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Propranolol Effects on Acute Marihuana Intoxication in Man

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Abstract. To investigate the possible interaction of a beta adrenergic blocking agent and marihuana, six healthy experienced marihuana smokers received the two drugs separately and in combination. Propranolol (120 mg per os) reduced resting *HR* and *BP*; there were no changes in performance on tasks designed to test psychomotor speed, attention, memory and learning. Marihuana (10 mg Δ^9-THC), administered in smoke, induced the typical subjective state ("high") with marked increases in *HR*, *BP* and conjunctival injection; it impaired performance on a learning test without significantly affecting attention. Pre-treatment with propranolol blocked effectively the cardiovascular effects of marihuana; it prevented the learning impairment and, to a lesser degree, the characteristic subjective experience.

Key words: Marihuana – Propranolol – Subjective drug effects – Attention – Learning.

Considerable experimental evidence has accumulated in recent years concerning the physiological, behavioral and subjective effects of marihuana in man (Marihuana and Health, DHEW Reports 1971–1974; Tinklenberg, 1975; Braude and Szara, 1976). The mechanism of action of the principal ingredient of marihuana, delta-9-tetrahydrocannabinol remains uncertain. There is evidence for the involvement of diverse pathways in various organ systems: cholinergic pathways (Drew and Miller, 1974), amino acid neurotransmitters (Sklenovsky et al., 1974), histamine receptors (Turker, Kaymakçalan and Ercan, 1975) and prostaglandins (Burstein et al., 1975; Kaymakcalan et al., 1975). The best known clinical effect of marihuana and Δ^9-THC is the cardio-acceleration (Clark, 1975); this effect is blocked by propranolol (Beaconsfield, Ginsburg, and Rainsbury, 1972). Cavero and Hoffman (1976) have shown that THC induces in a cross circulation preparation cardiovascular alterations by affecting the central autonomic outflow in dogs. This raises the question whether propranolol can reduce or prevent the central nervous system action of THC. Propranolol is distributed throughout the brain of man and other mammals. Direct evidence provided by post-mortem determinations (Myers et al., 1975) shows unequivocally that it penetrates into the CNS when administered in therapeutic dosages. Beta-adrenergic receptors have been reportedly identified and characterized in the rat brain homogenates (Alexander et al., 1975).

An attempt was made by Drew et al. (1972) to study the effects of propranolol on the cognitive dysfunctions induced by marihuana smoking. They did not report physiological data, leaving in doubt whether a beta blockade was achieved and whether the dose of Δ^9-THC (less than 1 mg) was sufficient to produce a "high"; marihuana alone impaired slightly the Reitan Trail Making and Stroop Color Word Performance without significantly affecting the Babcock Story Recall. There was no evidence of marihuana and propranolol interaction. On the other hand, the report of Beaconsfield et al. (1972) does not include observations on concomitant CNS functions or the subjective variables usually affected by marihuana.

The present study was designed to test the "beta-adrenergic hypothesis" with effective doses of the two drugs, and concomitant monitoring of the relevant dependent variables at all three levels: physiological, behavioral and subjective.

Just as the mechanism of action at the biochemical level is still unknown, the neurophysiological deficits induced by marihuana also remain unclear. Various investigators have experimentally identified an attentional deficit (DeLong and Levy, 1973), a short-term memory impairment (Abel, 1971; Dornbush, 1974) an altered temporal integration of experience

(Melges et al., 1970; Melges et al., 1974) to name a few. However, no single deficit can explain all the cognitive and affective changes seen in acute marihuana intoxication nor is it necessary to postulate a unitary deficit. We have observed (Vachon et al., 1974; Vachon and Sulkowski, 1976) that the learning of a relatively simple task is slowed during intoxication. The experimental conditions were designed to allow the measurement of attention, memory and psychomotor speed; these variables showed little or no changes and could not explain the lowering of the learning performance. We formulated the hypothesis that central processing and integration of information is less effective under the influence of marihuana.

Propranolol pretreatment should not only inhibit the marihuana induced tachycardia but should also prevent the deterioration of performance on the learning task which occurs after marihuana alone.

METHODS

Subjects

An advertisement in local newspapers called for young (18–30) male volunteers willing to participate in physiological experiments. An hourly stipend was offered for the time spent in the laboratory. Six subjects were admitted to the study after they had been screened by psychiatric interview, medical exam and psychological questionnaires. All of them had a history ($\bar{X} = 5$ years) of recreational (not more than twice a week) use of marihuana and had not been involved heavily in use of other drugs (up to the time of the study). They read and signed the Statement of Informed Consent describing in detail the drugs and procedures involved but agreed to remain blind, however, to the order of treatments. They also consented not to take any psychoactive substances throughout the experimental period.

