Chapter 9

THE CARDIOVASCULAR ACTION OF CANNABINOIDS

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I. INTRODUCTION

Those effects of cannabis attributible to cardiovascular activity were first observed in man before the era of animal experimentation.[1] They were not readily explicable and of no obvious benefit. When biological experimentation became commonplace the effects of administering preparations of cannabis or cannabinoids by various routes was found to differ in many cases, as between laboratory animals and human subjects. These findings obscured rather than illuminated the understanding which must exist before the rational use of a drug in human therapy can be proposed. As a consequence of the chronic nature of the ailments which affect the cardiovascular system of man (infarct, myocardial degeneration, hypertensive disease), there is every opportunity for the development of drug resistance or undesirable side effects during prolonged therapy; cannabis is a drug which is prone to generate tolerance if it is repeatedly administered at close intervals of time. These considerations have limited the usefulness of cannabinoids in the field of cardiovascular therapy. Nevertheless, as Lemberger[2] said in a review of the potential therapeutic value of marijuana, "if cannabinoids lower blood pressure by a mechanism unrelated to those listed — and if analogues can be synthesized that produce minimal side effects, then cannabinoids may present us with a new and unique approach to the treatment of hypertension."

II. THE HEART: RATE AND FUNCTION

The pharmacology of cannabis, and in particular of Δ^9- (or Δ-tetrahydrocannabinol) (Δ^9-THC) on the cardiovascular system has been the subject of many research publications, partly as a consequence of the puzzling discrepancies between man and animal, which have been attributed among other things to the fact that experimental animals are usually anesthetized and human subjects conscious during the conduct of tests. There have been a considerable number of reviews of the topic.[3-8] In cats, dogs, rats, etc. the intravenous administration of Δ^9-THC causes bradycardia and hypotension. When the elements of this response are analyzed, it can be readily shown that Δ^9-THC may cause a slight depression of cardiac function, under certain conditions. A bolus of 0.1 to 0.5 μg reduces the rate and force of contraction of the perfused rat heart,[9,10] although most of the effect may be attributed to the solvent required to disperse this water-resistant drug. There may be an 8 to 11% decline in the developed tension and V_{max} measured directly in strips of cardiac muscle from cat and rat[11] exposed to a concentration of 20 mcg Δ^9-THC per milliliter biophase, but an otherwise negligible effect on contractile performance, its time course, or the elastic recoil of the muscle. This concentration is very much higher than the plasma level of cannabinoid found after smoking one standard cigarette of 5 mg content of Δ^9-THC content, and the effect noted may well be irrelevant to the human situation. The bradycardia is atropine sensitive and attributed to dominance of vagal tone. Unlike Δ^9-THC, CBD is a cardiac stimulant,[12] increasing force and coronary artery flow.

In contrast to these findings the usual response in conscious man to effective single doses of cannabis or of Δ^9-THC is a dose-related tachycardia (see Figure 1) which develops over 20 or so minutes and may last for an hour or two; there may be an initial slight rise in systemic pressure, and therefore an enhancement of sinus and nodal function, cardiac outflow, etc.[13,14] Tachycardia is reflected in the electrocardiographic record and there has been controversy as to whether or not this drug has a harmful effect on the heart muscle or on conduction of the impulse in man.[15,16] Smoking is unlikely to give rise to anything more than an occasional palpitation in healthy young persons. The effect may be due to carbon monoxide in the combustion products, usually reported as being from 0.5 to 2.0% by volume of gas in the smoke, rather than to the

