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Introduction

IN the past several years, new and truly exciting developments have emerged in several areas of cannabis and cannabinoid research. These include substantial strides in our understanding of pharmacological, biochemical, and behavioral mechanisms of action for the cannabinoid compounds and of the smoked material. Accordingly, an international conference on cannabis and cannabinoids was held in July, 1990, in Kolymbari, Crete to address the newest research in the area. The organizing committee of the conference (Paul Consroe, Tucson, AZ; Alex Makriyannis, Storrs, CT; and Richard Musty, Burlington, VT) thought it was important to publish, in a single peer-reviewed volume, the proceedings of the conference which would provide the scientific community with a sample of the accomplishments and directions in the various areas. Matthew J. Wayner, Editor-in-Chief of *Pharmacology, Biochemistry and Behavior*, was enthusiastic in the development of the present issue.

This issue is dedicated to Professor Raphael Mechoulam (Jerusalem), who has contributed to our understanding of cannabis (marijuana; hashish) for over 25 years. His accomplishments began with the discovery of the structure and function of (−)-trans-delta-9-tetrahydrocannabinol (THC, the major psychoactive principle of cannabis) in 1964 and many other cannabinoids since that time. These discoveries, along with the development of many cannabinoid analogs, have contributed greatly to our understanding of the complexity and wide variety of actions found among the natural cannabinoids and their synthetic analogs.

Professor Mechoulam delivered the Keynote Address at our conference and his paper begins these proceedings. The first part of his paper is a scholarly and speculative analysis of political and historical aspects of cannabis. The second part is a presentation of data concerning a highly psychoactive THC analog (HU-210) which recently has become an important compound in the study of the cannabinoid receptor. Mechoulam speculates, with due modesty, that we may be on the verge of discovering a receptor or series of receptors which are involved in mood and emotional states. He also introduces a discussion of the (+)-isomer of the analog (HU-211) which lacks psychoactivity at several thousand times the dose of HU-210, but has highly potent antiemetic, antiseizure, and antitremor qualities. This novel compound is also a putative antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is believed to be involved in several neurodegenerative disorders. Taken together, this gives the research community a new tool to investigate potential clinical applications of cannabinoids.

The papers which follow that of Professor Mechoulam are new studies which further attempt to dissociate the multiplicity of cannabinoid and noncannabinoid effects through various syntheses and/or structure activity analyses.

CANNABINOID CHEMISTRY

Yamamoto and his colleagues studied two noncannabinoid compounds from marijuana, which are amides, the first being p-coumaroyl-tyramine and the second, a new amide, feruloyl-tyramine. The first compound appears to have cataleptic, hypothermic, and hypoactivity-inducing properties, while the latter appears to have only hypothermic properties. These data reinforce and expand the fact that consuming marijuana is quite different from the ingestion of pure THC. Further research on the pharmacological effect of noncannabinoid compounds is necessary if we are to understand the total effects of marijuana.

Martin and colleagues report that dimethylheptyl analogs of (−)-delta-8- and delta-9-THC were very potent in several animal tests. While the THC analogs were found to be potent, a surprising discovery was that a number of novel, noncannabinoid, aminoalkylindole compounds were found to have pharmacological profiles similar to (−)-delta-9-THC. The aminoalkylindole compounds are also potent analgesics in animal tests, and this might be due to their ability to act on the cannabinoid receptor. These data suggest that the cannabinoid receptor appears to respond to a diversity of compounds. This "structural diversity," according to Martin et al., provides the "opportunity to develop a pharmacophore for the cannabinoids using molecular modeling techniques."

Reggio et al. synthesized two new hydrohexahydrocannabinols using computer modeling and prediction methods. These new compounds were predicted to have analgesic effects, but minimal activity was found. These data provide further information on the structure-activity relationships of cannabinoids with receptors. The authors conclude that protrusion of portions of the carbocyclic ring into the alpha face is associated with reduced analgesic properties.

Baek et al. present data which demonstrate the synthesis of an optically active (−)-11-nor-delta-9-THC-9-carboxylic acid. Hui et al. report on isomers of two cannabinoid ketones. These papers represent the continued advances in our understanding of cannabinoid chemistry.

PHARMACOKINETICS OF CANNABINOIDS

Bioavailability of the cannabinoids is an important area of research which directly relates to the practicalities involved in the administration of cannabinoids for potential therapeutic uses. Elsohly et al. have demonstrated that various cannabinoid "prodrugs" of (−)-delta-9-THC have excellent bioavailability in suppository form. Since THC is now only available in oral capsule form for antinausea and antiemetic use in cancer chemotherapy, it is clear that this line of investigation is important for this purpose, and for the future development of cannabinoids for other therapeutic applications.

Charalambous et al. studied the biodistribution of a fluorinated delta-8-THC analog in baboon brain and mouse organs using Positron emission tomography. They report rapid uptake and fast clearance of this compound from all tissues. Interestingly, their findings of similar uptake in basal ganglia, thalamus, and cerebellum in baboon brain would not have been predicted from the previous histological autoradiography studies of Herkenham et al. This may suggest that subtypes of the cannabinoid receptor exist. In a second paper, Charalambous et al. describe the synthesis, activity, and cannabinoid receptor binding of halogenated analogs of (−)-delta-8-THC and report on one analog, (−)-9-I-8-THC which shows considerable separation between analgesic and psychotropic properties.

