Neuropharmacology, Vol. 19, pp. 567 to 573
Pergamon Press Ltd 1980. Printed in Great Britain

HYPOTHERMIC EFFECTS OF INTRAVENTRICULAR AND INTRAVENOUS ADMINISTRATION OF CANNABINOIDS IN INTACT AND BRAINSTEM TRANSECTED CATS

W. T. SCHMELING and M. J. HOSKO
Medical College of Wisconsin, Department of Pharmacology, Box 26509, Milwaukee, WI 53226, U.S.A.

(*Accepted* 25 *November* 1979)

Summary—Δ^9-Tetrahydrocannabinol (Δ^9-THC, 500 μg in 40 μl), and the synthetic cannabinoid Dimethylheptylpuran (DMHP, 75 μg in 6.0 μl) were injected into ventricles III or IV of chronically implanted unanesthetized cats to determine the effect on body temperature. The hypothermia induced by administration of Δ^9-THC into ventricle IV was faster in onset and reached a greater maximum than that induced by ventricle III administration. Five hundred μg (i.v.) of Δ^9-THC produced significantly less hypothermia than interventricular microinjection.

Administration of Δ^9-THC (2 mg/kg i.v.) to animals with a midcollicular transection produced significant decreases in blood pressure, heart rate, and body temperature when compared to animals receiving vehicle alone. Cats transected at C-1 were utilized to determine the rate at which body temperature was lost in animals unable to temperature regulate. Δ^9-Tetrahydrocannabinol had no effect in these preparations indicating that direct peripheral mechanisms have little or no role in Δ^9-THC induced hypothermia. It was further noted that Δ^9-THC had little effect on blood pressure or heart rate in C-1 transected animals. These findings suggest a caudal brain stem site of action for the hypothermic effect of the cannabinoids.

Tetrahydrocannabinols, the primary psychoactive components of marihuana, have a number of potent pharmacological actions, including the ability to lower body temperature in laboratory animals (Abel, 1972; Borgen, Lott and Davis, 1973; Haavik and Hardman, 1973a; 1973b; Schmeling and Hosko, 1976). Acute, lateral intraventricular injections of various cannabinoids have been shown to induce significant hypothermia in several species (Gill, Paton and Pertwee, 1970; Garattini, 1965). Hypothalamic, spinal and brainstem thermoregulatory areas have been implicated in the mediation of Δ^9-THC-induced hypothermia (Schmeling and Hosko, 1976; 1977). It has been established that the cardiovascular response to cannabinoid administration is severely compromised by high spinal section at the level of the first cervical vertebrae (C-1) but not by transection at midcollicular (MC) levels (Hardman, Domino and Seevers, 1957; 1971a,b; Hosko and Hardman, 1971; 1976; Dagirmanjian and Boyd, 1962; Vollmer, Cavero, Ertel, Solomon and Buckley, 1974). Transections of the neuraxis at C-1 and midcollicular levels differentially spare neuronal pools (Amini-Sereshki, 1975; Chambers, Siegel, Liu and Liu, 1974). Since neuronal sensor and effector pools subserving thermoregulation exist at spinal (Thauer, 1970; Simon, 1974), and at superspinal sites in hypothalamus (Hammel, 1968; Hensel, 1973), mesencephalon (Nakayama and Hardy, 1969; Cronin and Baker, 1977a,b), and rhombencephalon (Chai and Lin, 1972; Lipton, 1973; Lee and Chai, 1976), it was decided to utilize differential transections of the neuraxis as well as "local" application of selected cannabinoids to investigate the role of various central neuronal pools as possible sites for the mediation of tetrahydrocannabinol-induced hypothermia.

Send reprint requests to: Michael J. Hosko, Department of Pharmacology, Medical College of Wisconsin, P.O. Box 26509, Milwaukee, WI 53226, U.S.A.

Key words: cannabinoids; hypothermia; intraventricular administration; brainstem transection; site of action.

