141P COMPARISON OF THE EFFECTS OF $PGF_2\alpha$ AND RELATED COMPOUNDS ON THE HUMAN ISOLATED MYOMETRIUM FROM NON-PREGNANT AND PREGNANT DONORS

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Previous studies in this laboratory have shown that on the human isolated myometrial strips from non-pregnant (NP) and pregnant (P) donors $PGF_2\alpha$ evokes a stimulant response, suggesting the presence of FP- receptors on these tissues (Senior *et al.*, 1992 & 1993). In the absence of a suitable FP-receptor antagonist two selective FP- receptor agonists were used in this study in order to confirm our earlier findings. The agonists used were fluprostenol (Coleman *et al.*, 1984) and the free acid of latanoprost (Stjernschantz & Resul, 1992).

Samples of human myometrium were obtained from NP pre-menopausal patients at hysterectomy (fundus) or from P donors (who had not gone into labour) during Caesarean section (lower uterine segment) (all patients gave written consent). The myometrial strips were set up for superfusion (2g tension) in Krebs' solution with 2.79μM indomethacin (37°C, 95% O_2/5% CO_2) at 2ml min^{-1} as previously described by Senior *et al.* (1991). After equilibration of the tissues bolus doses of $PGF_2\alpha$, fluprostenol or latanoprost were injected directly into the flow of the superfusate. As the profile of the spontaneous activity changed throughout the course of the experiments, comparisons were made between preparations in a non-paired manner. Because of the variations in myogenic activity results have been normalised to take this into account (Senior *et al.*, 1991). Briefly, excitatory potency was expressed as an ED_1 value. ED_1 values were expressed as geometric means (nmol) with 95% confidence limits in parentheses, n=5 in all cases.

On the human myometrium from NP and P donors $PGF_2\alpha$ (0.0001-100nmol), fluprostenol (0.0001-100 nmol) and latanoprost (0.0001-300nmol) all evoked an increase in myometrial tension. In NP tissues the curves to $PGF_2\alpha$ and fluprostenol were bell shaped, with a decline in the contractile responses occurring after 10nmol for $PGF_2\alpha$ and 0.1nmol for fluprostenol. This was not seen in tissues obtained from P donors.

Table 1 Mean ED_1(nmols) values of the prostanoids on NP and P tissues.

	NP	P
Compound	ED_1 value	ED_1 value
$PGF_2\alpha$	0.04 (0.01-0.14)	0.50 (0.28-0.66)
Fluprostenol	0.04 (0.013-0.1)	0.61 (0.50-0.75)
Latanoprost	0.007 (0.005-0.008)	0.60 (0.50-0.80)

As can be seen from table 1 the rank order of potency of the natural and selective prostanoids in the human myometrium from NP donors is as follows: latanoprost > $PGF_2\alpha$ = fluprostenol. However, in tissues from P donors all three agonists were of the same order of potency. There was a marked difference between NP and P tissues in that the agonists were 10-100 times less effective in stimulating P tissue.

The results from the present study confirm our earlier findings that the human myometrium does contain FP- receptors. The FP- receptor population may also be greater in the NP myometrium than in the non-labouring P myometrium.

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Senior, J. Marshall, K., Sangha, R. *et al.* (1991) *Br. J. Pharmacol.* **102**, 747-753.
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142P SPICE - A SIMPLE PROGRAM IDENTIFYING CURVACEOUS ELEMENTS

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The most commonly used model for the relation between effect (E) and concentration ([A]) is the equation (Parker & Waud, 1971):

$$E = \frac{M[A]^P}{[A]^P + [A_{50}]^P} \quad \ldots\ldots 1$$

where M is the maximum, $[A_{50}]$ produces a half- maximum effect and P is an exponent which determines the steepness of the curve. This empirical model, often called "logistic", has the same form as the equation used by Hill (1913) to describe the binding of oxygen to haemoglobin and P is the same as the Hill coefficient (n_H). When P=1 the equation describes binding according to the law of mass action, i.e. the relation between agonist concentration and receptor complex. Increasingly curves are appearing in the literature which are "flat", i.e. P<1. This implies that the order of the process(es) occurring after binding is less than one but there may be other reasons, such as that a maximum or baseline which has been incorrectly calculated or that more than one process is contributing to the effect. This program has been written to identify possible causes for flatness and to identify component elements. It offers:

1 a fit to equation 1

2 a fit to equation 1 + calculation of a baseline, which can be deducted before further analysis.