Husain and Ahmed demonstrated a decrease in glutathione levels in liver and kidney of mice following THC administration. No effects were observed in brain, testis, heart, or plasma. They suggest potential dispositional and metabolic interactions between THC and commonly available drugs, such as acetaminophen, could occur at this level.

Consroe, Kennedy and Schram report on the blood levels of cannabidiol (CBD) in patients with Huntington's Disease. Pharmacokinetics of CBD are reported, and the bioavailability and other kinetic aspects are discussed in relation to both CBD and (−)-delta-9-THC.

In a later paper, Consroe and his colleagues illustrate the possible importance of bioavailability in the discrepancy between clinical and preclinical findings. In virtually every previous animal study, CBD given most often by parenteral administration, has been shown to have antiseizure effects and antidystonic effects. Yet in these human studies using oral CBD administration reported by Consroe, these effects were not found. This raises the possible importance of bioavailability to the ultimate pharmacological effects of cannabinoids, and suggests further detailed research in this area.

CANNABINOID METABOLISM

In a group of three papers, Harvey and colleagues and Yamamoto and colleagues examine aspects of cannabinoid metabolism. The authors present beautifully documented comparisons of cannabinoid metabolism in seven species, and Harvey presents data on the oxidative metabolism of the cannabinoid side chain in the dog, rat, and human. These papers point out the similarities and differences among species. Given the wide variation in cannabinoid metabolism among species, it would seem critical to begin studies of individual differences in cannabinoid metabolism in genetically defined strains of animals, and in genetically different subgroups of humans. Such data may reveal striking differences which might lead us to an understanding of the basis of the differential effects of marijuana among individuals.

MECHANISMS OF ACTION AND PUTATIVE RECEPTORS OF CANNABINOIDS

Papers by Makriyannis and colleagues, Howlett and colleagues, and Burstein and colleagues, all examine aspects of the molecular biology and biochemistry of cannabinoid action. At each of several levels, these researchers theorize and present data which reveal aspects of the mechanisms underlying the cannabinoid receptor. In two papers, Makriyannis and his colleagues have presented the clearest data so far which demonstrate how cannabinoids enter into, orient within, and interact with putative receptor membranes in the lipid bilayer of synaptosomal tissue. Audette et al. tested THC actions on arachidonic acid release. They suggested that the THC receptor is coupled to phospholipases through one or more G-proteins. If confirmed, this would integrate for the first time, two of the currently most popular mechanisms of cannabinoid activity (prostaglandin alterations and cannabinoid receptor binding) into a single unified mechanism of action. Howlett et al. report that the cannabinoid desacetyl levonantrodol might lead to a degradation of cannabinoid receptors following relatively short exposure to the compound.

In an elegant paper, Gardner demonstrates that THC is not an anomalous drug as some had thought, but rather that it shares the enhancing action on electrical brain-stimulation reward and dopamine agonist-like actions in the brain reward systems. He hypothesizes that the THC receptor interacts with dopamine receptors to produce this effect.

Pertwee and his colleagues conducted studies to test the hypothesis that THC effects are mediated by GABA. GABA agonists and antagonists were administered with THC in tests of antinociception, pentylenetetrazole-induced convulsions, and hypothermia. In vitro experiments with guinea pig ileum were also conducted. The data clearly demonstrated that GABA mediation of THC effects did not occur in these tests.

Casteneda et al. measured concentrations of dopamine, DOPAC, homovanillic acid, and 5-HIAA following oral administration of THC using microdialysis. No changes in extracellular concentrations were found. Similarly, no behavioral differences were observed. These data seem to suggest little interaction of THC with these receptor systems, but other research does not support this conclusion. Further work needs to be done to further understand these potential interactions.

NEUROHORMONAL EFFECTS OF CANNABINOIDS

In a series of papers which examine relatively diverse neurohormonal topics, several findings reported here are of particular interest.

Rodriguez de Fonseca et al. reported that chronic exposure to a crude hashish extract from day five to 24 in rats leads to shifts in dopamine receptors and mechanisms, over time. The data seem to suggest that these changes occur in the corpus striatum but not in the hypothalamus or the forebrain. Wenger and colleagues report data in rats which suggest the hypothesis that a very low dose of THC, given chronically during prenatal development produces an attenuation or inhibition of the hypothalamo-pituitary-gonadal axis. Murphy and colleagues found that THC antagonizes the capacity of estrogen to augment pituitary growth in female rats treated from 23 to 26 days postnatally. They hypothesize that THC antagonized estrogen by direct action at the adenohypophyseal level. Finally Schuel, Chang, and their colleagues reported that THC, CBD, and cannabinol reduce the fertilizing capacity of the sea urchin sperm. It now seems relatively clear that neurohumoral effects of cannabinoids seem to have differential effects according to species, developmental period, and chronicity of administration. One obvious goal of these studies is to elucidate the mechanism(s) which may lead to the neurohumoral changes that have been reported. Further developments in this area may assist us in understanding the potential negative neuroendocrine consequences of cannabis or cannabinoid exposure in humans.