METHODS

Ventricle III microinjection

Seven female and two male cats (2.3–3.5 kg) were chronically implanted for ventricle III microinjection. Implantation techniques were similar to those in general use. Under Na-pentobarbital anesthesia, (32–35 mg/kg), the skull was burred open at stereotaxic coordinates: Fr + 13.0, L = 0.0 (atlas of Jasper and Ajmone-Marsan, 1954). Care was taken to maintain the integrity of the superior sagittal sinus. A twenty gauge stainless-steel guide tube with a screw cap obdurator was stereotaxically lowered on one side of the falx cerebri to D = −2.0. The obdurator was removed and positioning confirmed by visualization of cerebrospinal fluid flow. The guide tube was fixed to the skull with 0–80 ss screws and dental epoxy. Skin and fascia were reapproximated and sutured.

All animals used for ventricle III and ventricle IV microinjections had temperature sensitive telemetry devices implanted in the peritoneal cavity. The tele-

metry units were modified from those described by McKay (1970).

Experiments were initiated no earlier than 10 days after surgery. After recovery, animals received sterile microinjections of Δ^9-tetrahydrocannabinol (Δ^9-THC), the synthetic tetrahydrocannabinol dimethyl-heptylpuran (DMHP) and cannabinoid vehicle in a Latin square design with drug administrations at least one week apart. Preparation of microinjection solutions will be presented elsewhere (Hosko and Schmeling, unpublished).

Animals were held in environmentally controlled quarters. Experiments were performed in a temperature and humidity regulated chamber. Ambient temperature was 24 ± 0.5°C. Relative humidity was $50 \pm 10\%$. Prior to microinjection, deep core temperature and behavior were recorded for at least 2 hr to establish a baseline.

Upon completion of the experimental sequence, each animal was sacrificed with an overdose of pentobarbital, the brain removed, and injection sites verified by block sectioning.

Intracisternal microinjection

Five female and two male cats (2.3–3.2 kg) were utilized for intracisternal microinjections. Three of these animals also had chronic ventricle III implants. The animals were lightly anesthetized with halothane. A sterilized 20 gauge spinal needle was inserted into the cisterna magna through the atlanto-occipital membrane. Placement was confirmed by clear cerebrospinal fluid flow. A 26 gauge needle, the same length as the spinal needle, was inserted through the guide needle for intracisternal microinjection of cannabinoids.

After the microinjection sequence had been completed in each animal, an equivalent dose of cannabinoid was administered intravenously to determine the effect of systemic administration.

Neuraxis transections

Fifteen female and five male cats (2.3–5.0 kg) were used in this series. Under halothane, the trachea, femoral artery, and cephalic vein were cannulated. The carotids were bilaterally ligated. A temperature probe was inserted 10 cm into the rectum.

Midcollicular transection was performed in 10 animals by means of suction, and the forebrain was destroyed by coagulation. Anesthesia was discontinued.

Transection of the neuraxis at the first cervical segment was performed in ten other cats. After exposing the atlas and axis by blunt dissection, the dorsal arch of the atlas was removed with rongeurs, and cord was severed at the level of C-1. A needle was passed axially along the rostral reticular formation and coagulating current was applied to destroy the brainstem. Anesthesia was discontinued. Both midcollicular and C-1 animals were mechanically respired.

Arterial blood pressure, rectal temperature, and heart rate were recorded. All animals were allowed to stabilize for 60 min. At this time each animal received an injection of vehicle equivalent to 2 mg/kg (i.v.) of Δ^9-THC. Sixty minutes later, 5 of the 10 MC transected animals (Group I) and 5 of the 10 C-1 transected animals (Group III) received 2 mg/kg (i.v.) doses of Δ^9-THC. The remaining MC animals (Group II) and C-1 animals (Group IV), received a second 2 mg/kg injection of vehicle intravenously to provide a "control in time." Two hours later, Groups I and III received a 4 mg/kg dose of Δ^9-THC, while Groups II and IV received a dose of vehicle equivalent to 4 mg/kg Δ^9-THC. At the completion of each experiment transections were confirmed by dissection.

RESULTS

Ventricle III microinjection (chronic unanesthetized cats)

Microinjection of 100 μg Δ^9-THC (in 8.0 μl) into ventricle III elicited minimal hypothermic effects. Microinjections of 500 μg of Δ^9-THC (in 40.0 μl) produced a significant hypothermic response (Fig. 1). Onset of temperature depression was slow with little effect during the first hour post-injection. Peak hypothermia, 1.0–2.5°C., was reached 2–4 h after microinjection. Behavioral manifestations included bilateral nictitating membrane relaxation, mild ataxia and tremor, slight decrease in response to auditory or tactile stimuli, and some autonomic effects including defecation, urination, and emesis.

