation (Rand, Burton & Ing 1965), thus dilation of the tail blood vessels will promote heat loss while constriction will conserve heat. Histamine induced hypothermia has been suggested to be related to peripheral vasodilation (Lomax & Green 1975) and it was of interest to determine what role the tail vessels played in this process.

Core and tail skin temperature was measured in male Sprague–Dawley rats (270–350 g) restrained at an ambient temperature of 17 ± 1°C (Cox, Kerwin & Lee, 1978). Histamine acid phosphate (B.D.H.) was administered i.p. dissolved in 0.9% NaCl. Control rats received acidified saline (pH 4). The results obtained 30 min later are presented in the Table as the change in temperature (°C) relative to the average of three consecutive readings taken immediately before drug administration. Histamine produced a dose related fall in core temperature over the range 1.8–28.9 mg/kg. The hypothermic effect of histamine (36.2 mg/kg) was not as great as that produced by 28.9 mg/kg ($P < 0.05$) or 14.5 mg/kg. Histamine also produced a fall in tail temperature that was dose related over the range 1.8–7.2 mg/kg, larger doses produced no further falls in temperature.

The results demonstrate that the fall in core temperature following histamine is not mediated by peripheral vasodilation and suggest that other thermoregulatory processes should be investigated.

Table 1

Temperature change °C at 30 min
(mean ± s.e. mean n = 5–9)

Treatment	*Core*	*Tail*
Saline	+0.1 ± 0.1	−0.26 ± 0.1
Histamine (free base mg/kg)		
1.8	−0.24 ± 0.15*	−0.77 ± 0.31
3.6	−0.28 ± 0.16	−1.25 ± 0.27*
7.2	−0.59 ± 0.09*	−1.60 ± 0.38*
14.5	−0.83 ± 0.20*	−1.50 ± 0.24*
28.9	−1.10 ± 0.12*	−1.49 ± 0.30*
36.2	−0.58 ± 0.12*	−1.48 ± 0.28*

* Significance of difference v saline ($P < 0.05$).
Mann Whitney 'U' test.