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Postural syncope after marijuana: a transcranial Doppler study of the hemodynamics

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Abstract

Twenty-nine volunteers participated in a randomized, double-blind, placebo-controlled study. Cerebral blood velocity (CBV), pulse rate, blood pressure (BP), skin perfusion (SP) on forehead and plasma Δ^9 tetrahydrocannabinol (THC) levels were quantified during reclining and standing for 10 min before and after THC infusions and marijuana smoking. Both THC and marijuana induced postural dizziness, with 28% reporting severe symptoms. Intoxication and dizziness peaked immediately after drug. The severe dizziness group showed the most marked postural drop in CBV and BP and showed a drop in pulse rate after an initial increase during standing. Postural dizziness was unrelated to plasma levels of THC and other indices.

Keywords: Postural syncope; Marijuana; THC; Cerebral blood velocity; Forehead skin perfusion; Plasma THC levels

1. Introduction

In the United States, marijuana is the most commonly used illegal drug and the third of all abused drugs. Approximately one third of the population older than 12 years have tried marijuana at least once. Most of the marijuana users appear to fall between ages 18 and 25 years (National Household Survey on Drug Abuse, 1987). In 1994, the U.S. Department of Health and Human Services and the National Institute on Drug Abuse declared a special initiative on marijuana. Special emphasis was placed on the health consequences of marijuana use (Shalala, 1995).

Although a number of research reports are available on postural dizziness and syncope after marijuana smoking (Merritt et al., 1982; Nahas, 1986), the phenomenon has not received much clinical attention. In normal subjects and patients, postural hypotension was reported after the administration of Δ^9 tetrahydrocannabinol (THC) (Weiss et al., 1972a,b; Gross et al., 1983). Studies on the antianxiety effects of nabilone—a synthetic cannabinol—identified orthostatic hypotension as the most common side effect of concern (Ilaria and Fann, 1978; Ilaria et al., 1981). Dizziness was reported by 44% of the 210 participants in placebo-controlled studies of nabilone (Archer et al., 1986).

Orthostatic hypotension that results in postural syncope has considerable clinical relevance. In healthy individuals, it can cause injuries including lacerations and fractures. In individuals with preexisting cerebrovascular disorders, it can lead to stroke and sudden death (Glassman et al., 1987; Schatz, 1986; Streeten, 1987). Orthostatic hypotension was predictive of ischemic stroke even after the other risk factors for stroke were controlled (Eigenbrodt and Rose, 2000). In nursing home residents, it was found to be an independent risk factor for recurrent falls (Ooi et al., 2000). In Alzheimer's disease, an association was found between autonomic dysfunction and frontal hypoperfusion during orthostatic testing (Siennicki-Lantz et al., 1999). Orthostatic hypotension complicates a variety of diseases including multiple sclerosis, diabetes mellitus, Shy Drager syndrome, diabetes nephrosis, chronic fatigue syndrome, parkinsonism, organic dementias and cervical myelopathy (Flachenecker et al., 1999; Senard et al., 1997; Mathias and Kimber, 1999; Ogi et al., 1998; Streeten and Anderson, 1998; Misra et al., 1991; De Lorenzo et al., 1997; Frisbie and Steele, 1997; Passant et al., 1997). In elderly ambulatory men, orthostatic hypotension was found to be a significant independent

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predictor of mortality (Masaki et al., 1998). A number of commonly used drugs including tricyclic antidepressants, hypotensives, antipsychotics, vasodilators, etc., can cause postural hypotension and syncope (Cohen et al., 1998; Coperchini and Kreeger, 1997). Drugs that are frequently abused in combination with marijuana—ethyl alcohol, solvents, etc.—are also known to induce postural syncope (Cohen, 1979; Sheffer, 1965; Stimmel, 1979). Alterations in gravity have been associated with orthostatic intolerance (Ramsdell et al., 2001; Cheung et al., 1999; Madsen et al., 1998). Thus, sudden changes in the gravitational force such as helicopter flights, driving up or down steep slopes, etc., might increase the likelihood of orthostatic hypotension and syncope (Madsen et al., 1998). Such risk may be enhanced by concomitant use of marijuana.

In 1992, we reported a preliminary study on the effects of smoked marijuana on postural syncope and associated hemodynamic changes (Mathew et al., 1992b). Ten right-handed male subjects with a previous history of marijuana exposure took part. Participants were physically and mentally healthy and drug free for a minimum of 3 months. Middle cerebral artery blood velocity (CBV), blood pressure (BP) and pulse rate were recorded during reclining and standing before and after smoking a marijuana cigarette or a placebo cigarette administered during two separate visits to the laboratory. CBV was measured with transcranial Doppler (TCD) (Arnolds and Von Reutern, 1986). The participants were questioned about dizziness during the upright position. Six of the 10 subjects reported moderate to severe dizziness during standing after marijuana but not after placebo. Subjects who experienced severe dizziness during standing showed marked decreases in BP and CBV.

The present project sought to replicate and extend the findings of the preliminary study with a larger sample and improved methodology. We used TCD to examine postural changes in CBV in the middle cerebral artery. Several previous investigators used the technique to study autoregulatory mechanisms (Aaslid et al., 1989, 1991; Giller, 1990; Deihl et al., 1999; Chern et al., 1999). This technique is uniquely suited to study autoregulation as it provides continuous measurement of intracranial blood velocity. The validity of TCD in the study of cerebral autoregulation was established by comparing the flow index derived using TCD with a venous outflow velocity recording technique (Aaslid et al., 1991). In addition to CBV and peripheral circulation, we measured forehead capillary perfusion (Fagrell, 1985; Holloway and Watkins, 1977). The effects of both THC infusion and marijuana smoking were evaluated.

2. Method

CBV in the middle cerebral artery was measured with TCD ultrasonography (Aaslid et al., 1989, 1991; Aaslid, 1986) and skin perfusion (SP) on the forehead was measured with laser Doppler (Fagrell, 1985; Holloway and Watkins, 1977). On each of 2 days of testing, CBV, SP, BP and pulse rate were measured throughout the testing period. To evaluate postural changes, the subjects had two recording periods consisting of 10 min standing preceded and followed by 10 min periods of reclining. The first standing period was before drug/placebo (baseline) and the second period started immediately after receiving drug/placebo. Subjects also rated the severity of their dizziness while standing.