Ventricle III microinjection of DMHP, 150 μg (in 12.0 μl), was lethal to two cats. Deep core body temperature decreased 7.8–8.3°C within 24 hr and remained at these levels (31.5 and 31.0°C) until death occurred 5–6 days post-injection. The cats assumed a sprawled body position. They were indifferent to peripheral stimuli. Pupils were bilaterally dilated and the nictitating membranes were relaxed. In the first 24 hr autonomic effects (urination and defecation) were also observed.

Ventricle III microinjection of 75 μg (in 6.0 μl) of DMHP produced consistent hypothermic responses without fatalities (Table 1). Body temperature decreased over a 12 hr period, remained depressed for 24 hr, and approached normal 28 hr post injection. Behaviorally, the animals exhibited varying degrees of ataxia and tremor. Bilateral pupillary dilation and "plaintive" vocalization occurred in all cats.

Microinjection of vehicle into ventricle III produced no significant change in body temperature or behavior (Table 1).

Intracisternal microinjection (subacute unanesthetized cats)

Microinjection of Δ^9-THC (500 μg in 40.0 μl) into ventricle IV produced significant hypothermic responses (Fig. 1). Temperature decrease began within 15 min of administration and reached peak levels of 1.5–3.0°C within 1–2 hr. After injection, cats exhibited bilateral pupillary dilation and nictitating membrane

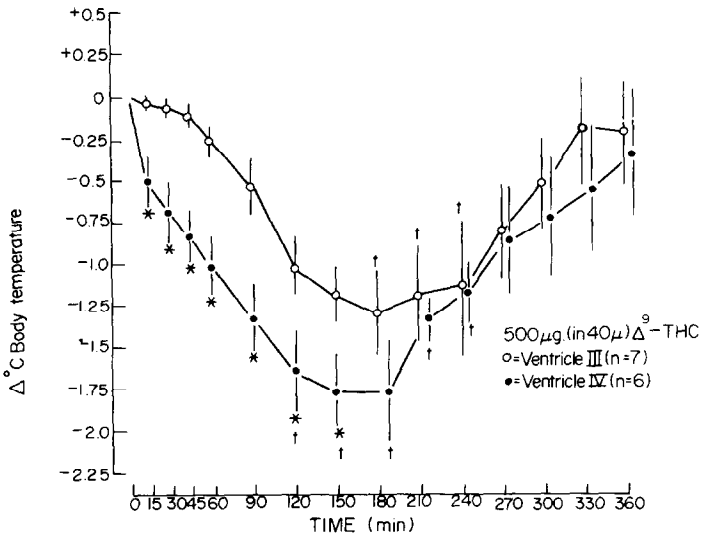

Fig. 1. Hypothermia induced by Δ^9-THC administration to ventricle III and IV in chronic unanesthetized cats. Vehicle produced no significant hypothermia. *Significantly different ($P < 0.01$) from ventricle III administration. $^+$Significantly different ($P < 0.05$) from equivalent dose administered intravenously.

relaxation. Vocalization and urination or defecation was also seen in 3 animals. Vehicle microinjections did not elicit changes in body temperature or behavior.

Figure 1 compares the hypothermic effect of 500 μg of Δ^9-THC administered into ventricle III or ventricle IV. The hypothermic response to intracisternal administration of Δ^9-THC resulted in a more rapid onset and reached a greater maximum than that produced by ventricle III administration.

Intravenous administration of 500 μg of Δ^9-THC produced significantly less hypothermia than intracisternal or intraventricular administration (Table 1 and Fig. 1). Vehicle produced no significant alteration in body temperature.

Neuraxis transections (acute unanesthetized cats)

Midcollicular transection produced classical decerebrate rigidity in all animals within 15 min after termination of halothane anesthesia. Intravenous administration of Δ^9-THC to midcollicular transected (Group I) animals produced significant decreases in blood pressure (Fig. 2) and heart rate when compared to vehicle controls. Within 30 min after Δ^9-THC administration, body temperature was significantly depressed when compared to controls (Group II) (Fig. 3). The hypotension and bradycardia elicited by Δ^9-THC administration in these unanesthetized cats with midcollicular transections agree well with previous reports using anesthetized cats with similar transections, and is comparable to the responses obtained in intact anesthetized cats (Hosko and Hardman, 1976). Administration of the second dose (4.0 mg/kg) of Δ^9-THC, 2 hr after the initial 2.0 mg/kg dose, produced minimal additional effects. The somatic effects produced by the cannabinoids characteristically exhibit tachyphylaxis in experimental animals. Vehicle produced no significant effects on body temperature, heart rate, or blood pressure.