Treatments

Three treatments were administered at least 3 days apart, in randomized order:

1. *P-plm*: propranolol (120 mg) per os followed one hour later by a placebo marihuana cigarette (Δ^9-THC exhausted);
2. *plP-M*: placebo propranolol followed 1 h later by a marihuana cigarette (10 mg Δ^9-THC).
3. *P-M*: propranolol (120 mg) per os followed in 1 h by a marihuana cigarette (10 mg Δ^9-THC).

The subjects received 3 tablets containing each 40 mg of propranolol ("INDERAL", Ayerst Laboratories). As a placebo for the propranolol, the subjects received similar looking tablets containing Vitamin C. The marihuana cigarettes (1.0 mg) were supplied by the NIDA. Analysis (A. D. Little Co., Cambridge, MA), at the end of the study, showed that their Δ^9-THC content was 1.0%, i.e. 10 mg Δ^9-THC. The placebo cigarettes were prepared from Δ^9-THC-extracted Cannabis material identical in taste and smell to natural marihuana. The smoking was supervised by one of the investigators. The cigarette was placed in a cigarette holder in order to lower the temperature of the smoke to comfortable levels and avoid any loss of active ingredients in a long "roach". The subject was asked to inhale deeply and hold his breath for at least 10 s after each smoke inhalation. The average time of smoking was 10 min.

Measurements

A. Physiological. 1. Heart rate (*HR*) was monitored on the EKG (lead II) which was simultaneously displayed on an oscilloscope and recorded on a strip chart throughout the subject's stay in the laboratory. For statistical analysis the *HR* was counted during 30 s periods between the performance tasks, at 0, 20, 60, 90 and 110 min of the testing.

2. Blood pressure (*BP*) was measured with a sphygmomanometer immediately following the completion of smoking and at the same points at *HR*.

3. Conjunctival injection (*CI*) or "eyes reddening" was rated on a 0–4 points scale following each *BP* measurement.

B. Subjective. 1. Ratings of the intensity and quality of the "high". The intensity of intoxication was rated by the subjects on a 0–100 point scale where "0" corresponds to "not hight at all" and "100" to "the highest I've ever been on marihuana." The "pleasantness" of this high was rated on a analogous scale; unpleasant feelings were given a negative sign.

2. The Marihuana and Depressant Scales of the Addiction Research Center Inventory (ARCI). A modified version of the scales (the non-discriminating items had been removed in a prior investigation) was filled by the subjects at the end of each experimental session.

C. Behavioral. 1. The Continuous Performance Test (CPT). The subject was asked to press a button immediately after the appearance of the letter "X" if it was just preceded by an "A" amidst a random sequence of 10 different letters. The trial lasted 5 min with the presentation of approximately 200 stimuli, 25% of which were critical, i.e. an A-X sequence. To increase the difficulty of the CPT, we have reduced the duration of the stimuli to 30 ms ($^1/_3$ of the duration used previously) and the interstimuli interval was randomized between 0.75 to 1.5 s.

2. The Automated Digit Symbol Substitution Test (ADSST). The subject was presented with 10 letters in a serial random sequence; the stimulus duration was 0.2 s. The subject was asked to press the corresponding number-button on a touch tone keyboard according to a code placed next to the stimulus display. A new stimulus followed one second after each response. The code was presented to the subject only during the trial. Each trial lasted 3 min; there were 5 trials, interrupted by 2 min rest periods. A response was classified as "correct" (*C*) when it was according to the code and within 2 s after the appearance of the stimulus. It was "late correct" (*L*) when it occurred more than 2 s after the stimulus (*S*) but still according to the code; it was "incorrect" if it did not correspond to the code or occurred more than four seconds after the stimulus. If a subject pressed twice in response to a stimulus, the second response was considered an "over-push": (O_p). The result of each trial is calculated as the General Index (*GI*). The general index (*GI*) is weighted for both speed and accuracy of performance:

$$GI = (2C + 2S + L) - O_p$$

3. The Test of Memory (TOM) was presented at the end of each ADSST trial. The subject was presented each letter once and asked to press the corresponding code number as he remembered it. A response was scored as correct if it did correspond to the code; the available response time was 4 s. The trial took about 30 s.

4. The Matching Task was administered essentially the same way as the ADSST except that the stimulus was a digit, from 0 to 9. The subject was instructed to press the corresponding identical number on the keyboard. The scoring was the same as for the ADSST.

