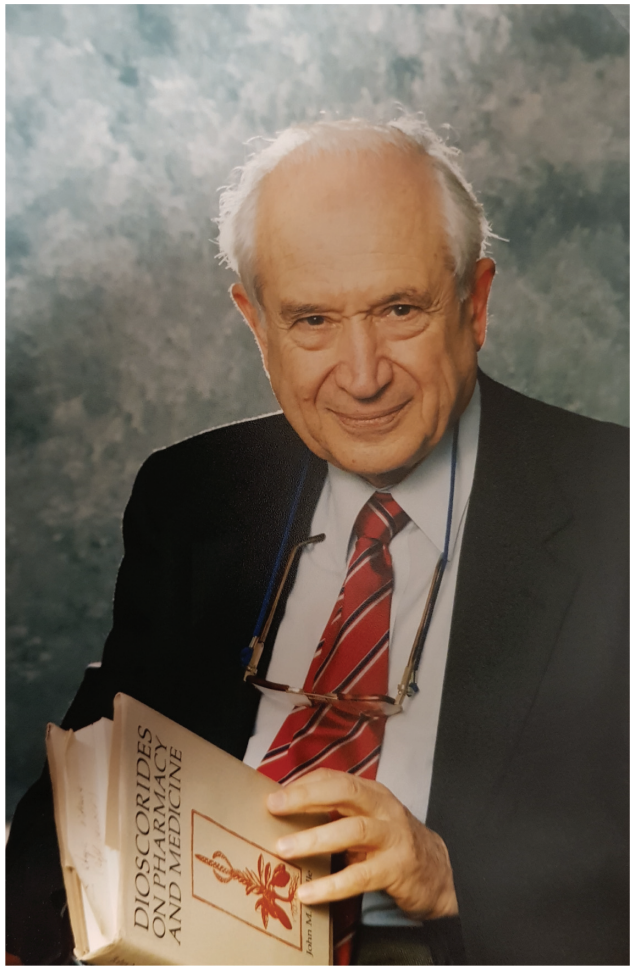

Raphael Mechoulam

ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

A Delightful Trip Along the Pathway of Cannabinoid and Endocannabinoid Chemistry and Pharmacology

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Keywords

anandamide, 2-AG, tetrahydrocannabinol, cannabidiol, endocannabinoid-like compounds, autobiography

Abstract

After a traumatic childhood in Europe during the Second World War, I found that scientific research in Israel was a pleasure beyond my expectations. Over the last 65 year, I have worked on the chemistry and pharmacology of natural products. During the last few decades, most of my research has been on plant cannabinoids, the endogenous cannabinoids arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol, and endogenous anandamide-like compounds, all of which are involved in a wide spectrum of physiological reactions. Two plant cannabinoids, Δ^9-tetrahydrocannabinol and cannabidiol, are approved drugs. However, the endogenous cannabinoids and the anandamide-like constituents have not yet been well investigated in humans. For me, intellectual freedom—the ability to do research based on my own scientific interests—has been the most satisfying part of my working life. Looking back over the 91 years of my long life, I conclude that I have been lucky, very lucky, both personally and scientifically.

CHILDHOOD

I was born in Sofia, Bulgaria, in 1930. My father, who had studied in Vienna, Austria, was a prominent physician and head of a hospital in Sofia. My mother had studied in Berlin, Germany. For them, a broad education, in many languages, was regarded as the obvious pathway for their children. For several years I went to an American grade school in Sofia. For me, Mrs. Woodruff, the principal, was then, and still is, the best of America. Her message, which I well recall, was "help the less fortunate and struggle against the villains in the world." In 1941, with the Second World War going on, the pro-German government closed the American School and later even declared war on the United States. It passed severe anti-Semitic laws and made the day-to-day life of Jews extremely difficult. My parents believed that our family would be safer in small villages in the Balkans that badly needed physicians. We spent most of the war years in these poor villages, where little had changed over decades. I recall my daily trips to the common village pump to bring home pails of water for our needs. And I read the few available books by sitting close to a candle in the evenings. Although my father was the only physician in the village and its nearby area, he was taken to a concentration camp in 1944, but survived.