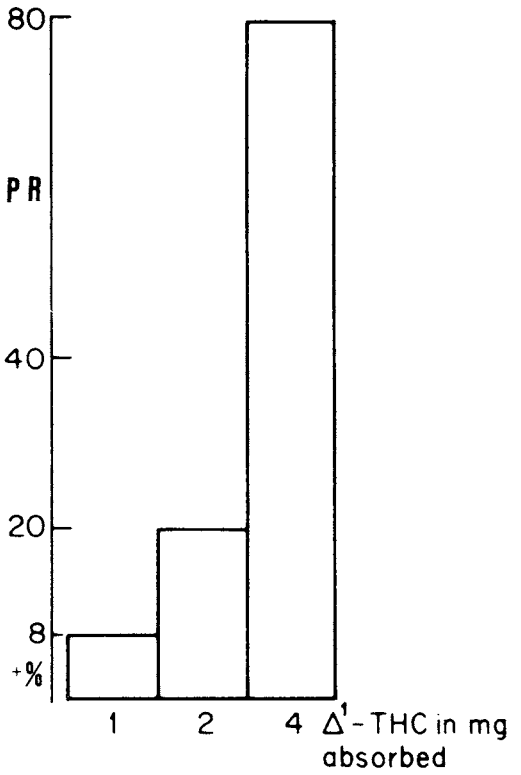

FIGURE 1. The effect on the resting pulse rate of experienced male subjects, related to the estimated dose of Δ⁹-THC absorbed; tachycardia is expressed as percentage increase above initial level, recorded 15 to 30 min after smoking; derived from many published reports. (From Graham, J. D. P., Ed., *Cannabis and Health*, Academic Press, London, 1976, 164. With permission.)

cannabinoid directly. As with tobacco smoking there is no therapeutic value in it and probable harmful effects on persons suffering from anginal pain after exercise or other cardiac illness.[17-19] It reduces exercise tolerance during effort[20], and may compound the risks from sympathomimetic amines included in mixtures for local analgesia. The rise and subsequent decline of the increased resting pulse rate parallels the onset and decline of the psychic changes ("high"). There has been a difference of opinion as to whether these two phenomena can be disassociated, but it has become clear that a combination of atropine (parasympathetic blockade) and a beta-adrenoceptor blocker (cardiac sympathetic blockade) will prevent the pulse increment but not the cognitive and psychomotor impairment,[21,22] and that tachycardia occurs despite loss of general consciousness in anesthetized patients.

III. THE VASOMOTOR SYSTEM AND BLOOD PRESSURE

In anesthetized animals (cat, dog, rat, etc.) intravenous injection of cannabis or of Δ⁹-THC causes a fall in blood pressure which may persist for an hour or two (see Figure 2). Pharmacological analysis shows that this effect is the result of a loss of vascular tone, of reflex activity, and of cardiac output. In cats in which the peripheral resistance was measured in the arterial tree of autoperfused hind limbs, injection of Δ⁹-THC causes a fall in systemic blood pressure and a reduction in vascular resistance.[23] These effects have been shown to be preceeded by a reduction of "traffic" in the sympathetic

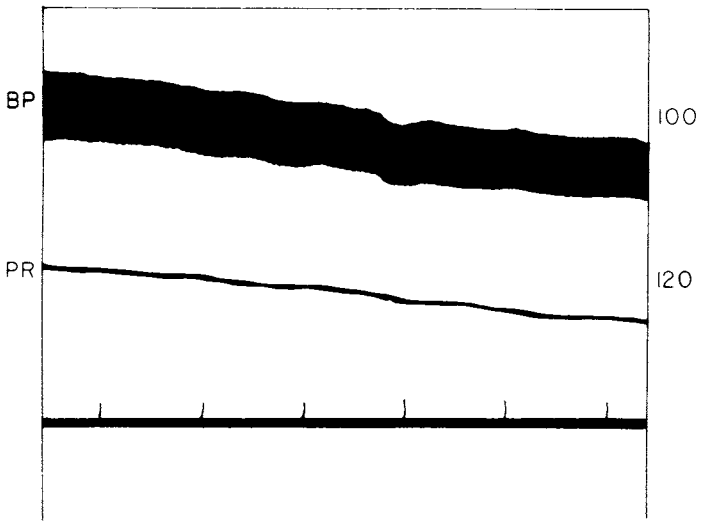

FIGURE 2. In the anaesthetized animal, as in the human repeatedly exposed over time, a dose of Δ^9-THC lowers blood pressure (BP), and slows the heart rate (PR). (From Graham, J. D. P., Ed., *Cannabis and Health*, Academic Press, London, 1976, 188. With permission.)