Procedures

The three treatments were given on separate experimental days. The subjects had been told that on any day any one of the possible

Table 1. Schedule of measurements

Time		Duration
0	Physiological measures (1)	
20 min	Physiological measures (2)	
22 min	CPT	5 min
32 min	Matching Test	23 min
60 min	Physiological measures (3)	
65 min	ADSST and Test of Memory	23 min
90 min	Physiological measures (4)	

Time zero marked the beginning of the observation period. For the baseline measurements, this was the time of the first blood pressure measure; for the post-treatment measurements, this was the end of the smoking. The test session always began between 9.30 and and 10.00 a.m. The duration of each psychomotor test is exact. Between each test, there was a 4-min rest period

drug combinations might be given. Before each session, the subject was interviewed as for his previous night's sleep, drug and food intake, and mood. General appearance and conduct, pupils' size and reactivity, nystagmus, Romberg sign, *BP* and *HR* were recorded. The experiment began if the findings were within normal limits. The subject was seated in the testing room; 30 min were allowed for electrodes placement, equipment checks and adaptation to the laboratory setting. Then the test battery was performed, according to a pre-set schedule (see Table 1).

After completion of the baseline observations, either propranolol (*P*) or placebo propranolol (*plP*) tablets were administered orally with a glass of tap water. Fifty minutes after the propranolol ingestion, the subject was given a cigarette (either placebo or marihuana). Immediately after the completion of smoking, the *BP* and *HR* were taken, the *CI* was rated, and the test battery followed the same order as for the baseline session. At the end of the post drug testing period the subject rated the "high" and its pleasantness and answered the questionnaire. The subject stayed in the laboratory until all objective signs of intoxication had disappeared.

Statistics

An analysis of variance for repeated measures on the same subjects (Keppel, 1973) was used for the physiological measures and the psychomotor tests. The baseline values were subtracted from the corresponding post-treatment values to obtain a difference score for each subject per drug treatment per measurement occasion. The self-rating and the questionnaire each have a single result; the treatments were compared using a one way ANOVA. All graphs show the actual groups means (± S.E.) at the various observation points, without any mathematical transformation.

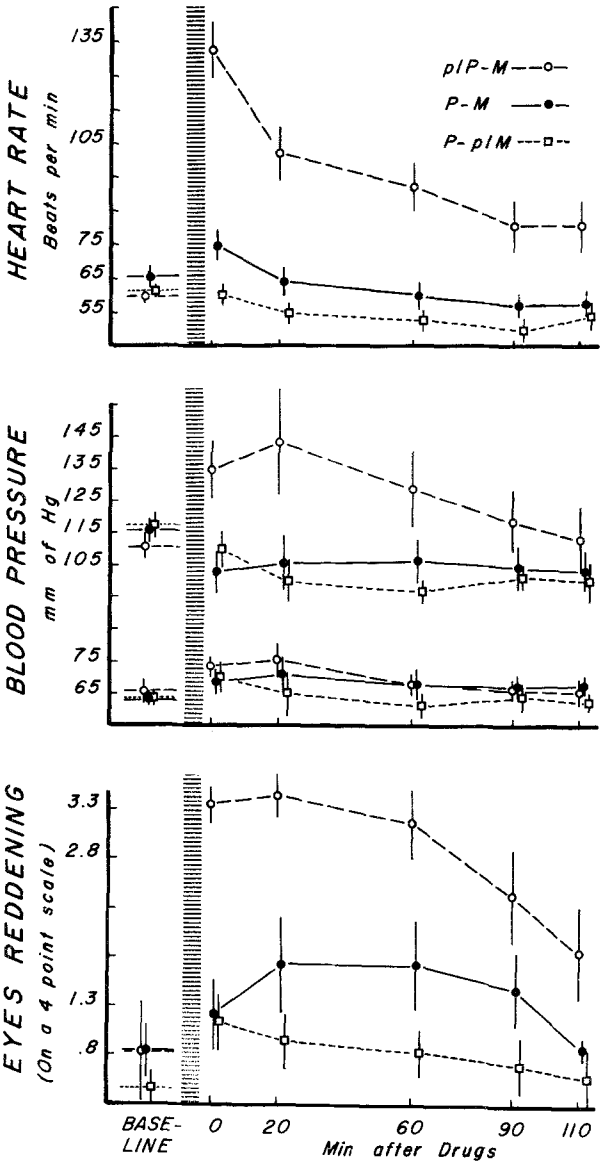

Fig. 1. Physiological effects. The mean ± S.E. are presented for each observation points after the drugs administration. Only the last baseline value is presented since there were no changes during that period. Time is counted from the end of smoking

RESULTS

Physiological effects (Fig. 1 and Table 2). The heart rate was increased significantly after marihuana preceded by the placebo propranolol (*plP-M*); it was lowered consistently by the propranolol and placebo treatment (*P-plM*). After both active medications (*P-M*), there was a small, short-lived but significant increase immediately after smoking. The systolic blood pressure was increased after the *plP-M* treatment and decreased slightly after the *P-plM*; the *P-M* treatment had no significant effect. The conjunctival reddening was clearly observable after the *plP-M* but negligible after the other treatments.