In the autumn of 1942, the Bulgarian government planned to send the Bulgarian Jews, about 50,000, to the death camps in Poland, as it had done with the Jews in the territories it had occupied from former Yugoslavia. And then a miracle happened. The supposedly unbeatable German Field Marshal Erwin Rommel lost the battle at El-Alamein in Egypt and started withdrawing. Within a few months, the Germans lost North Africa and were defeated at Stalingrad (now Volgograd). The Bulgarian King Boris—a dictator—apparently realized that the Germans might lose the war and that sending the Jews to the death camps would not help him retain royal power after the war. He cancelled the expulsion. It was claimed that the strong opposition to the expulsion by the Bulgarian Church and by some politicians led to the change of mind by the King. Indeed, all the metropolitans of the Church and a parliament member had the courage to oppose the expulsion.

Many years later, I realized that the defeat of Rommel at El-Alamein—which saved us—was due to computer science. The British had built a highly secret computer, based on the advances made by Alan Turing, the early star cryptographer. This computer helped break the German military's Enigma code. British computer scientists were reading Rommel's battle plans and were also aware of the timing of shipments of supplies, in particular, spare parts for tanks being sent from Italy to Rommel's army. Accordingly, only 30% of shipments were getting through, and thus Rommel had no chance of winning the battle at El-Alamein. Science saved my life and the lives of many others. Years later, as Rector of the Hebrew University of Jerusalem, one of my first projects was to help establish a computer science department.

IN ISRAEL

In 1949 we immigrated to Israel. I studied at the Hebrew University of Jerusalem and graduated with a MSc degree in biochemistry. In 1953 I was conscripted and spent about two years doing research in an Army medical research unit. Most of my work was in chemistry, in collaboration with pharmacologists. We published several papers on insecticides (1, 2)—the first one was published 65 years ago. I found this type of work to be intellectually appealing. Indeed, much of my later work was in collaboration with biologists and clinicians. My PhD research (with Professor Franz Sondheimer at the Weizmann Institute in Rehovot, Israel) and postdoctoral work (with Professor William Pelletier at the Rockefeller Institute in New York) followed the same pathway: synthesis of novel molecules (3, 4) or extraction and identification of natural products and evaluation of their chemistry and, in collaboration with pharmacologists, their biological activity.

INDEPENDENT RESEARCH

In the early 1960s, I was appointed to an academic position at the Weizmann Institute and initiated independent research. A few years later, I moved to the Hebrew University of Jerusalem, where I continued my research for the next 55 years. My interest in natural products led me to read the literature on the chemistry and pharmacology of *Cannabis*. I was surprised to note that an active compound had apparently never been isolated in pure form and that its structure was only partially known. Even the structure of a major crystalline component, cannabidiol (CBD), which had been isolated more than two decades previously, was not fully elucidated. Their biological effects as pure or semipure compounds had barely been investigated.

How does one get *Cannabis*—a strictly regulated illicit drug—in sufficient amounts to initiate research? In 1963! Again, I was lucky. The administrative head of my Institute knew a police officer, who was presumably the number two (or possibly the number three) in the Israeli Police hierarchy. He phoned and told him that a Dr. Raphael Mechoulam needed hashish for research and that he—meaning me—was completely reliable (though he barely knew me). I just went to Police headquarters, had a cup of coffee with the policeman in charge of the storage of illicit drugs, and got 5 kg of confiscated hashish, presumably smuggled from Lebanon.

My colleague, Yehiel Gaoni, and I extracted the hashish and by repeated column chromatography were able to isolate about 10 compounds—most of them unknown—and elucidate their structures. All of them were either already crystalline or we were able to prepare crystalline derivatives. A few of these compounds were present both as acids and as neutral constituents. We assumed that the acids are the actual plant products, which upon decarboxylation lead to the neutral derivatives (5, 6). We thought that cannabigerolic acid (5) is the primary cannabinoid synthesized by the plant and that, by several mechanisms, is converted into the rest of the plant cannabinoids. Today, more than 100 cannabinoid molecules are known to be synthesized by *Cannabis*. However, the biological activities of only two constituents have been investigated in depth: CBD (7) and Δ^1-tetrahydrocannabinol (THC), the principal active constituent (8, 9) (**Figure 1**). Δ^1-THC was later renamed Δ^9-THC.