The C-1 transected animals were used to establish the rate of body temperature loss in cats incapable of significant centrally mediated thermoregulation. Figure 3 demonstrates that the rate of temperature loss in C-1 transected animals receiving Δ^9-THC was statistically indistinguishable from C-1 transected animals receiving vehicle alone. These data indicate that in C-1 transected preparations, Δ^9-THC produced few if any peripheral effects that contributed to body temperature loss. The cardiovascular effects of Δ^9-THC were also absent in C-1 transected animals (Fig. 2). Figure 3 further demonstrates that administration of Δ^9-THC to midcollicular preparations resulted in a rate of body temperature loss that closely approximated the rate seen in C-1 transected animals.

In summary, the hypothermic response to Δ^9-THC, however mediated, was largely absent after low neuraxis transection at C-1, but was essentially unaffected by higher midcollicular transections which spared neuronal pools that subserve the autonomic nervous system. The hypothermic response exhibited by the midcollicular transected animals was essentially the same as that observed in intact animals (Hosko and Schmeling, unpublished).

DISCUSSION

The tetrahydrocannabinols typically elicit a series of autonomic effects in experimental animals which include bradycardia, hypotension, and hypothermia (Hardman *et al.*, 1957, 1971a, b; Hosko and Hardman, 1971, 1976; Cavero, Solomon, Buckley and Jandhyala, 1973a, b). The Δ^9-THC-induced hypotension

Table 1. The effect of intraventricular administration of DMHP and vehicle on telemetered body temperature. The effect of intravenous Δ^9-THC in the same dose as that used for intraventricular administration is also tabulated. (Temperature = Mean change °C ± SE)

Time after administration (hr)																
0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	12.0	24.0	48.0
Ventricle III—DMHP 75 μg (n = 5)																
−0.04	−0.12	−0.30	−0.50	−0.54	−0.40	−0.72	−0.98	−1.18	−1.32	−1.62	−1.94	−1.88	−2.04	−3.82	−3.70	−1.58
±0.10	±0.13	±0.28	±0.30	±0.36	±0.38	±0.34	±0.26	±0.24	±0.28	±0.32	±0.28	±0.39	±0.49	±0.71	±1.07	±0.71
Ventricle III—vehicle (n = 5)																
+0.10	−0.28	+0.28	+0.48	+0.20	+0.20	+0.28	+0.42	+0.46	+0.54	+0.54	+0.48	+0.42	+0.52		+0.10	
±0.11	±0.17	±0.10	±0.10	±0.05	±0.14	±0.17	±0.17	±0.30	±0.26	±0.24	±0.23	±0.27	±0.29		±0.40	
Intracisternal (ventricle IV)—vehicle (n = 5)																
−0.06	−0.06	0	−0.02	−0.10	+0.02	+0.04	0	+0.02	+0.06	+0.06	−0.02	+0.08	+0.16		+0.23	
±0.07	±0.07	±0.09	±0.11	±0.09	±0.12	±0.13	±0.24	±0.14	±0.10	±0.10	±0.10	±0.11	±0.13		±0.26	
Intravenous— Δ^9-THC 500 μg (n = 8)																
−0.24	−0.46	−0.66	−0.69	−0.59	−0.46	−0.59	−0.41	−0.39	−0.30	−0.13	−0.19	−0.03	+0.10		−0.05	
±0.18	±0.24	±0.30	±0.33	±0.39	±0.39	±0.34	±0.26	±0.23	±0.27	±0.30	±0.35	±0.33	±0.31		±0.35	
Intravenous—vehicle (n = 4)																
−0.18	−0.08	+0.08	+0.13	−0.10	+0.08	+0.03	+0.10	+0.15	+0.15	+0.15	+0.23	+0.28	+0.33		−0.02	
±0.09	±0.10	±0.21	±0.20	±0.44	±0.39	±0.35	±0.31	±0.26	±0.19	±0.13	±0.08	±0.11	±0.17		±0.43	

