207P A COMPUTER SIMULATION OF THE CAT NICTITATING MEMBRANE PREPARATION FOR UNDERGRADUATE PHARMACOLOGY STUDENTS

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Computer-assisted learning (CAL) programs can support many aspects of teaching and learning in undergraduate pharmacology courses and many examples of these have been demonstrated to the Society in recent years. Laboratory-based practicals which use live animals or animal tissue have long been used to provide a basis for learning by investigation, teaching experimental design and teaching and practicing a wide range of laboratory and research skills. Many universities have been forced to reduce the amount of laboratory work 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 animal experiments. Simulations may be particularly appropriate where the animal experiment is costly to perform, or requires a high level of technical expertise. One such experiment is the *in vivo* superior cervical ganglion – nictitating membrane preparation of the anaesthetised cat and we present here a computer simulation of experiments that may be performed on this preparation to teach the basic pharmacology of transmission at autonomic ganglia and sympathetically innervated smooth muscle.

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: *Introduction*: provides information about the program and it's curricula context; *Tutorial:* presents diagrammatic representations of the effector junction and the superior cervical ganglion. This section of the program uses animated sequences to demonstrate the stages of transmission at both the synapse and neuroeffector junction and highlights possible sites of action of drugs; *Methods:* describes the preparation, protocols for nerve stimulation and administration of drugs to the superior cervical ganglion and the nictitating membrane, and the method of recording contractions of the nictitating membrane. *Experiments:* allows students to perform simulated experiments on the preparation and provides recordings of the force of contraction of both ipsilateral and contralateral nictitating membranes which are displayed on a screen designed to emulate a chart recorder. A sub-menu gives students some control over experimental parameters (they can choose: 1. to administer an agent from a list: saline (vehicle control), acetylcholine, noradrenaline, atropine, phentolamine, propranolol, isoprenaline, hexamethonium, physostigmine, nicotine (low and high dose), tyramine, an unknown (which is randomly selected from the list above when the program is run); 2. the site of administration; 3. whether to electrically stimulate preganglionic nerves (half-maximal stimulation). Although it is envisaged that the tutor will develop a set of tasks for students to address when using the simulation which will meet their own teaching objectives, this section does also includes some suggested tasks to aid independent use of the program.

208P THE CARDIOVASCULAR ACTIONS OF CANNABINOIDS: MORE QUESTIONS THAN ANSWERS

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Endogenous cannabinoids (endocannabinoids), which were first identified in the central nervous system, exert cardiovascular actions. In this respect the prototypic endocannabinoid, derived from arachidonic acid, anandamide, is a vasorelaxant, especially in the resistance vasculature. The mechanism(s) by which this occurs has yet to be fully defined. To date, cannabinoids have been proposed to act via the release of endothelial autacoids (NO and prostanoids), to act via endothelium-dependent hyperpolarization, to activate K^+ channels, to modulate neurotransmission, and to interfere with Ca^{2+} mobilization (see Randall & Kendall, 1998). In the emerging literature, both the endothelial dependence and the involvement of cannabinoid receptors in the vasorelaxant responses are controversial.

The endogenous production of cannabinoids in the vasculature has also proved controversial, with several proposed sites. It was originally proposed that an endocannabinoid might be an endothelium-derived autacoid. In support of this, endothelium-derived hyperpolari zing factor (EDHF)-mediated relaxations are sensitive to inhibition of CB_1 receptor antagonists, although this is widely disputed. Furthermore, endothelial cells synthesise the endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG) (see Randall & Kendall, 1998). In the case of the latter it has recently been reported that stimulation of rat aortic endothelial cells with a releaser of EDHF is associated with the emergence of 2-AG (Mechoulam *et al.*, 1998). In contrast to these findings, it has been found in various vascular tissues that, although anandamide may cause hyperpolarization this is due to an endothelium-dependent action. There is clearly no consensus in the emerging literature that an endocannabinoid is an EDHF, although there is perhaps some evidence which points to them being a class of endothelium-derived vasorelaxants. It has also been proposed that endocannabinoids may be derived from white blood cells and platelets, and may play a role in the hypotension associated with haemorrhagic and endotoxic shock (Wagner *et al.*, 1997; Varga *et al.*, 1998). More recently, Ishioka & Bukoski (1999) have provided evidence that an endocannabinoid may be neuronally derived, causing vasorelaxation via K^+-channel activation.