My first publication on cannabinoids described the elucidation of the structure of CBD (7). This constituent does not cause any of the typical *Cannabis* effects but has many therapeutic effects (mostly only determined in animal assays) on inflammation, anxiety, type 1 diabetes, autoimmune diseases (such as rheumatoid arthritis), neurological diseases, and so on (10). CBD binds to many receptors. As it is essentially nontoxic, CBD is widely used as a drug for numerous diseases but unfortunately, in most cases, without a sufficient published medical background. It is US Food and Drug Administration (FDA) approved for certain epileptic conditions in children (see below). CBD, or its derivatives (for examples, see 11, 12), will also probably be approved for other diseases when sufficient biological/therapeutic data become available. **Table 1** presents some of the disease states for which many patients use CBD or medical marijuana with high levels of CBD. **Figure 2** is a photo of the author trying to explain the stereochemistry of CBD.

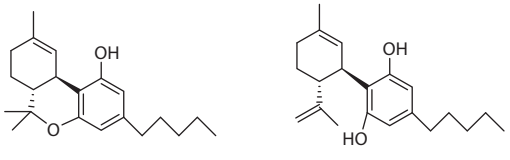


Figure 1

The structures of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

Table 1 A limited list of disease states that are positively affected by CBD

Disease	Reference(s)
Epilepsy	Cunha et al. (18), Devinsky et al. (19)
Inflammation	Pacher et al. (63)
Pain	Campos et al. (64)
Rheumatoid arthritis	Malfait et al. (65)
Depression	Kirkland et al. (66)
Schizophrenia	Kirkland et al. (66)
Obsessive-compulsive disorder	Kirkland et al. (66)
Anxiety and stress	Kirkland et al. (66)
Diabetes (type 1)	Weiss et al. (67)
Hypoxia/ischemia injury	Martínez-Orgado et al. (68)
Parkinson's disease	Giuliano et al. (69)
Huntington's disease	Cristino et al. (70)
Alzheimer's disease	Watt & Karl (71)
Airway obstruction	Dudášová et al. (72)
Cancer	O'Reilly et al. (73)

We isolated THC in pure form and elucidated its structure in 1964 (8). It is an approved drug for nausea and vomiting due to cancer therapy, but it is apparently a minor drug for this indication due to its side effects. Indeed, Nora Volkow (Director, National Institute on Drug Abuse) stated, regarding THC, that "It would be fantastic if we have a drug that would actually calm you when you need it, that makes you feel groovy, more social, and there are no negative consequences. But that's not the case. . .We're seeing an increase in the number of people that end up in emergency departments with acute psychosis from cannabis use, which may be due to the increased potency of cannabis products on the market today" (N. Volkow, personal communication).

In the 1960s and early 1970s, in collaboration with colleagues at a nearby biological institute, we tested the major plant cannabinoids for typical *Cannabis* activities in monkeys. Although all the cannabinoids assayed were rather closely related chemically, only THC was active (9). Hence,

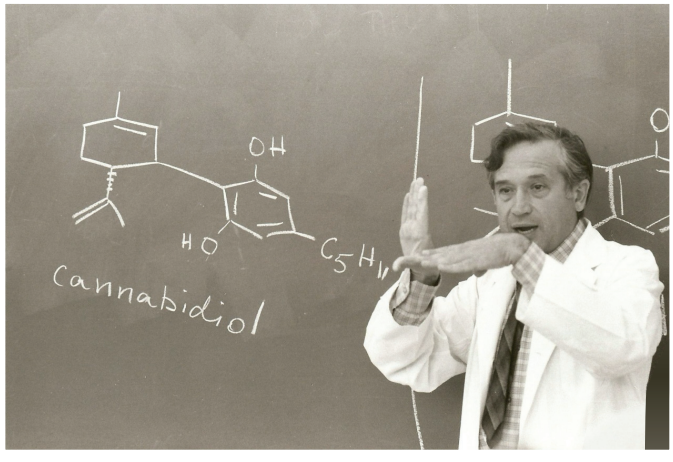


Figure 2

Raphael Mechoulam showing the stereochemistry of cannabidiol in 1970.

except for CBD and THC, very little research was published on the other cannabinoid constituents for a few decades. However, over the last few years, interest in them has increased. Pharmacological work in numerous areas has indicated that some of these constituents are active in a variety of assays (13). Thus, we found that cannabigerol (CBG) derivatives reduce inflammation, pain, and obesity (14) and cannabidiolic acid (as its methyl ester) suppresses nausea and anxiety (15), reduces depression-like effects (16), and is a potent antihyperalgesic molecule (17).