nervous outflow from the brainstem in anesthetized animals,[24] and in the rat made hypertensive by stress or surgical intervention, large doses of Δ^9-THC injected parenterally consistently lower the systemic blood pressure.[25-27]

In man the single acute dose usually has little or no effect on the blood pressure; it may cause a slight rise (supine). Due to the attenuation of the cardiovascular reflex responses to change of posture or to stress, orthostatic hypotension occurs in a minority of smokers, and may be severe enough to initiate dizziness if the smoker rises suddenly from a recumbent posture. An increase in blood flow in the limbs after smoking marijuana or injection of Δ^9-THC has been demonstrated by plethysmography in volunteers,[28,29] and there is evidence for a considerable loss of venous tone which may be an important factor in the response.[30,31] The loss of peripheral arterial tone, presumed to be a consequence of sympathetic inhibition, may come first and the tachycardia be a consequential baroreceptor reflex, or at least that is one suggestion. No experiments in which the arterial circulatory pressure is sustained artificially while the heart rate is monitored have been reported. The well-known but rather puzzling phenomenon of the "red eye" is due to a dilatation of the vessels in the conjunctiva, but just why it is so marked a phenomenon there is not clear. When the human subject is supine, as are experimental animals, there is either no change or a slight rise in pressure after the single dose.[32] It has been known for some time that cannabis may exert a beneficial effect in cases of glaucoma and the opportunity has been taken to relate changes in heart rate, systemic blood pressure, and intraocular pressure (IOP) in patients who have open-angle glaucoma and normal or high blood pressure.[33-35] The sequence of events which follows within a few minutes of inhalation has been described as first, venous dilatation, then a fall in diastolic pressure, reflex tachycardia, and a subsequent change in IOP. In all patients the blood pressure was lowered, more so in hypertensive subjects than in normotensives.

IV. CANNABINOIDS OTHER THAN Δ^9-THC AND SYNTHETIC ANALOGS

The number and variety of cannabinoids now recognized has greatly increased of

recent years, but cannabinol (CBN), which is probably an artifact, and cannabidiol (CBD), cannabigerol (CBG), and cannabichromene (CBC), probably natural, are the ones about which most is known. CBD and CBN have a high affinity for hepatic oxidative enzyme, being rated as Type 1 binders to microsomes. They are not psychoactive but by drug interaction processes modify the distribution and degradation of Δ^9-THC and thus its effects. One trial of a mixture has been reported[36] in which 40 healthy volunteers took 30 mg Δ^9-THC orally or 15 to 60 mg CBD and mixtures thereof. The effects of the THC on psyche and on tachycardia were diminished. CBC has been shown to exert a hypotensive action by itself in anesthetized rats[37] in the high dosage of 10 mg/kg i.v.; this effect is additive to that of Δ^9-THC but there was no evidence of other drug interaction. The natural cannabinoids other than Δ^9-THC are thus of little interest in terms of likely therapeutic value in the cardiovascular field, but abnormal cannabinoids hold out some hope; e.g., CBD in which the phenolic hydroxyl has been transposed with the pentyl side chain is powerfully hypotensive in dogs without producing any obvious behavioral effects.[38] The possibility of producing a useful antihypertensive agent from the cannabinol structure thus lies with the synthetic analogs. Hollister et al.[39] demonstrated more than a decade ago that the *n*-hexyl analog known as synhexyl or pyrahexyl (see Appendix I) exerted a similar effect to Δ^9-THC. In their trial 16 volunteers ingested Δ^9-THC and 13 the analog. Both drugs increased the resting pulse rate without causing any abnormality in the ECG record; Δ^9-THC reduced diastolic pressure and synhexyl additionally reduced systolic pressure, but this effect manifested more obviously as orthostatic hypotension than a decline in supine pressure. More active in every respect is the dimethylheptyl analog (see Appendix I) known as DMHP.[40,41] This compound produces a decline in basic blood pressure as well as postural hypotension in man in a dose of less than 3 μg/kg i.v. These early findings initiated the search for a hypotensive analog of cannabinoid which would be devoid of psychic activity and of loss of efficacy on repetitious dosing, and might escape the bugbear of orthostatic action. Nabilone, the first widely examined compound of the subsequent development[42] is not successful in cats in this respect and has an acute orthostatic effect in man.[43] In man 1 mg is inactive orally, 2.5 mg produced minimal effects,[44] and 5 mg causes orthostatic dizziness and some tachycardia without lowering the supine diastolic pressure.[45] Exploratory work has continued actively. Another class of analog which shows activity is a group of azacannabinoids with various substituents on the N atom.[46] Clinical trials on these and similar compounds have not yet been reported.

