73P A COMPUTER SIMULATION OF THE SCIATIC NERVE-TIBIALIS ANTERIOR MUSCLE PREPARATION OF THE CAT *IN VIVO* TO TEACH NEUROMUSCULAR PHARMACOLOGY TO UNDERGRADUATE STUDENTS

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Laboratory practicals which use live animals or animal tissue have long been used by pharmacologists. For a number of reasons many courses have reduced the number of practicals in their curricula and some have turned to computer simulations to provide a 'dry-lab' experience which fulfils some but not all of the objectives of the traditional practical class. These are no substitute if animal/tissue handling skills or specific laboratory skills are important learning objectives but can be effective in presenting data in an interactive manner and encouraging students to use it to learn and practice data-handling, data-presentation, data-interpretation and report writing skills.

Here we demonstrate a computer simulation of experiments which may be performed on the cat sciatic nerve-tibialis anterior muscle preparation *in vivo* to illustrate the important differences in the pharmacological action of depolarizing and non-depolarizing blocking agents and teach the essentials of neuromuscular pharmacology. The program was written using Macromedia Director version 6.5 for IBM compatible PCs running Windows (minimum specification: PC 486 running Windows 3.1 or better).

It has several sections accessible form a menu: A *Student Handbook* uses text and graphics to cover: an outline of the process of neuromuscular transmission; the methods (the preparation of the anaesthetised cat, the protocol for nerve stimulation and isometric recording of evoked muscle contractions); a summary of the actions of and the clinical relevance of different types of blocking agents. The ***Experiments*** section presents high-resolution graphic simulations of muscle contractions, in accelerated time, on a scrolling, chart-recorder like display. *Phase I experiments* - compare the action of a non-depolarizing blocker (d-tubocurarine) and a depolarizing blocker (decamethonium). For each there are traces illustrating the effects of: i.v. administration; i.a. administration; blocker + anti-cholinesterase, blocker + a different non-depolarizing or depolarizing blocker; tetanic stimulation; i.a. acetylcholine. *Phase II experiments* - the effects of 4 successive doses of decamethonium followed by the effects of tetanic stimulation and an anticholinesterase

Each experiment has an associated student activity designed to assess understanding of the experimental results. These might be a series of true/false statements or a table to complete. There are also some suggested questions which would form the basis of a report of the experiment.

We would like to acknowledge the financial support of the Lord Dowding Fund (NAVS) in developing this program.

74P DIABETIC NEUROPATHIES

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The incidence and severity of diabetes complications are increased by poor control of glycaemia. This implicates raised glucose as a primary component of their aetiology and focuses attention on biochemical aberrations downstream of hyperglycaemia. These include increased oxidative stress, post-translational glycation of proteins and exaggerated flux through aldose reductase and the polyol pathway. Our understanding of the cell biology of diabetic neuropathy, nephropathy and retinopathy indicates that the critical step in their development occurs when these biochemical anomalies cause sustained changes in cell phenotype. In neuropathy this occurs in neurones, Schwann cells and vascular elements of the endoneurium. Thus, we need to identify the transducers that promote these phenotype switches.

This presentation will review the evidence implicating MAP kinases as *de facto* glucose transducers for diabetic neuropathies. *In vitro*, the MAPKs are activated in sensory neurones by raised glucose and this activation is augmented by superimposition of oxidative stress. Activation of ERK or p38 MAPK provides a damage signal, because inhibition of this effect of glucose plus oxidative stress reduces the release of LDH into the culture medium.

We have not yet been able to test the effect of JNK inhibition. All three groups of MAPKs are activated in sensory neurones in diabetic rats and in diabetic patients. Inhibition of p38 activation in diabetic rats reverses neurological function deficits, such as decreased nerve conduction velocity. This latter change is also prevented by treatment of diabetic rats with sonic hedgehog. Thus, we have two dissimilar interventions with a common end-point and it is interesting to speculate on the extent to which the mechanisms differ.

Such effects provide useful tools for dissection of mechanisms and for identification of the transcriptional changes involved.