We were eager to find out whether the historical use of *Cannabis* for a variety of disease states, over thousands of years, was based on more than its antianxiety effects. We started with epilepsy. Together with colleagues in São Paulo, we tested THC and CBD for such activity in mice. Both were active. As CBD showed no toxicity or side effects, we undertook a small double-blind clinical trial on 18 patients with epilepsy, who were not helped by the existing drugs (18). Due to the high doses needed (200–300 mg per day), we had to obtain large amounts of hashish from the police and extract the CBD from it. The patients were treated for over 3 months, and the results were impressive. Some of the patients had almost no attacks, while others were significantly helped. The results were published in 1980 (18). As new antiepileptic drugs were badly needed, we assumed that these results would be expanded by pharmaceutical companies, but nothing happened for over 30 years. However, when parents of epileptic children—mostly in the United States—started treating their children with medical marijuana that had high levels of CBD, a British company initiated a large trial in the 2010s (19). On the basis of the positive results from this trial, a drug containing almost pure CBD (named Epidiolex) was approved by the FDA and is now widely used, particularly in children. Thousands of patients could have been helped over the four decades since our original publication. I believe that the stigma associated with *Cannabis* was the main reason for the delay.

During the late 1970s and 1980s, we and many groups throughout the world looked into various pharmacological aspects of THC, CBD, and novel, synthetic cannabinoids, including their metabolic pathways. A few clinical trials were also reported. However, the mechanism of THC activity remained obscure. As both enantiomers of THC were reported to be biologically active, it was generally assumed that THC acts through a nonspecific mechanism. However, when we addressed this problem again—with very potent (+) and (−) THC derivatives—we found that, actually, only the (−) enantiomer caused the well-known effects of marijuana (20). Hence, a specific activity mechanism was expected to exist.

In parallel to research on *Cannabis*, my interest in ancient drugs led me to investigate incense, the resin of the *Boswellia* plant, whose sacrificial burning has been a central ceremony in the religious and cultural life of many—probably most—ancient tribes and nations in the Middle East. In ancient Egypt, incense burning signified a manifestation of the presence of the gods and a tribute to them. The ancient Greeks burned incense as an offering to the gods. In ancient Judea, it was a central ceremony in the Temple. Wars were fought over incense in the ancient Middle East. Tiglath-Pileser III, who ruled Assyria in the eighth century BCE, attacked Gaza in order to control incense routes. Incense is still used today in religious ceremonies.

When we tested incensole acetate, a major constituent, in mice in standard assays, it lowered anxiety and caused antidepressive-like behavior. To investigate the action of incensole acetate on different brain regions, we studied its effect on c-Fos formation in mouse brains. We found that incensole acetate significantly changed c-Fos levels in brain areas known to be involved in the expression of emotions and in nerve circuits that are affected by antianxiety drugs (21, 22).

RESEARCH ON THE ENDOGENOUS CANNABINOID SYSTEM

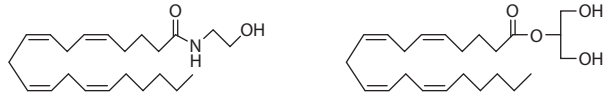
In the mid-1980s, Allyn Howlett reported the existence of a cannabinoid receptor, known today as CB1 (23). As receptors do not exist for compounds present only in a plant, we looked for the

endogenous molecules, which we thought would be present in the animal brain. As pigs are very close biochemically to humans, I presumed that pig brains would be the most promising source. Bill Devane, who had worked as a PhD student on the receptor in Howlett's lab and was now a postdoc in my group, and I would drive to Tel Aviv to buy such brains. We knew that immigrants from some of the Balkan states loved to eat cooked pig brain, and hence it was commercially available!

As THC is a lipid-soluble compound, we assumed that an endogenous agonist would also be a lipid and planned our research on this basis. First, we had to prepare a radiolabeled cannabinoid probe, as our route for the discovery of a CB1 agonist was based on the displacement of such a probe bound to the receptor (24). Then we looked at extracts of the pig brains, which were chromatographed for the separation of lipids. Promising fractions, namely those that displaced the probe, were further purified by low- and medium-pressure column chromatography and by thin layer chromatography. After about a year of column-after-column work, we were able to identify a brain constituent that inhibited the specific binding of the radiolabeled cannabinoid probe to the membranes in a manner typical of competitive ligands. It was then sent to Roger Pertwee in the United Kingdom, who found that this brain constituent produced a concentration-dependent inhibition of the electrically evoked twitch response of the mouse vas deferens, a characteristic effect of psychotropic cannabinoids. The isolated amounts of the agonist were minimal (0.6 mg from 4.5 kg of brain), but data from gas chromatography–mass spectroscopy and repeated nuclear magnetic resonance evaluations led us to propose a tentative structure—arachidonoyl ethanolamide (**Figure 3**)—which we found to be correct by undertaking a total synthesis (25). We named the brain constituent anandamide based on the Sanskrit word *ananda* meaning bliss—we believed that it had to do with emotions—and on the chemical nature (an amide) of the compound (25).