2.1. Subjects

Twenty-nine physically healthy volunteers (17 males and 12 females) with a mean age of 25.5 ± 4.37 years (range 20–38 years) were included. All were experienced marijuana smokers. Subjects were interviewed by the first author (RJM) and were excluded if they (a) had any significant physical or psychiatric disorder with special emphasis on alcohol abuse and alcoholism (DSM-III-R), (b) used other addictive drugs during the previous 6 months, (c) had current use of any prescribed or not prescribed medicine that would interfere with measurement, (d) had a history of vascular disorders including migraine and cluster headaches or (e) had heavy alcohol use (more than one drink per day for females and two drinks per day for males). All participants had a physical examination and EKG. Presented in Table 1 are characteristics of the subjects according to method of administering drug.

The Institutional Review Board at Duke University Medical Center reviewed and approved the project. Volunteers were recruited through local advertising. Prior to their participation in the study, the project and the associated risks and benefits were explained to the participants and their consents were obtained. The subjects were instructed not to consume any marijuana for 2 weeks before the study. They were also required to avoid alcohol for 24 h and caffeine and nicotine for 4 h before coming to the laboratory (Mathew and Wilson, 1991). Urine drug screens were performed during each visit to the laboratory to verify this.

Table 1
Demographic characteristics of subjects by method of drug administration: difference between infusion and smoking groups

Study variable	Infusion		Smoking		Diff[a]
	Mean	S.D.	Mean	S.D.	*t* test
Age	25.4	4.9	25.5	4.2	no
Weight (lb)	155.5	23.7	151.3	24.0	no
Height (in.)	68.6	4.6	68.9	5.4	no
THC per year[b]	1.6	0.68	1.9	0.63	no
	N	%	*N*	%	χ^2
Males	5	50.0	12	63.2	no
Smoke tobacco	5	50.0	9	47.4	no
Use alcohol	10	100.0	17	89.5	no

[a] Results of significance test between groups (*t* test or χ^2).
[b] Log estimated number of joints per year.

2.2. Drug administration

During two separate visits to the laboratory, the subjects received THC or placebo, or marijuana or placebo, using a repeated-measures design. Nineteen subjects were given a cigarette that was either placebo (marijuana with THC extracted) or marijuana (Δ^9 THC = 3.55%), which they smoked over a 10 min period while reclining. A second group of 10 subjects was given a 20 ml infusion that was either placebo (albumin) or THC (0.2 mg/ml Δ^9 THC in albumin) over a 20 min period while reclining (Perez-Reyes et al., 1972). Subjects got the THC and placebo in a double-blind, randomized order, separated by at least 1 week. Marijuana and THC supplies were obtained through the Federal Drug Enforcement Agency. There were 12 males and 7 females in the smoking group and 5 males and 5 females in the infusion group (χ^2 not significant). With the exception of the drug administration, the timing of all measurements was the same.

2.3. Measurements

Each volunteer was brought into the laboratory and asked to recline on a couch for $\sim$15 min while recording equipment was attached. The TCD ultrasound probe (2 MHz) was attached to the right temporal area. Recording was begun to establish the CBV. In young adults, it is usually possible to obtain good signals from a relatively large area. Middle cerebral artery runs laterally and slightly anterior as a continuation of intracranial internal carotid artery. It has the highest volume flow of all the branches from the circle of Willis, carrying about 80% of the flow to the hemisphere. First, ultrasonic gel was placed between the probe and the patient's skin in the temporal region. The probe was moved by a few millimeters over the surface and placed at different angles until a good signal (CBV more than 50 cm/s) was received. Once the ideal probe position was found, it was immobilized and held in that position by a headband (Aaslid, 1986).

TCD yields different flow indices; peak systolic velocity refers to the highest velocity during systole. End diastolic velocity is the maximum velocity, at the end of the diastole. Mean velocity is the time-averaged maximum velocity over the cardiac cycle.

In addition, an automatic BP arm cuff was placed on the right arm and used to record systolic and diastolic BP and pulse rate. SP on the forehead just above the nasion was measured with a skin laser Doppler (Fagrell, 1985; Holloway and Watkins, 1977). Recordings were made for all measures throughout the study period.

After the equipment was attached, the subjects remained supine for 10 min and then had a 10 min standing period. During this time, baseline measurements were made once per minute. Following this baseline period, the subjects again were required to recline and drug/placebo administration was begun. Subject-paced smoking continued during the next 10 min. Subjects who got the infusion received this over a 20 min period. The subjects remained in a reclining position while receiving drug or placebo (infusion or smoking). At the end of the drug/placebo administration period and for the next 10 min, the subjects were required to stand upright. Throughout this period of standing, BP and pulse rates were recorded each minute and cerebral and forehead blood velocities were recorded every 30 s. A technician stood on each side of the subject during standing to assure they did not fall. Thus, before standing, the subjects had been in a supine position for at least 10 min. At the end of the 10 min of standing, the subjects were required to lie back down.

Subjects reported their degree of dizziness experienced while standing on a rating scale that ranged from 0 to 4, with 4 = *very dizzy*. They reported dizziness twice while standing, immediately after standing and after 5 min of standing. Subjects also reported level of intoxication during each period on a 100 mm line, with 100 being the most intoxicated they have been.

Venous blood samples were drawn for plasma THC assays at baseline and before and after standing following drug/placebo administration. The mean of these latter two provides a measure of plasma THC during standing. The baseline plasma level on each day indicated if subjects had used marijuana. Δ^9 THC was assayed using radioimmunoassay with a kit supplied by NIDA.

3. Analyses

Preliminary analyses were undertaken to determine if there were differences between those who got the drug by smoking versus infusion. We compared the mean of the two plasma levels after drug and the following Δ_{max} from variables measured during standing after drug: CBV, systolic and diastolic BP and pulse rate. None of these variables were different between smoking and infusion. The number of subjects who reported severe dizziness was not different between these groups via χ^2. Based on these analyses, we have pooled the data and will present the results from this pooled analysis. Thus, the term ''Drug'' refers to the combined drug conditions (infusion and smoked).