The endocannabinoids represent a new class of vasoactive substances; their physiological actions and significance remain to be fully elucidated.

Ishioka, N. & Bukoski, R.D. (1999). *J Pharmacol. Exp. Ther.*, 289, 245-250.

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Wagner, J.A., Varga, K., Ellis, E.F. *et al.* (1997). *Nature,* 390, 518-521.

209P COGNITIVE ALTERATIONS FOLLOWING CANNABIS USE IN HUMANS

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Acute intake of cannabinoids undoubtedly produces a spectrum of cognitive alterations both in first time and in chronic users. These alterations have mainly been viewed as effects of a transient intoxication with rapid onset and a "return to normal" within hours to days. Obviously, no severely disabling effects of cannabinoids can be proven even in heavy longterm users. Recent elegant studies, however, trying to circumvent problems inherent to this kind of research (e.g. residual drug effects due to the high lipophilicity of cannabinoids or the influence of premorbid personality on study results) provide evidence for complex but subtle lasting impairments in chronic users, affecting organization and integration of complex attention and memory processes. The existence of endogenous cannabinoids and cannabinoid receptors supports the hypothesis that chronic challenge of these systems by frequent/continuous exogenous "substitution" may lead to specific enduring irritations of these systems.

In a recent study we tested the hypothesis that chronic interference of cannabis with endogenous cannabinoid systems during peripubertal development causes specific and persistent brain alterations in humans. As an index of cannabinoid action, *visual scanning,* along with other attentional functions, was chosen. Visual scanning undergoes a major maturation process around age 12 to 15 and, in addition, the visual system is known to react specifically and sensitively to cannabinoids. From 250 regularly cannabis-consuming individuals, 99 healthy pure cannabis users were selected. They were free of any other past or present drug abuse, or history of neuropsychiatric disease. After an interview, physical examination, analysis of routine laboratory parameters, plasma/urine analyses for drugs, and MMPI-testing, users and respective controls were subjected to a computer-assisted attention test battery comprising *visual scanning, alertness, divided attention, flexibility* and *working memory.*

Of the potential predictors of test performance within the user group, including present age, age of onset of cannabis use, degree of acute intoxication (THC+THCOH plasma levels), and cumulative toxicity (estimated total life dose), an early age of onset turned out to be the only predictor, predicting impaired reaction times exclusively in visual scanning. Early-onset users (onset before age 16; n=48) showed a significant impairment in reaction times in this function, whereas late-onset users (onset after age 16; n=51) did not differ from controls (n=49).

These results suggest that beginning of cannabis use during early adolescence may lead to enduring effects on specific attentional functions in adulthood. Apparently, vulnerable periods during brain development exist that are subject to persistent alterations by interfering exogenous cannabinoids.

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The endogenous production of cannabinoids in the vasculature has also proved controversial, with several proposed sites. It was originally proposed that an endocannabinoid might be an endothelium-derived autacoid. In support of this, endothelium-derived hyperpolari zing factor (EDHF)-mediated relaxations are sensitive to inhibition of CB_1 receptor antagonists, although this is widely disputed. Furthermore, endothelial cells synthesise the endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG) (see Randall & Kendall, 1998). In the case of the latter it has recently been reported that stimulation of rat aortic endothelial cells with a releaser of EDHF is associated with the emergence of 2-AG (Mechoulam *et al.,* 1998). In contrast to these findings, it has been found in various vascular tissues that, although anandamide may cause hyperpolarization this is due to an endothelium-dependent action. There is clearly no consensus in the emerging literature that an endocannabinoid is an EDHF, although there is perhaps some evidence which points to them being a class of endothelium-derived vasorelaxants. It has also been proposed that endocannabinoids may be derived from white blood cells and platelets, and may play a role in the hypotension associated with haemorrhagic and endotoxic shock (Wagner *et al.,* 1997; Varga *et al.,* 1998). More recently, Ishioka & Bukoski (1999) have provided evidence that an endocannabinoid may be neuronally derived, causing vasorelaxation via K^+-channel activation.