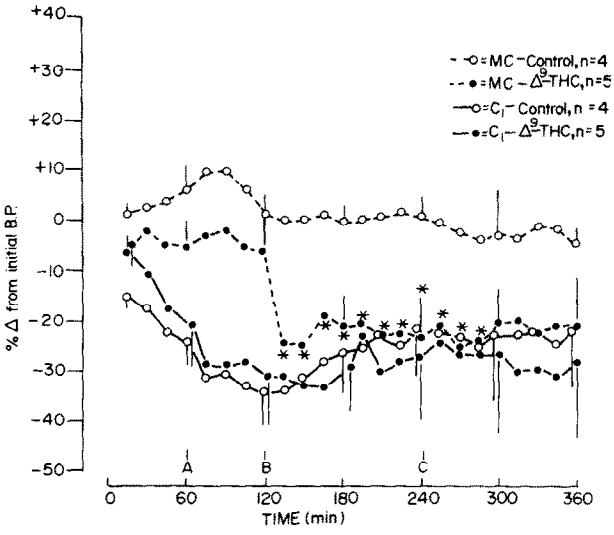

Fig. 2. Effect of Δ^9-THC on blood pressure in midcollucular (MC) and spinal (C-1) transected animals. Control animals received vehicle in appropriate volume at A, B and C. The Δ^9-THC animals received vehicle at A, 2 mg/kg Δ^9-THC (i.v.) at B and 4 mg/kg Δ^9-THC (i.v.) at C. *Significance at $P < 0.01$ level.

and bradycardia have been postulated to be due to reduced sympathetic tone to the cardiovascular system (Hardman *et al.*, 1957; Vollmer *et al.*, 1974; Hardman and Hosko, 1976; Hosko and Hardman, 1976).

Evidence for a central hypothermic action of Δ^9-THC is based on intracerebroventricular injection studies with Δ^9-THC and its metabolites (Abel, 1972; Christensen, Freudenthal, Gidley, Rosenfeld, Boegli, Testino, Brinc, Pitt and Wall, 1971; Garattini, 1965; Gill *et al.*, 1970; Schmeling and Hosko, 1976). Previous studies have demonstrated that the anterior hypothalamus plays a role in the modulation of Δ^9-THC-induced hypothermia (Schmeling and Hosko, 1976, 1979). Δ^9-Tetrahydrocannabinol blocks shivering induced by cooling of the preoptic region. However, microinjection of various cannabinoids into documented thermosensitive hypothalamic sites indicate that the hypothalamus is not the primary site of action for inducing hypothermia (Hosko and Schmeling, unpublished).

Fuxe and Ungerstedt (1966) and Glowinski, Iverson and Axelrod (1966) demonstrated that intraventricular action of many drugs is largely restricted to structures lying proximal to the ventricle. The maximum hypothermia with shorter latency to peak response

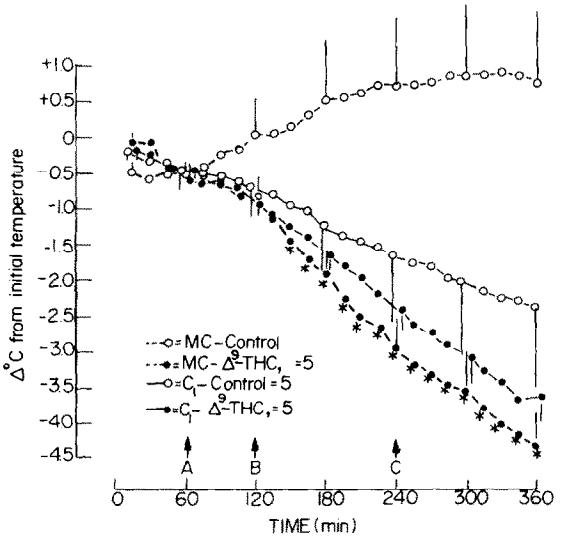

Fig. 3. Effect of Δ^9-THC on body temperature in midcollicular (MC) and spinal (C-1) transected animals. Control animals received vehicle in appropriate volume at A, B and C. The Δ^9-THC animals received vehicle at A, 2 mg/kg Δ^9-THC (i.v.) at B, and 4 mg/kg Δ^9-THC (i.v.) at C. *Significance at $P < 0.01$ level.

following microinjection of Δ^9-THC into ventricle IV as contrasted to ventricle III implies a caudal CNS site of action. The increased potency of intracerebroventricular DMHP as compared to Δ^9-THC in eliciting both autonomic and behavioral responses is consistent with results after systemic administration (Haavik and Hardman, 1973a,b). The greater hypothermic efficacy of the cannabinoids after intraventricular administration as opposed to intravenous administration supports a CNS site of action.