3 a fit to a 2-site binding equation

$$E = M_1 \frac{[A]}{[A] + [A_1]_{50}} + M_2 \frac{[A]}{[A] + [A_2]_{50}} \quad \ldots\ldots 2$$

where M_1 and M_2 are the two maxima and $[A_1]_{50}$ and $[A_2]_{50}$ are the concentrations producing the corresponding half-maximal effects.

4 a fit to the double logistic equation

$$E = M_1 \frac{[A]^{P1}}{[A]^{P1} + [A_1]_{50}^{P1}} + M_2 \frac{[A]^{P2}}{[A]^{P2} + [A_2]_{50}^{P2}} \quad \ldots\ldots 3$$

5 a fit to a 3-site binding equation (eqn 2 with a term for M_3 and $[A_3]_{50}$).

Procedures for fitting data to such equations based on the methods of Parker & Waud (1971) have been available for some time (e.g. Barlow, 1983) but do not appear to be in general use, perhaps because, with four or more parameters to be calculated, it is difficult to make starting guesses which lead to convergence. This program displays the curve corresponding to the starting values so that appropriate guesses can be obtained by inspection before iteration is attempted. Improvement in fit is estimated from the ratio of the sum of $(E_{observed} - E_{calculated})^2$ for equation 1 to the sum for the equation chosen: it is also expressed as the variance ratio and as the ratio of the coefficients of variation. Critical values of F for 5% probability are included and used to indicate a significant improvement. When there is only one result for each concentration, the appropriateness of the equation used is also indicated by the strings of points lying consistently above or below the line.

It has been particularly useful for analysing the effects of agonists on 5HT receptors in arteries and veins in the horse, fitted to the double logistic equation (3) and for the effects of compounds on rat mesenteric vessels and small arteries in patients, where 3 processes appear to be involved. Its scope is also illustrated by a survey of curves appearing in many recent papers in the British Journal of Pharmacology. The program is offerred (free) to anyone interested.

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Hill, A.V. (1913) Biochem.J., 7, 471-480.
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143P A COMPUTER SIMULATION OF AN INVESTIGATIVE APPROACH TO TEACHING RENAL FUNCTION IN HUMANS TO UNDERGRADUATE STUDENTS

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Computer-simulations of laboratory investigations can be extremely useful for teaching undergraduate students particularly where it is difficult for students to undertake these practicals for themselves. Practical investigation of renal function in humans is time-consuming, requires a variety of analytical equipment and technical expertise and, if the investigation is to include diuretics, a clinician must be on hand. Many of the student tasks are repetitive and involve using collected urine and plasma data to calculate glomerular filtration rate (GFR), urine flow and electrolyte output. Here we demonstrate an interactive computer-based learning (CBL) package designed to allow students to collect urine and plasma data (mean values presented from groups of healthy male students: n=10) who took part in the following investigations: (1) control experiment (no water loading), (2) water loading, (3) the action of four diuretics (acetazolamide, amiloride, hydrochlorothiazide, bumetanide) in water loaded subjects.

For each experiment, data are presented graphically for: (1) plasma electrolytes (Na^+, K^+, Cl^-, HCO_3^-) and creatinine concentrations and plasma osmolality, (2) urine electrolyte (Na^+, K^+, Cl^-, HCO_3^-), creatinine and total solute output, urine osmolality and urine flow. Students observing data from water-loaded subjects may superimpose control data to give a visual comparison. Similarly, water loading data can be superimposed for each of the diuretic experiments.