The mean of the two ratings of dizziness during the period of standing after drug was used to divide subjects into two groups as More DZ (n = 13) and Less DZ (n = 16). We reviewed the data and found that the two ratings were uniform across the two measurements, i.e., the More DZ remained more dizzy and the Less DZ remained less dizzy. t tests between the first and the second ratings for the whole group, the Less DZ and the More DZ groups, did not show significant differences. However, the possibility of some individual subjects showing some variations between rating 1 and rating 2 cannot be excluded. None showed wide variations, e.g., a score of 1 during one measurement and a score of 4 during the next. For most dependent variables, the value of maximum change (Δ_{max}) was computed for each

reclining-to-standing period. This was done by first computing the mean of the last 5 min of reclining (immediately preceding standing); then, this mean was subtracted from the values while standing, and Δ_{max} was determined. Repeated-measures ANOVA was utilized for Group × Drug × Period analyses that were computed on the Δ_{max}. Descriptive analyses were also undertaken to examine differences in the pattern of change over time during each period of standing between the DZ groups. Analyses of sex differences were not possible in a full model because there were too few subjects. Therefore, separate Sex × Drug × Time models were used. Multiple regression analyses looked at the relationship between change over time of CBV and the other variables during the 10 min standing period after drug.

4. Results

Before separating subjects into the two dizziness groups, analysis of the mean of the two ratings of dizziness on standing during the two periods (before and after drug/placebo) found a significant Drug × Time interaction ($F=31.55$, $df=3,83$, $P<.001$), indicating an increase in dizziness after drug (Table 2). The mean of ratings after drug was used to sort subjects into Less DZ and More DZ, and all other analyses used this grouping variable. In the Less DZ group, this mean ranged from 0 to 1.5, with a mean of 0.9 ± 0.44, and in the More DZ group, the sum ranged from 2.0 to 3.5, with a mean of 2.88 ± 0.5 ($t=11.05$, $df=27$, $P<.001$). Of the 13 More DZ, 8 had at least one rating of 4 (severe dizziness), but none of the Less DZ group did. There was no difference in the dizziness on standing as a function of route of drug administration ($F<1.0$, ns). Females tended to rate themselves as more dizzy ($t=3.18$, $df=27$, $P<.004$); consequently, there were more females (9 of 13) in the More DZ group ($\chi^2=7.53$, $P<.006$). Therefore, we examined sex differences in subsequent analyses. We did analyses of peak CBV, systolic and diastolic BP and pulse rate during the time of standing after getting drug and an analysis of the mean plasma level during the time of standing after drug.

Table 2
Mean of two ratings of dizziness while standing after placebo and drug

Number of subjects with each mean dizziness rating[a] on standing									
Placebo									
Mean ratings	0	0.5	1	1.5	2	2.5	3	3.5	4
Less DZ group	9	4	1	2	0	0	0	0	0
More DZ group	7	4	2	0	0	0	0	0	0
Drug									
Mean ratings	0	0.5	1	1.5	2	2.5	3	3.5	4
Less DZ group	1	4	7	4	0	0	0	0	0
More DZ group	0	0	0	0	2	2	6	3	0

Numbers of subjects at each level of dizziness sorted by More DZ versus Less DZ.

[a] Ratings reflect mean of two evaluations while standing after drug and placebo.

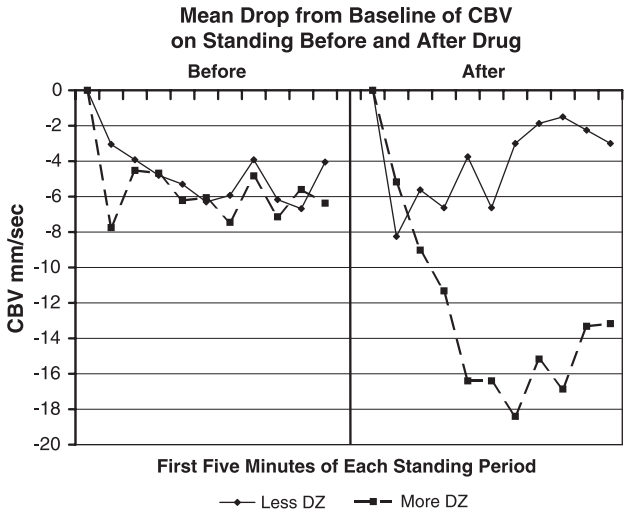

Fig. 1. Mean changes in CBV on standing before and after receiving drug compared with the reclining CBV just before standing. Data are separated by dizziness groups.

None of these showed a difference between the two methods of drug administration; therefore, we believe that pooling the data is justified.

Intoxication ratings were not normally distributed; therefore, we did an analysis of the ratings only after drug and compared the two groups on log normalized data. This analysis indicated that the More DZ group rated itself as higher (More DZ = 1.83 ± 0.12 vs. Less DZ = 1.62 ± 0.32, $t=2.12$, $P<.043$). There were no sex differences in the reported level of intoxication after drug (Male = 1.73 ± 0.28 vs. Female = $1.68 \pm .26$, t = ns).

There was a significant difference in the pattern of response for the two groups on standing after drug (Fig. 1). Analysis of the Δ_{max} CBV on standing indicated a significant Group × Drug × Time interaction, showing a greater drop in CBV following drug than placebo ($F=8.70$, $df=1,27$, $P<.007$). A post hoc t test of Δ_{max} following drug indicated that the More DZ group had a significantly greater drop in CBV ($t=2.92$, $df=27$, $P<.007$). Presented in Table 3 are the mean CBV at the point of Δ_{max} for the standing periods. Six of the 13 (46.2%) of the More DZ group had CBV at the point of Δ_{max} that was less than 40 mm/s after drug, but only 2 of the Less DZ group had CBV less than 40 mm/s. There was no significant sex effect for the Δ_{max} CBV ($t=1.39$, P = ns).

We computed the mean arterial BP (MAP) and determined the Δ_{max} of the decrease on standing. The More DZ group had greater decreases in MAP on standing (Group × Time $F=12.76$, $df=1,27$, $P<.001$). MAP during standing after marijuana/THC dropped from 60 to 55.4 mm Hg (S.D. = 12.5) in the More DZ group. There were eight who dropped below 60 and six of whom dropped below 50. The range of values for those who dropped below 60 was from 36.3 to 55.0. Analysis of systolic BP showed a similar significant change ($F=10.71$, $df=1,27$, $P<.003$).

