similar to those seen in the FHL muscle. The highest dose of quazodine increased the peak tension of maximal twitches by 8 to 15%. Incomplete (8-10 Hz) and maximal (100 Hz) tetanic contractions were also enhanced but, unlike the effects in the FHL muscle, incomplete tetani were no more responsive than maximal tetani. The time course of enhanced contractility was similar to that observed in the FHL muscle. Following the period of enhancement of contractility of the soleus muscle, twitch tension and submaximal tetanic tension were reduced. No such effect was seen in maximal tetani. The depressant effect on incomplete tetanic tension was more marked (up to 30%) than the effect on twitches (up to 12%). It reached a peak within 5 min of injection of quazodine and was associated with defusion of the contractions. All effects in the FHL and soleus muscle were observed both in fully curarized, directly stimulated muscles and in indirectly stimulated muscles, indicating that they were not a result of actions of quazodine on neuromuscular transmission (Nott & Winslow, 1973).

The enhancing effect of quazodine on contractions of the FHL and soleus muscles was similar to that observed with theophylline (2-20 mg/kg i.a.) and as with the methylxanthines (Sandow, 1965), probably involves mobilization of calcium ions. The secondary phase in the soleus was similar to the depression seen following treatment with β-adrenoceptor agonists (Bowman & Nott, 1970), and in the present experiments was reduced or abolished by prior treatment with (±) propranolol (100-200 μg/kg i.v.).

References

AVIADO, D.M., FOLLE, L.E. & PISANTY, J. (1967). The cardiopulmonary effects of a quinazoline (MJ 1988): cardiac stimulant, pulmonary vasodilator and bronchodilator. *J. Pharmac. exp. Ther.*, **155**, 76-83.

BOWMAN, W.C. & NOTT, M.W. (1970). Actions of sympathomimetic bronchodilators and beta-adrenoceptor blocking drugs on contractions of the cat soleus muscle. *Br. J. Pharmac.*, **38**, 37-49.

LISH, P.M., COX, R.H., DUNGAN, K.W. & ROBBINS, S.I. (1964). Some non-adrenergic bronchodilator and cardiac stimulating agents. *Pharmacologist*, **6**, 181.

NOTT, M.W. & WINSLOW, EILEEN (1973). Effects of quazodine on contractions of the isolated hemidiaphragm of the rat and the biventer cervicis muscle of the chick. *Br. J. Pharmac.*, **48**, 409-417.

PARRATT, J.R. & WINSLOW, E. (1972). Haemodynamic and coronary effects of quazodine in cats with developing myocardial infarcts. *J. Pharm. Pharmac.*, **24**, 673-680.

SANDOW, A. (1965). Excitation-contraction coupling in skeletal muscle. *Pharmac. Rev.*, **17**, 265-320.

The relationship of ascorbic acid to leptazol-induced convulsions in guinea-pigs

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Hepatic ascorbic acid (AA) is reduced to about 9% (Hurley, Jones & Hughes, 1972; Odumosu & Wilson, 1973a), and adrenal AA to almost zero (Odumosu & Wilson, 1970), in scorbutic guinea-pigs. In contrast, brain AA is only reduced to 48% of normal (Hurley, Jones & Hughes, 1972). Supplementary AA disappears more slowly from the brain than from other tissues (Hornig, Weber & Wais, 1972). The function of ascorbic acid in the brain is unknown, although it may be involved in olfaction (Ash, 1969), taste (Loh & Wilson, 1973) and in the production of anorexia arising from fenfluramine (Odumosu & Wilson, 1973b, c). Clonic and tonic convulsions are produced in normal guinea-pigs by administration of leptazol, 60 mg/kg i.p., resulting in 100% mortality, whereas 40 mg/kg produces clonic seizures in only 50%. At the time of death, brain AA is significantly reduced to 56-70% of normal, and plasma AA is elevated to 142% of normal by 60 mg/kg leptazol. In guinea-pigs receiving 40 mg/kg leptazol, brain AA falls to 83% of normal, but plasma AA is unaltered, indicating that brain AA is being catabolized. The incidence, and time preceding onset, of convulsions is related to the concentration of brain AA. A second dose of 40 mg/kg of leptazol was administered over 60 min to animals which had not developed convulsions, and to convulsing animals 15 min after the last tonus. All developed clonic convulsions in 12 minutes. Brain AA was reduced to 54% and plasma AA was raised to 130% of control values.