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211P ANANDAMIDE – AN ENDOGENOUS MODULATOR OF VANILLOID RECEPTORS?

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Anandamide, an endogenous cannabinoid (CB) receptor agonist, causes vasodilatation in isolated blood vessels and vascular beds. The mechanism by which anandamide exerts these vascular effects is unclear. Since anandamide shows some structural similarity to capsaicin and olvanil, both of which act on sensory nerves and cause vasodilatation, we hypothesised that the "vanilloid receptor" on perivascular sensory nerves is the target for anandamide.

Role of sensory nerves. The vasodilatation evoked by anandamide in isolated arteries did not occur in vessels pre-treated with capsaicin. Furthermore, anandamide released calcitonin gene-related peptide (CGRP) and increased cyclic AMP in isolated blood vessels, effects which were not observed after pre-treatment with capsaicin. Also, the vasodilator effect of anandamide was inhibited by the CGRP receptor antagonist 8-37 CGRP.

Role of CB receptors. The CB1 receptor blocker SR141716A (0.3 μM) did not affect relaxations to anandamide. Other endogenous (2-arachidonylglycerol, palmitylethanolamide) and synthetic (HU 210, WIN 55,212-2, CP 55,940) CB1 and CB2 receptor agonists were unable to mimic the action of anandamide.

Role of vanilloid receptors. The vasodilator response and outflow of CGRP induced by anandamide were inhibited by the "vanilloid receptor" antagonist capsazepine. Direct evidence that anandamide activates the "vanilloid receptor" was obtained in patch-clamp experiments on cells expressing the cloned "vanilloid receptor" (VR1).

Our results indicate that the vasodilator effect of anandamide is caused by activation of the "vanilloid receptor" on perivascular sensory nerves and subsequent release of the vasodilator peptide CGRP. It is thus possible that anandamide and/or structurally-related lipids act as endogenous "vanilloid receptor" modulators in the nervous and cardiovascular systems.

212P A WHOLE-PLANT CANNABIS EXTRACT FOR ANOREXIA-CACHEXIA IN CANCER PATIENTS

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Weight loss in cancer patients has long been recognised as an important prognostic factor which affects response to chemotherapy and duration of survival. Most evidence suggests that cancer cachexia results from a combination of metabolic abnormalities, malnutrition and circulating humoral factors. The central purpose of the pharmacological treatment of cachexia is to antagonise its two main symptoms, anorexia and chronic nausea. The latter should be controlled adequately before any pharmacological intervention for the patient's anorexia is attempted. This finding suggests that a pharmacotherapy aimed at reversing chronic nausea *and* improving appetite may enhance quality of life in cancer patients, and plays an important role in the overall management of the wasting syndrome in advanced cancer.

Delta-9-Tetrahydrocannabinol (THC), the major psychoactive component of cannabis, is approved by the FDA for the treatment of anorexia associated with weight loss in patients with AIDS or cancer. In addition, the whole plant *Cannabis sativa L.* - by means of marihuana smoking or hashish ingestion - has also long been reported to increase hunger and appetite, and a growing number of cancer patients experience improvement of nausea, appetite and mood by their self-medication with cannabis. In order to determine these therapeutic effects scientifically and to achieve legalisation of cannabis for medical purposes (as spasticity, glaucoma, migraine, chronic pain etc are also included) controlled clinical trials are necessary.

We therefore started, in June this year, a multinational, randomised, double-blind, placebo-controlled, three-arm parallel multicentre-study in patients with cancer who lost at least 5% of their body weight over the previous six months. The main objectives are to document the effficacy of THC and Cannabis sativa extract that will be administered as soft gelatine capsules in the treatment of anorexia and cachexia, and to compare tolerance and effficacy of both medications. The patients are randomised to receive either Cannabis extract (2.5 mg THC b.i.d.) that is standardised on its THC content, THC 2.5 mg b.i.d. or placebo for a period of 12 weeks.