Table 3
Mean level of CBV, MAP and pulse rate at the point of maximum effect on standing before and after drug and placebo

Mean levels of perfusion variables on standing at the time point of Δ_{max}								
	Placebo				Drug			
	Pre		Post		Pre		Post	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
CBV (mm/s)								
Less DZ	44.9	10.5	45.5	9.9	45.1	9.6	45.5	8.3
More DZ	44.8	9.3	45.7	9.7	47.4	8.7	37.7	11.3
MAP (mm Hg)								
Less DZ	73.5	4.9	66.3	6.2	69.2	8.2	67.8	8.5
More DZ	70.6	7.1	66.8	6.5	72.0	7.6	55.4	12.5
Pulse rate (beats per second)								
Less DZ	97.6	13.2	96.9	12.1	102.1	8.9	135.2	21.2
More DZ	100.2	12.1	100.8	14.6	101.5	15.9	143.3	25.6

The mean drop in systolic BP was 23.3 ± 14.4 mm Hg for the Less DZ group and 39.8 ± 15.1 mm Hg for the More DZ group ($t = 2.90$, $df = 27$, $P < .01$). There was a Drug × Time effect for diastolic BP, but the interaction with DZ group did not reach significance. The data in Table 3 are the mean MAP at the point of Δ_{max}.

Females tended to have a greater drop in MAP on standing than males in both Less DZ and More DZ groups, and this change approached significance in the drug condition compared with the placebo condition ($F = 3.62$, $P < .07$).

Because there is typically an increase in pulse rate after marijuana/THC (which we also observed in this study), we computed the mean resting pulse rate before standing for each of the two testing periods. Analysis of the resting pulse rate from before to after drug indicated a significant increase for both groups ($F = 87.46$, $df = 1,27$, $P < .001$), but there were no difference between the DZ groups. Pulse rate (Table 3) did not meet the assumption of homogeneity of variance, and the data were log normalized before analysis. The Δ_{max} pulse rate analysis indicated a significant Drug × Time interaction ($F = 106.66$, $df = 1,27$, $P < .001$). However, while post hoc analysis showed there was significantly greater increase after drug than placebo, the overall ANOVA failed to indicate a difference between the DZ groups in maximum change. Females tended to have higher pulse rates than males, but they did not show a greater increase in pulse rate on standing after drug than males.

SP of the forehead measured with laser Doppler showed a significant Group × Drug × Time interaction ($F = 6.06$, $df = 1,27$, $P < .021$). However, post hoc t test at Δ_{max} failed to indicate a significantly greater drop for the More DZ group. There were also no sex differences in SP changes on standing.

Analysis of plasma levels indicated that the peak plasma level occurred just before standing after receiving drug. To examine the plasma level while standing, we computed the mean of the two samples on standing. We compared the mean level (after log normalization) between the two DZ groups. This analysis indicated that the Less DZ group had slightly higher plasma levels (45.5 ± 23.2 ng/ml) than the More DZ group (37.3 + 17.5 ng/ml), but the difference was not statistically significant. Males tended to have higher mean plasma levels (24.5 ± 11.1 ng/ml) than females (17.9 ± 9.3 ng/ml); however, when log normalized, there was no significant difference between them.

5. Results for time course

Inspection of the percent changes plots for pulse rate indicated a difference between the DZ groups after drug (Fig. 2). The time interval shown in the figure continues for 5 min after again reclining. There were no differences after placebo so we have not shown these curves. While both groups had a rise in pulse rate on standing, the More DZ group also had a rapid drop following this increase while they were still standing. However, the Less DZ group continued to show the increased pulse rate that persisted until after they were again reclining. We did t tests between the two groups at each time point to determine when they showed a significant separation. It became significant at 3 min after standing (see S in Fig. 2) and remained significant when the subjects were again reclining (see R in Fig. 2).

6. Multiple regression

A multiple regression to predict change in CBV over time as a function of change in measures of peripheral perfusion (systolic BP, SP and pulse rate) over time was computed at Post 1 for all subjects combined. These predictors were entered in a single step and partial correlations were

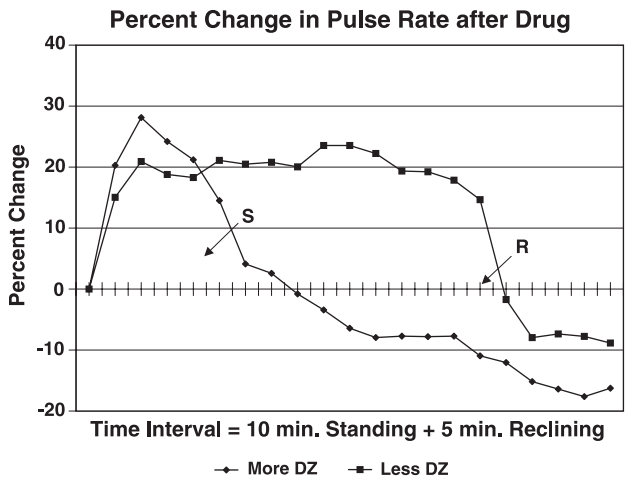

Fig. 2. Percent change in pulse rate on standing after drug. Multiple t tests between the two dizziness groups at each time point to determine when they showed a significant separation indicated significant difference ($P \leq .05$) at 3 min after standing (see point marked S) and remained significant until subjects again reclined (see R in figure).

Table 4
Multiple regression analysis of each dizziness group predicting change in CBV as a function of peripheral measures perfusion variables

Multiple regression analyses of change post THC			
Variable[a]	Partial *r*	*F*	Sig. *F*
Less DZ subjects: not statistically significant (multiple r=.146, F=1.71, P>.16)			
Forehead BF	−.04	0.377	.540
Pulse rate	.01	0.016	.900
Systolic BP	−.13	3.781	.053
More DZ subjects: statistically significant (multiple r=.370, F=8.50, P<.001)			
Forehead BF	.22	8.329	.004
Pulse rate	.04	0.226	.635
Systolic BP	.25	11.075	.001

[a] All data log10 normalized for model.

computed to determine the relative contribution of each predictor to variation in CBV. This analysis found a significant *r* between CBV and three peripheral measures of perfusion. To further examine this model, two regressions were computed, one for each DZ group. This subgroup analysis (Table 4) found that the regression model was only significant for the More DZ subjects. In this model, systolic BP is the most significant predictor. This is important because under normal conditions brain perfusion is autoregulated and does not change with BP.