Anandamide and THC are structurally completely different. THC is a terpene-resorcinol derivative, while anandamide is a fatty acid amide with ethanolamine. And yet, we found that their biological activities were closely related (26, 27). A few years later, we isolated a second endogenous agonist, 2-arachidonoyl glycerol, best known as 2-AG (28) (**Figure 3**). Amounts of 2-AG in the body are considerably larger than those of anandamide.

These two endocannabinoids have been extensively investigated. Our original publications on these two compounds have been cited thousands of times. The main reason for this interest is that they represent the chemical basis of a new biochemical/physiological network: the endocannabinoid system. This system, as seen today, in addition to the two endocannabinoids, also covers the enzymes needed to synthesize and hydrolyze the endocannabinoids as well as two receptors: CB1 and CB2. The endocannabinoid system is of central importance in the animal body and represents an important modulatory network in the brain (29, 30). Indeed, Pacher & Kunos (31, p. 1918) have suggested that "modulating endocannabinoid system activity may have therapeutic potential in almost all diseases affecting humans" and have summarized published data on a large number of such diseases, citing publications on obesity/metabolic syndrome; diabetes and diabetic complications; neurodegeneration; inflammatory, gastrointestinal, and skin diseases; and pain and cancer, among many others.



Anandamide **2-AG**

Figure 3

The structures of anandamide and 2-arachidonoyl glycerol (2-AG).

However, although extensive data are available for the endocannabinoids, they have not been investigated in, or even administered to, humans—more than 25 years since they were reported! Are we missing something?

After the discovery of anandamide and 2-AG, we spent several years examining their effects. We undertook this research in close collaboration with pharmacologists who work on various assays in numerous countries. We found that inactive endogenous fatty acid glycerol esters enhance 2-AG cannabinoid activity and named this action an entourage effect (32). It differs from the better-known symbiotic effect, which addresses the interaction of two active compounds. In the popular press, entourage effects are also assumed to be relevant to the notion that extracts from the *Cannabis* plant are more active than THC, but there are very few publications on this topic.

In collaboration with colleagues and members of my laboratory, we examined the actions of anandamide and 2-AG on the hypothalamo-pituitary-adrenal axis (33), feeding and suckling (34), cognitive function and levels of neurotransmitters and corticosterone (35), the inhibition of the pharmacological effects of THC by low doses of anandamide (36), the reduction of sperm fertilizing capacity in sea urchins (37), myocardial resistance to arrhythmogenic effects of coronary occlusion (38), and a few other biological systems. We were then, and still are today, amazed at the huge number of effects of anandamide.

Together with E. Shohami, we initiated a project on the effects of endocannabinoids on brain trauma. We found that after brain trauma in mice, the level of 2-AG in the brain was significantly elevated. We thought that this was a protective reaction. We administered synthetic 2-AG to the mice after the injury. The treated mice compared to control mice had a significant reduction of brain edema, better recovery, and reduced inflammation, infarct volume, and hippocampal cell death (39). When 2-AG was administered together with inactive 2-acyl-glycerols that are normally present in the brain, functional recovery was significantly enhanced. The beneficial effect of 2-AG was dose-dependently attenuated by SR-141761A, an antagonist of the CB1 receptor. Moreover, improved recovery of neurobehavioral functions was noted in mice that received 2-AG up to 3 months after the brain trauma. Later, we found that 2-AG also protected the blood-brain barrier after closed head injury and inhibited messenger RNA expression of proinflammatory cytokines (40). As drugs to treat brain trauma are badly needed, these results may help in the development of such drugs.