Additionally, Tahir et al. found that tublin and actin mRNA levels were reduced in hamster ovary cells following THC exposure in vitro. Cannabidiol and cannabinol had no effect. These data seem to suggest that THC could affect cytoskeletal proteins in this organ system.

Lastly, Husain and Anwar found that cocaine, when administered in combination with THC leads to a greater decrease in glucose metabolism in rat testis, than with THC alone. Cocaine alone seems to produce an increase in utilization of glucose. These data seem to suggest that multiple drug use patterns have complex interactions at this level of organ function.

RESPIRATORY EFFECTS OF CANNABINOIDS

Pulmonary effects of marijuana smoking have been studied for over 20 years. As time has passed, the research methodologies have improved dramatically. This has yielded new data which have begun to give us a picture of what happens to lung function during chronic marijuana smoking both in humans and in animals. In spite of these studies, much work is still required to understand the actual risks, and the mechanisms, of marijuana effects in the lung. Huber and his colleagues conducted a rigorous set of highly controlled experiments with marijuana in rats. Cytotoxic effects and mechanisms appear to be highly similar to tobacco.

Fligiel et al. identified small airway changes in periadolescent monkeys after one year of daily marijuana smoke inhalation. The authors argue that further studies are needed to evaluate the prognostic significance of these changes. Cabral and his col-

leagues investigated the effects of marijuana smoke exposure on macrophages in rhesus monkeys for one year. Comparisons were made with animals which were subjected to ethanol-extracted marijuana cigarettes and to those exposed to smoking conditions. Alveolar macrophages showed abnormalities as well as functional differences. The authors concluded that chronic THC exposure changes both the morphology and the function of macrophages for as long as seven months following one year of chronic smoke exposure.

In two papers, Tashkin et al. conducted exquisite smoking studies in humans. In the first study, they demonstrated that the longer the breath-holding time the greater the boost in carboxyhemoglobin and THC absorption. Puff volume did not seem to affect these outcomes. The second study examined delivery of THC, the amount of water-insoluble smoke particulates (tar), and carbon monoxide, delivered in the first half versus the second half of a marijuana cigarette. As might be expected, the second half of the smoked cigarette delivered more tar, carbon monoxide, and THC to the lungs of the smoker, suggesting that smoking marijuana cigarettes to butt length is potentially more harmful than smoking them to shorter lengths of the cigarette. Finally, Sherman et al. studied aveolar macrophages obtained by broncoaveloar lavage from nonsmokers, smokers of marijuana only, smokers of tobacco only, and smokers of both substances. He studied oxidant content, which has been implicated in the etiology of emphysema. He found higher levels of oxidants only in the tobacco and marijuana plus tobacco groups, which may help to explain the absence of small airway dysfunction in marijuana only users.

NEURAL AND BEHAVIORAL TOXICITY OF CANNABINOIDS

In a review of the neurotoxicity literature by Scallet et al., studies suggest that cell destruction in the hippocampus may occur, but in monkeys and rats, the numbers of studies showing positive results are approximately equal to the number of studies with negative results. The review suggests that many experimental issues remain unresolved.

Ali and his colleagues examined the effects of chronic marijuana smoke in the rhesus monkey on neurotransmitter levels in the brain. No differences were found. Acute and chronic in vivo studies in the rat did not lead to significant changes in neurotransmitter levels of any type. They conclude that no residual neurotransmitter effects of chronic THC exposure are found using these techniques.

Among the human research studies in this issue, there is a report by Solowij and colleagues who studied neuropsychological functions in a small number of chronic cannabis users. During abstention, attention and cortical event-related potentials (ERPs) were measured. Users reacted with normal reaction times, had poor discrimination performance on the attention task, had reduced P-300 amplitudes and early processing negativity in the ERP. In another study, Emrich and his colleagues reported an attenuation of binocular depth inversion in subjects who smoked cannabis resin. Perez-Reyes and colleagues found that chronic smoking of a marijuana cigarette for thirteen days per ingestion of a 1% THC cinnamon cookie did not lead to tolerance in pharmacologic responsivity, THC plasma concentrations, subjective ratings of the high, or heart rate acceleration. These data assist in determining the potential lower limit for tolerance. It is clear that tolerance requires longer ingestion than 13 days at this dose.

THERAPEUTIC EFFECTS OF CANNABINOIDS

Two groups reported on cannabinoid therapeutic studies. Plasse and his colleagues reported that Dronabinol (THC in capsule form) improved mood and appetite in patients with AIDS, and patients with cancer receiving chemotherapy. Consroe and his colleagues found that CBD had no beneficial or toxic effects in patients with Huntington's disease. The authors speculate that a very low bioavailability might be involved in the therapeutic failure.

Richard E. Musty
Paul Consroe
Alex Makriyannis
Guest Editors