7. Comment

All but one of the subjects who received marijuana or THC reported some degree of dizziness. Fourteen out of 29 (48%) reported severe dizziness (a rating of 3 or 4) and 28% reported had the most severe rating (a rating of 4). Eight were so dizzy that they had to be supported. Females tended to be dizzier. There was no difference in dizziness between the THC and the marijuana groups. Marijuana/THC intoxication and dizziness were unrelated. Similarly, there was no relationship between plasma THC levels and dizziness. There was a significant drop in CBV during standing after the drug, with the group that reported severe dizziness showing significantly more CBV drop. The More DZ group also had a steeper drop in MAP and systolic BP. The groups did not differ significantly on diastolic BP. The Less DZ group showed persistent increase in pulse rate while they were standing; however, in the case of the More DZ group, the pulse dropped off following an initial increase. This difference was significant between 3 and 9 min after standing after the administration of the drug. Changes and SP on the forehead did not differentiate between the More DZ and the Less DZ groups. Multiple regression analysis identified systolic BP as the most significant predictor of dizziness in the More DZ subjects.

We chose to group subjects into those who had different degrees of dizziness by using the mean of their two ratings while standing. For the severe dizziness group, this approach may involve a loss of information on three potential subgroups: (1) those who became severely dizzy initially on standing and then recover somewhat, (2) those who became and remained severely dizzy while standing and (3) those who become increasingly dizzy while standing. These would be represented by subjects who had (for example) ratings of 3.1 versus 2.2 versus 1.3, all leading to a mean of 2. We recognize that these three may have different implications for the underlying process of adapting to upright posture. However, given the small numbers of subjects in these subgroups and the fact that none of our subjects had extreme ratings (e.g., 0–4 vs. 4–0), we did not believe that there was sufficient justification for further analyses.

The most significant finding of the project is that 28% of the participants reported severe postural dizziness after drug. Postural dizziness can be associated with injuries in healthy individuals and with stroke and sudden death in predisposed people (Eigenbrodt and Rose, 2000; Ooi et al., 2000; Masaki et al., 1998). It complicates a number of common diseases (Flachenecker et al., 1999; Senard et al., 1997; Mathias and Kimber, 1999; Ogi et al., 1998; Streeten and Anderson, 1998; Misra et al., 1991; De Lorenzo et al., 1997; Frisbie and Steele, 1997; Passant et al., 1997; Masaki et al., 1998). Marijuana can exacerbate postural hypotension and syncope associated with a number of prescription drugs and drugs of abuse (Cohen et al., 1998; Coperchini and Kreeger, 1997; Cohen, 1979; Sheffer, 1965; Stimmel, 1979). A number of studies have been conducted on the effects of marijuana on driving and flying (Solowij, 1998). Both driving and flying involve up and down movements and sudden shifts in gravitational pull, which might produce dizziness and syncope (Ramsdell et al., 2001; Cheung et al., 1999).

Normally, when standing up, there is a caudal shift of 500–700 ml of thoracic venous blood and decrease in venous return by about 20%, stroke volume by 40% and cardiac output between 15% and 20%. As BP begins to fall, splanchnic, renal, pulmonary and skeletal muscle vascular beds contract, increasing the peripheral vascular resistance by about 40%. This is accompanied by a 20% increase in heart rate. Standing evokes different cardiovascular compensatory mechanisms depending on whether there is active or passive muscle use. Passive standing (tilting) causes a slow gradual increase in heart rate and BP, whereas active standing results in a modest decrease in BP within 3–7 s and a large bimodal increase in heart rate within 3–30 s (Schatz, 1986; Streeten, 1987).

Physiological responses that help maintain BP upon standing include reflex arteriolar constriction, reflex venal constriction (probable), increase in plasma catecholamines, activation of renin–angiotensin–aldosterone system, release of arginine vasopressin, augmentation of respiration and increased striated muscle tone (Schatz, 1986; Streeten, 1987).

Reflex arteriolar constriction may be the single most important mechanism that operates to maintain BP on standing. It is mediated through the arterial baroreceptor reflex activated by the initial drop in BP. Increased sympathetic activity leads to peripheral vasoconstriction, especially in the limbs, splanchnic vasculature, kidney and lungs. Although there is abundant data that reflex vasoconstriction does occur, there is little evidence that this plays a major role. With active standing, there is an immediate bimodal tachycardia lasting 20 s. The response during the first 5 s is probably caused by contraction of the skeletal muscular groups and consequent vagal inhibition. This is followed by a second cardiac acceleration between 5 and 10 s after standing. On standing, an immediate two- to fourfold increase in plasma norepinephrine occurs, the likely peripheral source of which are the sympathetic ganglia. The adrenal medulla may also participate to some extent (Schatz, 1986; Streeten, 1987).

After marijuana/THC, there was a failure for the systolic BP to hold up. The More DZ group showed more severe drop in MAP and systolic BP. Similarly, the anticipated increase in pulse rate was not sustained for the More DZ group. This suggests failure of the protective mechanisms that ensure sustained BP during standing. As was mentioned above, these physiological changes are mediated through multiple mechanisms including sympathetic activation, vagal stimulation, vagal inhibition, cardiac acceleration, plasma catecholamine increase, cardiac stimulation, etc. We did not monitor all these mechanisms; therefore, how marijuana produces this effect is not clear.

Since the brain does not store oxygen and glucose, its functional integrity is totally dependent upon an adequate blood supply. This becomes even more critical during standing when the head occupies a position higher than the heart. The brain possesses a number of mechanisms that ensure an adequate blood flow in the face of modest decrease in BP (Paulson et al., 1990; Strandgaard and Paulson, 1984; Harper, 1966; McCulloch, 1988). These mechanisms are collectively known as autoregulation.