Additional endocannabinoids have also been reported. We isolated linoleoyl ethanolamide and docosatetraenoyl ethanolamide, which are chemically and pharmacologically closely related to anandamide (41). In docosatetraenoyl ethanolamide, the fatty acid chain is two carbon atoms longer. In contrast to the many publications on anandamide, there are very few papers on these active endocannabinoids (42). Again, are we missing something?

ACTIONS OF ANANDAMIDE-LIKE COMPOUNDS

The biosynthetic pathway for the synthesis of anandamide involves a fatty acid and an amino acid derivative. As numerous fatty acids and amino acids are present in the animal body, a large number of anandamide-like compounds are biosynthesized (43) (**Figure 4**). Some of these compounds have been found to play major roles in animal biochemistry (for reviews, see 44, 45).

Vasodilation

We found that both anandamide and arachidonoyl serine (ArA-S) produce endothelium-dependent vasodilation of rat mesenteric arteries and abdominal aorta, with ArA-S being considerably more active (46). It stimulates phosphorylation of p44/42 mitogen-activated protein kinase

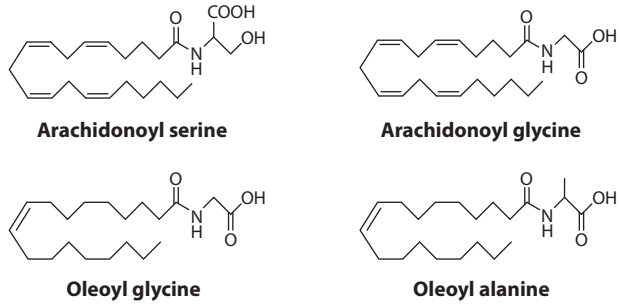


Figure 4

The structure of some representative endocannabinoid-like molecules.

and protein kinase B/Akt in cultured endothelial cells. ArA-S also suppresses lipopolysaccharide-induced formation of tumor necrosis factor-α in a murine macrophage cell line in wild-type mice, as well as in mice deficient in CB1 or CB2 receptors, indicating that it does not act through the endocannabinoid mechanism (46).

Bone Formation

In the early 2000s, my late colleague Itai Bab and I were looking at the biochemistry of bone formation. We were aware of a publication that indicated that Greeks had a lower incidence of osteoporosis than did citizens of northern European countries, which was attributed to their olive oil consumption—an oil with high levels of oleic acid (47). Nevertheless, we were quite surprised to find that oleoyl serine (OS), an endogenous *N*-acyl amide, was a bone constituent that modulated bone remodeling and mass (48). OS is the amide of oleic acid with the amino acid serine. We found that OS triggers a Gi protein–coupled receptor, mitigates osteoclast number by promoting osteoclast apoptosis through the inhibition of Erk1/2 phosphorylation and receptor activator of nuclear factor κB ligand (RANKL) expression in bone marrow stromal cells, and enhances osteoblast activity. In healthy mice it has minor activity, but in a model for osteoporosis, OS rescues bone loss by increasing bone formation and restraining bone resorption (48, 49). Thus, OS represents a novel lipid regulator of bone remodeling. May an OS-type drug be a future treatment for osteoporosis?

An Endogenous Antiaddiction Mechanism

Until recently, addiction was assumed to be mainly a psychological state. Now it is believed that it represents a central nervous system disorder. George Koob, an eminent researcher in the addiction field, and colleagues (50, p. 26) state in their book on addiction, "The view that drug addiction and alcoholism are the pathology that result from an allostatic mechanism that usurps the circuits established for established natural rewards provides an approach to identifying the neurobiological factors that produce the vulnerability to addiction and relapse."

Assuming that an animal's body recognizes addiction as an undesirable state, it was plausible to think that the body may try to establish ways to lower the effects of such a disorder. Indeed, some individuals do not get addicted using addictive drugs, while others become addicted. The reason for these differences is not known.

On the above basis we—a joint group from Canada (L. Parker and E. Rock), Italy (V. Di Marzo), United States (A. Lichtman), and my lab—looked for a natural antiaddiction defense mechanism. We started this research based on an observation made by Naqvi et al. (51), who

reported that cigarette smokers with traumatic brain injury, which included insula cortex damage, abruptly ceased their nicotine addiction. This observation, along with more recent data showing that the insula may control processes that moderate or inhibit addictive behavior (52), suggested the existence of a neurochemical, sensitive to brain injury, that might counteract nicotine reward and dependence.