AA administration (200 mg/kg i.p.) 1 h before leptazol 60 mg/kg results in a lower incidence of tonic convulsions after a prolonged latent period, but brain AA decreases to the same level as in unsupplemented animals. The incidence is increased and the latent period of convulsions is shortened by leptazol in scorbutic guinea-pigs. Their brain AA is reduced to 37% of normal, and AA is released into the plasma during the convulsions. AA concentrations fall to 63% in the mid-brain and 91% in the fore-brain, of normal

values, and are raised to 128% of normal in the hind-brain, after administration of 60 mg/kg of leptazol producing 100% clonic convulsions. It is concluded that AA is catabolized in the mid- and fore-brain, and is absorbed into the hind-brain, during clonic and tonic convulsions. Under normal circumstances brain AA is retained in a stable pool. This cannot be depleted by convulsions in combination with a scorbutogenic diet. Deficiency of AA exacerbates, and raised brain AA reduces, frequency and incidence of seizures. It is suggested that AA may play a major metabolic role in the brain.

References

ASH, K.O. (1969). Ascorbic acid cofactor in rabbit olfactory preparation. *Science*, **165**, 901-902.

HORNIG, D., WEBER, F. & WISS, O. (1972). Autoradiographic distribution of (−[^{14}C]) ascorbic acid and (−[^{14}C]) dehydroascorbic acid in male guinea-pigs after intravenous injection. *Internat. J. Vit. Nutr. Res.*, **43**, 224-241.

HURLEY, R.J., JONES, P.R. & HUGHES, R.E. (1972). The uptake of ascorbic acid by the tissues of ascorbic-acid deficient guinea-pigs. *Nutr. Metabol.*, **14**, 136-140.

LOH, H.S. & WILSON, C.W.M. (1973). Vitamin C: plasma and taste threshold circadian rhythms, their relationship 0o plasma cortisol. *Internat. J. Vit. Nutr. Res.* (In press.)

ODUMOSU, A. & WILSON, C.W.M. (1970). The relationship between ascorbic acid concentrations and cortisol production during the development of scurvy in the guinea-pig. *Br. J. Pharmac.*, **40**, 548P.

ODUMOSU, A. & WILSON, C.W.M. (1973a). Metabolic availability of Vitamin C in the guinea-pig. *Nature, Lond.*, **242**, 519-521.

ODUMOSU, A. & WILSON, C.W.M. (1973). Ascorbic acid and cholesterol mobilisation by fenfluramine. *Br. J. Pharmac.*, **48**, 326P.

ODUMOSU, A. & WILSON, C.W.M. (1973). The status of Vitamin C in obesity. European Nutrition Conference Proc. Comm. 62. *Br. J. Nutr.* (In press.)

Uptake of propranolol by the isolated perfused rat liver

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In the isolated perfused rat liver, propranolol at low concentrations was almost completely extracted from the perfusion fluid at the 'first pass' through the liver. This is in agreement with the work of Shand and co-workers. The extraction ratio (E.R.) of the propranolol decreased from 0.96 to 0.68 as the propranolol concentration increased from 1-1000 μM. The percentage of unchanged propranolol remaining in the liver at the end of the perfusion period increased from 4 to 68% as the concentration increased from 1-1000 μM. This high clearance or 'first pass' effect of propranolol consists of both uptake and metabolism. A decrease in the metabolism and clearance of propranolol (1 μM) was observed at a lower perfusion temperature and during simultaneous perfusion with nortriptyline (100 μM) another drug known to exhibit the 'first pass' effect. However, in similar experiments with either the microsomal inhibitor SKF 525A (100 μM) or lignocaine (100 μM), which is also well cleared by the liver, selectively decreased the percentage of propranolol metabolized in the liver from 96% to 55% and 38% respectively, but was without effect on the clearance of the propranolol. P-hydroxyacetanilide (paracetamol) is also well cleared by the liver but had no effect on either the metabolism or the clearance of propranolol. It appears that the mechanisms of the high hepatic clearance and metabolism of several drugs such as propranolol, p-hydroxyacetanilide and lignocaine are different.

Reference

SHAND, D.G., RANGNO, R.E. & EVANS, G.H. (1972). The disposition of propranolol II. Hepatic elimination in the rat. *Pharmacology*, **8**, 344-352.