Based on a variety of investigative procedures, current theories of temperature regulation suggest that information from temperature sensitive neurons within the CNS is combined with other convergent afferent thermal information from CNS and peripheral thermosensors. An appropriate "load error" response is generated (Cabanac, 1975; Hensel, 1973; Hammel, 1968; Satinoff, 1974). Activation of physiological and behavioral mechanisms occurs which results in appropriate thermoregulatory responses. Convergence of afferent and efferent thermal information occurs at hypothalamic (Nutik, 1971), mesencephalic (Nakayama and Hardy, 1969), rhombencephalic (Chai and Lin, 1972), and spinal sites (Hensel, 1973). These sites may function conjointly as true centers for integration or may function as control circuits mediating independent sensor and effector functions depending on the physiological state of the organism (Satinoff, 1974; Hammel, 1968). Neuraxis transection releases lower thermoregulatory centers from tonic rostral control thereby allowing lower thermoregulatory centers to function independently (Simon, 1974; Chambers *et al.*, 1974; Hensel, 1973).

Based on previous transection studies (Hardman *et al.*, 1957; Dagirmanjian and Boyd, 1962; Hosko and Hardman, 1971, 1976), a central neuronal site located between the mesencephalon and C-1 was proposed as the site responsible for the hypotensive action of Δ^9-THC. Dagirmanjian and Boyd (1962) implicated the reticular formation of this area as mediating Δ^9-THC-induced hypotension and bradycardia. Hosko and Hardman (1976), on the basis of pressor responses to stimulation of hypothalamic, medullary, and reticular formation sites in cats, have suggested that two mechanisms are responsible for tetrahydrocannabinol-induced alteration of cardiovascular homeostasis. The first is a suppression of inhibitory influences impinging on medullary vasopressor neurons, and the second is a reduction of spontaneous discharge of sympathetic neurons in medullary and other brainstem vasopressor areas. The latter effect appears to dominate after administration of Δ^9-THC to experimental animals with resultant hypotension and bradycardia. The former mechanism could explain the tachycardia usually observed after cannabinoid administration to humans.

Similar mechanisms may be responsible for the lack of consistent hypothermia in humans after Δ^9-THC administration. While reports on hypothermia in man after administration of medium to large doses have been reported (Gourves, Viallard, Leluan, Girard and Aury, 1971; Bro and Schou, 1975; Dittrich and Woggon, 1972; Hosko, Kochar and Wang, 1973), it appears that man is less sensitive to cannabinoid-induced hypothermia than many experimental animals.

The temporal concurrent decrement of cardiovascular homeostasis induced by cannabinoid administration in C-1 and midcollicular transected animals suggests a possible relationship. Δ^9-Tetrahydrocannabinol may be decreasing the discharge of facilitory medullary thermosensitive neurons thereby attenuating the ability to thermoregulate. Depression in this putative integrative thermoregulatory "center" disposes the animal to imprecision in thermal balance with subsequent production of a hypothermic state.

Respiratory changes induced by the cannabinoids have also been shown to be at least partially mediated at brainstem levels (Hosko and Schmeling, 1979). What emerges is a pharmacological profile for the cannabinoids characterized by significant autonomic effects mediated at the rhombencephalon. In these terms, *in situ* depression of neuronal networks dominates except when countered by other alterations in ascending or descending inhibitory or facilitory mechanisms. This interpretation explains the apparent primary action of the cannabinoids in inducing hypothermia (and other autonomic alterations) mediated at low brainstem levels. Cannabinoid-induced hypothermia may be the result of decreased tonic excitation as well as imprecise convergence of thermal information and subsequent processing mediated at the level of the rhombencephalon. More rostral CNS centers in mesencephalon, diencephalon, and telecephalon may subserve to modulate and control this imprecision. The exact interaction of these CNS neuronal pools after administration of the cannabinoids requires further elucidation.

Acknowledgement—This study was supported by USPHS Grant No. DA-00124.

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