Autoregulation of blood flow can be defined as the physiological regulatory mechanism that maintains a constant flow over wide range of arterial BP or the perfusion pressure (Johnson, 1985). For the brain, the perfusion pressure is the MAP minus the intracranial pressure. Autoregulation of CBF is mediated through dilation of the cerebral blood vessels (resistance vessels) in response to a decrease in cerebral perfusion pressure (PP) and vasoconstriction in response to increased PP. In the absence of any significant changes in intracranial pressure, changes in PP are due to changes in arterial pressure.

$$CBF = PP/CVR$$

$$CVR = PP/CBF$$

where CVR is the cerebral vascular resistance.

Completely effective autoregulation implies that CBF remains constant and that CVR changes proportionately in the same direction as changes in PP. When autoregulation is completely absent, CBF changes proportionately with changes in PP and CVR remains constant. It can be seen that autoregulation depends upon the integrity of the resistance results, i.e., cerebral arterioles (Paulson et al., 1990).

Autoregulation of CBF is effective over a wide range of arterial pressures. Under normal conditions, the lower limit of MAP is around 60 mm Hg and the upper level is around 150 mm Hg. As was discussed earlier, upon standing, various protective mechanisms prevent the BP from dropping significantly. If, for whatever reason, BP decreases, cerebral resistance changes to keep CBF constant. If the BP decrease is below 60 mm Hg, the cerebral resistance vessels will not be able to dilate any further and CBF reduction will occur (Paulson et al., 1990; Strandgaard and Paulson, 1984; Harper, 1966; McCulloch, 1988).

In the present experiment, in the More DZ group, the MAP during standing after marijuana/THC dropped from 60 to 55.4 mm Hg (S.D. = 12.5). This was accompanied by a significant decrease in CBV. This would indicate a lack of response by the cerebral resistance vessels, i.e., failed cerebral autoregulation.

Cerebral ischemia is the state in which cerebral energy metabolism is restricted. Under normal conditions, the brain receives two to three times its normal requirements of oxygen per minute and seven times that of glucose (Siesjo, 1980). Positron emission tomography (PET) studies have shown that fractional extraction of oxygen under normal conditions is 30–40%. The remainder finds its way into the cerebral venous effluent, unused (Frackowiak, 1985). A fallen CBF does not necessary imply ischemia since a compensatory increase in oxygen extraction can maintain cerebral metabolism without any decrease. Impairment of cerebral metabolism and cerebral ischemic symptoms occur only when the BP is below 30 mm Hg (Merritt et al., 1980).

MAP did not fall below 30 mm Hg after THC/marijuana; yet, symptoms of cerebral ischemia, i.e., dizziness, occurred. This suggests at least three factors: failure to maintain perfusion pressure, failure of cerebral autoregulation and impairment of oxygen extraction/utilization by the brain.

Marijuana/THC has multiple effects on sympathetic drive, vascular smooth muscle, vagal tone and brain function. There is no evidence that marijuana increases intracranial pressure. It has been shown to decrease intraocular pressure (Merritt et al., 1980). Several individuals have reported changes in BP during standing up after smoking marijuana or the administration of other cannabinoids (Gross et al., 1983; Merritt et al., 1980; Glass et al., 1981; Lemberger et al., 1982; Weiss et al., 1972a,b). Unfortunately, none of these investigators reported systolic and diastolic BP while lying down and standing after marijuana. All of them gave the postural changes in MAP except Merritt et al. (1980) who reported only systolic BP. In the

present experiment, we found decrease in MAP and systolic BP in the More DZ group. There were no significant changes in diastolic pressure.

Although the mechanisms of cerebral autoregulation are poorly understood, three hypotheses have been put forward: the myogenic hypothesis, the metabolic hypothesis and the neurogenic hypothesis (Paulson et al., 1990). According to the myogenic hypothesis, the smooth muscle of cerebral blood vessels respond to changes in transmural pressure; the small arteries and arterioles constrict and dilate in response to increases or decreases in the transmural pressure, respectively. The autoregulatory responses initiate within a few seconds and completed within 15–30 s (Kontos et al., 1978; Symon et al., 1973). The mechanism resides in the vascular smooth muscle and is dependent upon the extracellular calcium (Harder, 1984). Marijuana is vasoactive: it dilates conjunctiva (Hollister et al., 1981; Ohlsson et al., 1980) and muscle blood vessels (Hollister et al., 1981). Endothelium-derived relaxation factor and contractile factor may be involved in the autoregulatory mechanism (Furchgott et al., 1984; Rubanyi et al., 1986).

Cerebral autoregulatory mechanisms trigger cerebral vasodilatation in the face of reduced perfusion pressure. If cerebral vasodilatation is already maximal, additional vasodilatation may not be possible and this can cause failure of autoregulation (McCulloch, 1988). We have reported increased cerebral blood flow (Mathew and Wilson, 1993) and increased CBV (Mathew et al., 1992a) after smoking marijuana. However, marijuana-induced CBF and CBV increases, though statistically significant, were not very substantial. Carbon dioxide inhalation, which produces much more potent cerebral blood flow increase (Mathew and Wilson, 1988), does not cause failure of autoregulation.

Increasing metabolic demand of the brain by neural activity increases CBF. A variety of vasoactive molecules have been proposed as mediators of the coupling between brain activity and CBF: these include carbon dioxide, hydrogen, oxygen, adenosine and adenosine nucleotides, potassium and calcium (Kuschinsky and Wahl, 1978). According to the metabolic theory of autoregulation, reduction in cerebral perfusion leads to the release of one of these chemicals that dilate cerebral blood vessels. Of the various chemicals implicated, only adenosine has received experimental support (Rubio et al., 1978). Marijuana is not associated with any known effects on adenosine or the other agents mentioned above.

Cerebral blood vessels are innervated in a manner comparable with that of peripheral blood vessels. Nerve fibers originating from cranial ganglia provide sympathetic, parasympathetic and sensory input to cerebral circulation (Edvinsson, 1975; Uddman and Edvinsson, 1989). Autonomic system influences primarily the larger cerebral blood vessels; smaller resistance changes downstream are believed to be responsible for autoregulation (Edvinsson et al., 1993). These resistance results, as was mentioned earlier, are believed to mediate autoregulation. Marijuana certainly produces autonomic changes, the most marked of which is pulse rate (Ohlsson et al., 1980; Hollister, 1988). However, in the present study, forehead cutaneous vessels that receive sympathetic innervation from the superior cervical ganglion showed minimal differences between More DZ and Less DZ groups. Therefore, it would seem unlikely that THC-induced postural hypotension and syncope are related to associated changes in sympathetic tone.