After a long period of research we found that, after trauma, mouse insula produces another anandamide-type molecule [oleoyl glycine (OlGly)], which has powerful antinicotine addiction properties (53). OlGly is the amide of oleic acid with the amino acid glycine. OlGly in mice blocked the establishment of nicotine conditioned place preference (CPP), a test for addiction formation, and reduced withdrawal responses in nicotine-dependent mice. In morphine-dependent rats, OlGly reduced withdrawal responses but did not affect morphine CPP, demonstrating selectivity (54). We also found a tentative mechanism of the antinicotine addiction effect: OlGly activated peroxisome proliferator–activated receptor alpha (PPAR-α) in vitro, and a PPAR-α antagonist restored nicotine CPP in OlGly-treated mice (53).

We assumed that, as an amide, OlGly might be readily degraded by amidases in the body. Hence, we synthesized a derivative, oleoyl alanine (OlAla), in which the amide bond is somewhat protected (55). Indeed, we noted that OlAla, which turned out to also be an endogenous molecule, was a more stable and effective treatment for opiate withdrawal than was OlGly (55, 56). OlAla was effective in reducing opioid withdrawal responses in rats experiencing both acute and chronic opioid withdrawal. However, neither OlGly nor OlAla modifies tolerance to nociception and hyperthermia or suppression of activity produced by morphine (56).

On the basis of the above recent discoveries, we believe that administration of OlAla, or compounds with similar characteristics, may help prevent the nicotine addictive state and nicotine and opiate withdrawal.

ANTIMICROBIAL ACTION AGAINST METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Infections caused by antibiotic-resistant strains of *Staphylococcus aureus* are of major medical importance (57). Staphylococci form biofilms that are associated with increased antimicrobial resistance and are generally less affected by host immune factors. Therefore, there is an urgent need for novel agents that not only treat multidrug-resistant pathogens but also will act as antibiofilms. My colleague D. Steinberg and I investigated the antimicrobial activity of anandamide and the above-mentioned AraS against methicillin-resistant *S. aureus* (MRSA) strains (58). We observed that both agents strongly inhibited biofilm formation of all tested MRSA strains and reduced metabolic activity of preformed MRSA biofilms. Moreover, staphylococcal biofilm-associated virulence determinants such as hydrophobicity, cell aggregation, and spreading ability were altered by both anandamide and AraS. In addition, the agents modified bacterial membrane potential. Importantly, both compounds prevent biofilm formation by altering the surface of the cell without killing the bacteria (59). These and related compounds may act as a natural line of defense against MRSA or other antibiotic-resistant bacteria. The antibiofilm action of these agents, together with suitable antibiotics, may be a promising advance in antibiotic therapeutics against biofilm-associated MRSA infections.

CANCER

Omega-3 fatty acids such as docosahexaenoic acid and eicosapentaenoic acid are known to inhibit breast and prostate cancer cell growth. Brown et al. (60, 61) found that the ethanolamides of these acids, namely docosahexaenoyl ethanolamide and eicosapentaenoyl ethanolamide, displayed

greater antiproliferative potency than did their parent omega-3 fatty acids in certain prostate cancer cells. These amides activated cannabinoid CB1 and CB2 receptors in vitro with significant potency.

FINAL THOUGHTS

The endocannabinoid system is a latecomer to our knowledge in chemistry, pharmacology, and physiology. Its involvement in biological processes is enormously wide, but most of the endogenous anandamide-like compounds and 2-AG-like compounds have yet to be investigated for their activity.

We have speculated (29) that the large cluster of chemically related anandamide-type compounds in the brain (43) may be related to the chemistry of human personality and individual temperamental differences. It is tempting to propose that the enormous possible variability of the levels and ratios of substances in such a cluster of compounds may allow an infinite number of individual differences, the raw substance that, of course, is sculpted by experience. Indeed Redlich et al. (62) have recently shown that there is a significant association between anandamide, brain function during reward feedback, and a personality measure of reward dependence.

The structure-activity relationships of most anandamide-like and 2-AG-like compounds are unknown. Investigations in these areas seem to me to be highly promising.

I want to stress that in the endocannabinoid area, as well as in other areas, close collaboration between scientists working in medicinal chemistry and pharmacology is a wonderful and fruitful pathway to the discovery of novel biological traits. It has been a pleasure to work with my colleagues in Israel and abroad. I have learned a lot from them. And I hope to learn more.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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