The program describes the protocol for each experiment and, in brief, the methods used to analyse urine and plasma. Accompanying each experiment are several interactive questions and tasks to emphasise the important physiological principles. These may be questions (e.g. multiple choice or true false with feedback), data interpretation exercises, or calculations. Thus, for each experiment, students are asked to calculate: glomerular filtration rate, total and fractional (%) water and Na^+ reabsorption). The calculations require them to take measurements from the graphical screen displays, enter it into well-established formulae and type in their answers. Assistance with the calculations is available via an on-screen "Help" and, if they get the answer incorrect, there is also a "Tell" facility which demonstrates how the correct answer is arrived at. These questions are designed to consolidate knowledge and to allow students to self-assess their understanding of the section they have completed. A summary of all calculated data is incorporated.

The program was developed using Multimedia Toolbook® (Asymetrix) to run on IBM PC compatibles (capable of running Windows™ version 3.1 or better (Microsoft), a 256 colour VGA monitor and a mouse).

It is suitable for undergraduate medical and science (physiology, biological sciences) students and may be used either as a debriefing aid to support students who perform similar experiments to this themselves in the laboratory (e.g. to provide data to students who only partially complete the experiments (to perform all of the experiments covered by the package would take about 20h)) or in advance of the practical to better-prepare them. Alternatively it can be used as a replacement where it would be particularly useful if the technical skills involved are not primary learning objectives.

144P ENDOCRINE GLANDS: AN INTRODUCTORY LEVEL COMPUTER-BASED INTERACTIVE TUTORIAL FOR UNDERGRADUATE STUDENTS

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At a recent meeting of the Society we presented a foundation level computer-based tutorial program to introduce the endocrine sysytem to undergraduate students (Dewhurst & Davies, 1997). The program has proved popular with students particularly as a revision aid and we have now extended it to include specific endocrine glands. The programs are highly interactive and include a variety of questions to reinforce learning and for self-assessment e.g. students must: label diagrams by "dragging" labels from a list and "dropping" them into the box corresponding to the correct position on the diagram; answer a variety of questions included in each section (these may be multiple choice, selecting correct phrases from a list to complete a statement, and true/false questions with feedback), some data interpretation e.g. data from glucose-tolerance tests, questions relating to a case study.

High quality colour graphics are used extensively throughout the programs and features such as animation and a Hypertext facility are used to enhance student learning. Each is designed to teach the basic physiology and covers functional anatomy, hormone synthesis, regulation of secretion, physiological effects and some of the main clinical disorders.

Three programs will be demonstrated.
1. Thyroid Hormones which covers: location and structure of the thyroid glands, synthesis, release, transport and mechanism of action of the thyroid hormones (T_3 and T_4), function of T_3 and T_4, principal abnormalities of thyroid function - hypothyroidism and hyperthyroidism.

2. Parathyroid hormone, calcitonin and Vitamin D in the regulation of plasma calcium which covers: location and structure of the parathyroid glands, synthesis, release, transport and action of the three hormones on bone, kidney and gastrointestinal tract, physiological role of calcium, structure of bone and bone remodelling, principal abnormalities of calcium metabolism - hyperparathyroidism, hypoparathyroidism, vitamin D deficiency and osteoporosis.

3. Pancreatic hormones (insulin and glucagon) and the regulation of blood glucose which covers: location and structure of the Islets of Langerhans, factors affecting release of the hormones and their effects on target cells, principal clinical disorders - Type I and Type II diabetes mellitus (causes, symptoms and treatment), hypoglycaemia and hyperglycaemia.

The programs were developed using Multimedia Toolbook® (Asymetrix) to run on 486 (or better) IBM PC compatibles running Windows™ version 3.1 or better (Microsoft), a 256 colour VGA monitor and a mouse.

They are suitable for first year undergraduates from a range of biological science, medical and health-related courses. The material in each program covers approximately two hours of lectures to first year students and would occupy students for 2-4 hours of self study.

Dewhurst, D. G. & Davies, D. (1997) Br. J. Pharmacol. **122**, 173P.