Other investigators have reported decrease in middle cerebral artery flow during postural hypotension (Titianova et al., 1997; Kawaguchi et al., 2001).

The results of the study clearly show loss of cerebral autoregulation and postural syncope after marijuana/THC. However, the mechanism responsible for these phenomena is unclear.

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References

Aaslid R. Transcranial Doppler examination techniques. In: Aaslid R, editor. Transcranial Doppler sonography. New York: Springer-Verlag; 1986. p. 39–59.

Aaslid R, Lindegaard K-F, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;20:45–52.

Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard K-F. Simultaneous arterial and venous transcranial Doppler assessment of cerebral autoregulation dynamics. Stroke 1991;22:1148–54.

Archer RA, Stark P, Lemberger L. Nabilone. In: Mechoulam R, editor. Cannabinoids as therapeutic agents. Boca Raton, FL: CRC Press; 1986. p. 85–103.

Arnolds BJ, Von Reutern G-M. Transcranial Doppler-sonography examination technique and normal reference values. Ultrasound Med Biol 1986;12:115–23.

Chern CM, Kuo TB, Sheng WY, Wong WJ, Luk YO, Hsu LC, et al. Spectral analysis of arterial blood pressure and cerebral blood flow velocity during supine rest and orthostasis. J Cereb Blood Flow Metab 1999;19:1136–41.

Cheung B, Hofer K, Goodman L. The effects of roll vs. pitch rotation in humans under orthostatic stress. Aviat Space Environ Med 1999;71:966–8.

Cohen S. The volatile nitrites. JAMA 1979;241:2077–8.

Cohen I, Rogers P, Burke V, Beilin LJ. Predictors of medicine use, compliance, and symptoms of hypotension in a community-based sample of elderly men and women. J Clin Pharm Ther 1998;23:423–32.

Coperchini ML, Kreeger LC. Postural hypotension from topical glyceryl trinitrate ointment for anal pain. J Pain Symptom Manage 1997;14:263–4.

De Lorenzo F, Hargreaves J, Kakkar VV. Pathogenesis and management of delayed orthostatic hypotension in patients with chronic fatigue syndrome. Clin Auton Res 1997;7:185–90.

Diehl RR, Linden D, Chalkiadaki A, Diehl A. Cerebrovascular mechanisms in neurocardiogenic syncope with and without postural tachycardia syndrome. J Auton Nerv Syst 1999;76:159–66.

