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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.

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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