V. LONG-TERM USAGE

Repeated dosing of rhesus monkey with 0.5 mg/kg Δ^9-THC i.v. 6 hourly for 3 weeks induced initially a marked tachycardia and hypotension, occasionally interrupted by a brief and slight rise in pressure. The cardiac response lessened or disappeared as time passed, but not the hypotension.[47] Benowitz and Jones[48] had earlier illustrated this inversion after prolonged usage in hospitalized volunteers, with tachycardia changing to bradycardia (abolished by atropine) and unchanged or raised blood pressure to hypotension, accompanied by impairment of postural pressure reflexes and a marked increase in plasma volume. The lowering of supine blood pressure remained unaffected. Similar changes have been noted since that time;[49,50] e.g., 97 heavy and regular smokers of marijuana, with a minimal duration of 5 years of usage, still experienced the desired psychointoxication after smoking but had largely lost the tachycardia and dryness of the mouth which they initially encountered.[51] These adaptations to autonomic imbalance are not consistent. Forty-eight experienced smokers were given low and high doses of marijuana, a herbal, or a placebo smoke.[52] In this case, tachycardia was retained but pressure changes were lost with the passage of time.

VI. MECHANISM OF ACTION

The cardiovascular system works under the influence of a tightly balanced control by the autonomic nerves, which varies somewhat from one species to another, and is affected by a considerable number of drugs including not merely the obvious blockers but the centrally acting drugs, anesthetics, etc. It has been shown beyond doubt that ingestion of cannabis or Δ^9-THC induces tachycardia in conscious man which is diminished or abolished by the beta-adrenoceptor blocker propranolol,[6] or attenuated by the development of tolerance. This cardiostimulant effect must be the result of increased sympathetic outflow in the accelerans nerves in the absence of evidence of a discharge of adrenal catecholamine into the blood stream. According to one report, it involves alpha-adrenoceptors located in the neighborhood of the cerebral ventricle.[53] Δ^9-THC has little direct effect upon the heart nor does it block peripheral autonomic receptors of either sort, although it can to a moderate extent deplete the sympathetic nerve terminals of their quota of neurotransmitter. The effect of Δ^9-THC on transmission in the vagal nerves is very slight. Nevertheless the balance of vagal and sympathetic control of the heart rate is upset; in man sympathetic activity dominates initially and then fades, but in animals it is the vagus which dominates at all times. Barbiturate anesthesia in man does not abolish the THC-induced tachycardia,[54] but repeated dosing does so, and conscious man and anesthetized animal then react in a more nearly similar fashion.[55,56] Sympathetic efferent flow to the vascular bed is modulated, partly by the suppression of inhibitory mechanisms and alteration of vascular reflexes. Hence the orthostatic hypotension, but not necessarily or wholly the persisting decline in supine blood pressure, which at best is a modest reduction in vascular tone. It is this latter part of the overall response which needs must be enhanced in the absence of tachycardia if a clinically useful antihypertensive drug is to emerge. Aspirin reduces or abolishes Δ^9-THC-induced hypotension,[57] which directs attention away from central action on the autonomic (which may be the dominant mechanism for control of the heart rate) to the possibility of examining lipid-soluble drugs, cannabinoid or other, which affect the prostaglandin cycle in smooth muscle. Unitary explanations of mechanisms of action are logically preferable to disconnected multiple causes; herein may lie the key to progress in cannabinoid therapy for hypertension.

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