Edvinsson L. Neurogenic mechanisms in cerebral circulation. Acta Physiol Scand Suppl 1975;427:1–35.
Edvinsson L, MacKenzie ET, McCulloch J. Cerebral blood flow and metabolism. New York: Raven Press; 1993. p. 553–80.
Eigenbrodt ML, Rose KM. Orthostatic hypotension as a risk factor for stroke: the atherosclerotic risk in communities (ARIC) study. Stroke 2000;31:2307–13.
Fagrell B. Dynamics of skin microcirculation in humans. J Cardiovasc Pharmacol 1985;7(Suppl 3):S53–8.
Flachenecker P, Wolf A, Krauser M, Hartung HP, Reiners K. Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. J Neurol 1999;246:578–86.
Frackowiak RSJ. The pathophysiology of cerebral ischemia: a new perspective obtained with positron tomography. Q J Med 1985; 57:713–27.
Frisbie FH, Steele DJ. Postural hypotension and abnormalities of salt and water metabolism in myelopathy patients. Spinal Cord 1997; 35:303–7.
Furchgott RF, Cherry PD, Zawadiki JV, Jothianandan D. Endothelial cells as mediators of vasodilation of arteries. J Cardiovasc Pharmacol 1984; 6:S336–43.
Giller CA. The frequency-dependent behavior of cerebral autoregulation. Neurosurgery 1990;27:362–8.
Glass RM, Uhlenhuth EH, Hartel FW, Schuster CR, Fischman MW. Single dose study of nabilone in anxious volunteers. J Clin Pharmacol 1981; 21:383S–96S.
Glassman AH, Roose SP, Giardina EV, Bigger JT. Cardiovascular effects of tricyclic antidepressants. In: Meltzer HY, editor. Psychopharmacology: the third generation of progress. New York: Raven Press; 1987. p. 1437–42.
Gross H, Ebert MH, Faden VB, Goldberg SC, Kaye WH, Caine ED, et al. A double-blind file of delta$_9$ tetrahydrocannabinol in primary anorexia nervosa. J Clin Psychopharmacol 1983;3:165–71.
Harder DR. Pressure-dependent membrane depolarization in cat middle cerebral artery. Circ Res 1984;55:197–202.
Harper AM. Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. J Neurol Neurosurg Psychiatry 1966;29:398–403.
Hollister LE. Cannabis. Acta Psychiatr Scand Suppl 1988;345:108–18.
Hollister LE, Gillespie HK, Ohlsson A, Lindgren J-E, Wahlen A, Agurell S. Does plasma concentrations of delta$_9$tetrahydrocannabinol reflect the degree of intoxication? J Clin Pharmacol 1981;21: 171S–2S.
Holloway JR, Watkins DW. Laser Doppler measurement of cutaneous blood flow. J Invest Dermatol 1977;69:306–9.
Ilaria RL, Fann WE. Nabilone, a cannabinol in anxiety neurosis. Fed Proc 1978;2147:619.
Ilaria RL, Thornby JI, Fann WE. Nabilone, a cannabinol derivative in anxiety neurosis. Curr Ther Res Clin Exp 1981;29:943–9.
Johnson PC. Autoregulation of blood flow. Circ Res 1985;59:483–95.
Kawaguchi T, Uyama O, Konishi M, Nishiyama T, Iida T. Orthostatic hypotension in elderly persons during passive standing: a comparison with young persons. J Gerontol 2001;56:M273–80.
Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. Am J Physiol 1978;234H:371–83.
Kuschinsky W, Wahl M. Local chemical and neurogenic regulation of cerebral vascular resistance. Physiol Rev 1978;58:656–89.
Lemberger L, Rubin A, Wolen R, DeSante K, Rowe H, Forney R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat Rev 1982;9:17–23.
Madsen P, Svendsen LB, Jprgensen LG, Matzen S, Jansen E, Secher NH. Tolerance to head-up tilt and suspension with elevated legs. Aviat Space Environ Med 1998;69:781–4.
Masaki KH, Schatz IJ, Burchfield CM, Sharp DS, Chiu D, Foley D, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. Circulation 1998;98:2290–5.
Mathew RJ, Wilson WH. Cerebral blood flow changes induced by CO_2 in anxiety. Psychiatry Res 1988;23:285–94.
Mathew RJ, Wilson WH. Substance abuse and cerebral blood flow. Am J Psychiatry 1991;148:118–28.
Mathew RJ, Wilson WH. Acute changes in cerebral blood flow after smoking marijuana. Life Sci 1993;52:757–67.
Mathew RJ, Wilson WH, Humphreys D, Lowe JV, Wiethe KE. Middle cerebral artery velocity during upright posture after marijuana smoking. Acta Psychiatr Scand 1992a;86:173–8.
Mathew RJ, Wilson WH, Humphries DF, Lowe JV, Wiethe KE. Changes in middle cerebral artery velocity after marijuana. Biol Psychiatry 1992b; 32:64–169.
Mathias CJ, Kimber JR. Postural hypotension: causes, clinical features, investigation, and management. Annu Rev Med 1999;50:317–36.
McCulloch J. The physiology and regulation of cerebral blood flow. In: Knezevic S, Maximilan VA, Mubrin Z, Prohovnik I, Wade J, editors. Handbook of regional cerebral blood flow. New Jersey: Lawrence Erlbaum; 1988. p. 1–24.
Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marijuana on intraoccular and blood pressure in glaucoma. Ophthalmology 1980;87:222–8.
Merritt JC, Cook CE, Davis KH. Orthostatic hypotension after delta$_9$ tetrahydrocannabinol marijuana inhalation. Ophthalmic Res 1982;14: 124–8.
Misra UK, Kalita J, Kapoor R. Postural hypotension in a patient with cervical myelopathy due to craniovertebral anomaly. Clin Auton Res 1991;7:223–6.
Nahas GG. Toxicology and pharmacology. In: Nahas GG, editor. Marijuana in science and medicines. New York: Raven Press; 1986. p. 109–246.
National Household Survey on Drug Abuse, National Institute on Drug Abuse, 1987.
Ogi M, Kojima S, Kuramochi M. Effect of postural change on urine volume and urinary sodium excretion in diabetes nephropathy. Am J Kidney Dis 1998;31:41–8.
Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta$_9$tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 1980;28:409–16.
Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. Am J Med 2000;108:106–11.
Passant U, Warkentin S, Gustafson L. Orthostatic hypotension and low blood pressure in organic dementia: a study of prevalence and related clinical characteristics. Int J Geriatr Psychiatry 1997;12:395–403.
Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Brain Metab Rev 1990;2:161–2.
Perez-Reyes M, Timmons MC, Lipton MA, Davis KH, Wall ME. Intravenous injection in man of delta 9 tetrahydrocannabinol and 11-OH-delta 9 tetrahydrocannabinol. Science 1972;177:633–5.
Ramsdell CD, Mullen TJ, Sundby GH, Rastoft S, Sheynberg N, Aljuri N, et al. Midodrine prevents orthostatic intolerance associated with simulated space flight. J Appl Physiol 2001;90:2245–8.
Rubanyi GM, Remero JC, VanHoutte PM. Flow-induced release of endothelium-derived relaxing factor. Am J Physiol 1986;250(19): H1145–9.
Rubio R, Berne RM, Winn HR. Production, metabolism and possible functions of adenosine in brain tissue in situ. Cerebral vascular smooth muscle and its control. CIBA Foundation Symposium. Amsterdam: Elsevier; 1978. p. 355–73.
Schatz IJ, editor. Orthostatic hypotension. Philadelphia: FA Davis; 1986.
Senard JM, Rai S, Lapeyre-Mestre M, Brefel C, Rascol O, Rascol A, et al. Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:584–9.
Shalala DE. Remarks at the First National Conference on Marijuana Use: Prevention, Treatment, and Research. Arlington, VA; July 19, 1995.
Sheffer N. Hypotension due to nitroglycerine combined with alcohol. Eng J Med 1965;273:1169.

Siennicki-Lantz A, Lilja B, Elmstahl S. Orthostatic hypotension in Alzheimer's disease: result or cause of brain dysfunction? Aging 1999; 11:155–60.

Siesjo BK. Brain energy metabolism. New York: Wiley; 1980.

Solowij N. Cannabis and cognitive functioning. Cambridge: Cambridge Univ. Press; 1998. p. 34–5.

Stimmel B. Cardiovascular effects of mood altering drugs. New York: Raven Press; 1979.

Strandgaard S, Paulson OB. Cerebral autoregulation. Stroke 1984;15: 413–6.

Streeten DHP, editor. Orthostatic disorders of the circulation. New York: Plenum Medical Book; 1987.

Streeten DS, Anderson GH. The role of delayed orthostatic hypotension in the pathogenesis of chronic fatigue. Clin Auton Res 1998;8:119–24.

Symon L, Held K, Dorsch NWC. A study of regional autoregulation in cerebral circulation to increased perfusion pressure in normocapnia and hypercapnia. Stroke 1973;4:139–47.

Titianova E, Karakaneva S, Velcheva I. Orthostatic dysregulation in progressive autonomic failure—a transcranial Doppler sonography monitoring. J Neurol Sci 1997;146:87–91.

Uddman R, Edvinsson L. Neuropeptides in the cerebral circulation. Cerebrovasc. Brain Metab Rev 1989;1:230–52.

Weiss JL, Wantanabe AM, Lemberger L, Tamarkin NR, Cardon PV. Cardiovascular effects of delta^{9} tetrahydrocannabinol in man. Clin Pharmacol Ther 1972a;13:681–4.

Weiss JM, Wantanabe AM, Lemberger L, Tamarkin NR, Cardon PV. Cardiovascular effects of delta$_{9}$ tetrahydrocannabinol in man. Clin Pharmacol Ther 1972b;13:691–4.