Subjective effects (Fig. 2). The intensity of the intoxication was given the highest rating after the marihuana (*plP-M*) and lowest after the propranolol (*P-plM*); the combined drug treatment (*P-M*) resulted in a intermediary "high" rating. Pleasantness was not significantly different between the three conditions. On the ARCI scales, marihuana smoking (*plP-M*) was associated with increased scores on both the "Mari-

Table 2. Summary of ANOVA on physiological variables (Pre-post scores)

	HR			BP-systolic			BP-diastolic			CI[a]		
	df	*F*	*P*	*df*	*F*	*P*	*df*	*F*	*P*	*df*	*F*	*P*
Source of variance												
Between treatments	2,10	33.15	< 0.001	2,10	16.51	< 0.001	2,10	1.68	NS	2,8	5.76	< 0.05
Between Times	4,20	38.07	< 0.001	4,20	6.90	< 0.005	4,20	5.17	< 0.005	4,16	21.46	< 0.005
Interaction	8,40	18.13	< 0.001	8,40	4.90	< 0.001	8,40	1.01	NS	8,32	2.88	< 0.05
Simple main effect of the interaction												
Treatments:												
P-plM	4,20	3.15	< 0.025	4,20	3.46	< 0.05	Does not apply			4,16	0.76	NS
P-M	4,20	14.52	< 0.001	4,20	0.59	NS				4,16	5.29	< 0.01
plP-M	4,20	36.78	< 0.001	4,20	7.16	< 0.001				4,16	11.18	< 0.001
Measurement time:												
End of Smoking	2,10	48.19	< 0.001	2,10	12.08	< 0.005				2,8	8.41	< 0.025
+20 min	2,10	34.78	< 0.001	2,10	17.15	< 0.001				8	5.74	< 0.05
+60 min	2,10	23.79	< 0.001	2,10	16.51	< 0.001				2,8	5.54	< 0.05
+90 min	2,10	14.51	< 0.005	2,10	13.73	< 0.005				2,8	2.62	NS
+110 min	2,10	16.40	< 0.001	2,10	3.84	NS				2,8	2.82	NS

[a] Conjunctival injection or eyes reddening

Table 3. Summary of the CPT results

Treatment		Errors				Correct Responses	
		Omission		Commission			
		Pre	Post	Pre	Post	Pre	Post
P-plM	$\bar{x}$	10.9	9.5	0	1.0	88.7	87.9
	SD	5.0	6.0	–	1.6	5.5	8.3
P-M	$\bar{x}$	8.4	14.0	1.4	1.6	89.6	82.0
	SD	6.2	5.3	1.7	2.1	5.7	6.0
plP-M	$\bar{x}$	15.1	8.8	1.7	4.5	81.4	84.9
	SD	3.5	4.9	1.9	4.7	4.4	5.3

A 2-way ANOVA (treatments, response class, interaction) on the difference score (Post-Pre) shows no significant differences. (All F's are < 1.0)

Table 4. Summary of ANOVA for the MT, ADSST and TOM

Source of variance		Matching test	ADSST	Memory
Treatments	$F_{2,10}$	0.16 NS	4.77 $P < 0.05$	2.09 NS
Trials	$F_{4,20}$	2.82 NS	1.55 NS	4.33 NS
Treatments × Trials	$F_{8,40}$	0.31 NS	0.58 NS	0.29 NS

The very strong learning effect between trial 1 and 5 (learning curve) was eliminated by subtracting the baseline score from the post-drug score for each corresponding trial. This made the test sensitive to changes in the learning slope ("Trials") due to the treatments, if any; the Test of Memory just fails to reach significance

huana" and the "Depressant" scales. With the combined treatment (*P-M*) the latter was lowered but not the former. The effect of propranolol (*P-plM*) was identical with the effect of a "no-drug" treatment used in another experiment (unpublished data: $N = 6$, mean $\pm$ SD; "Depressant": 14.2 $\pm$ 1.3; "Marihuana" 13.4 $\pm$ 6.2).

Behavioral effects. The CPT (Table 3) was not affected by any of the treatments. The ADSST learning curve (Fig. 3 and Table 4) was lowered by marihuana (*plP-M*) but not by the other treatments. The matching task and the performance on the test of memory were not affected (Fig. 3).

DISCUSSION

The primary purpose of this experiment was to investigate the interaction of propranolol and marihuana. A prerequisite is that each drug, in the dosage used, shows its typical effects when interacting with the placebo preparation of the other.

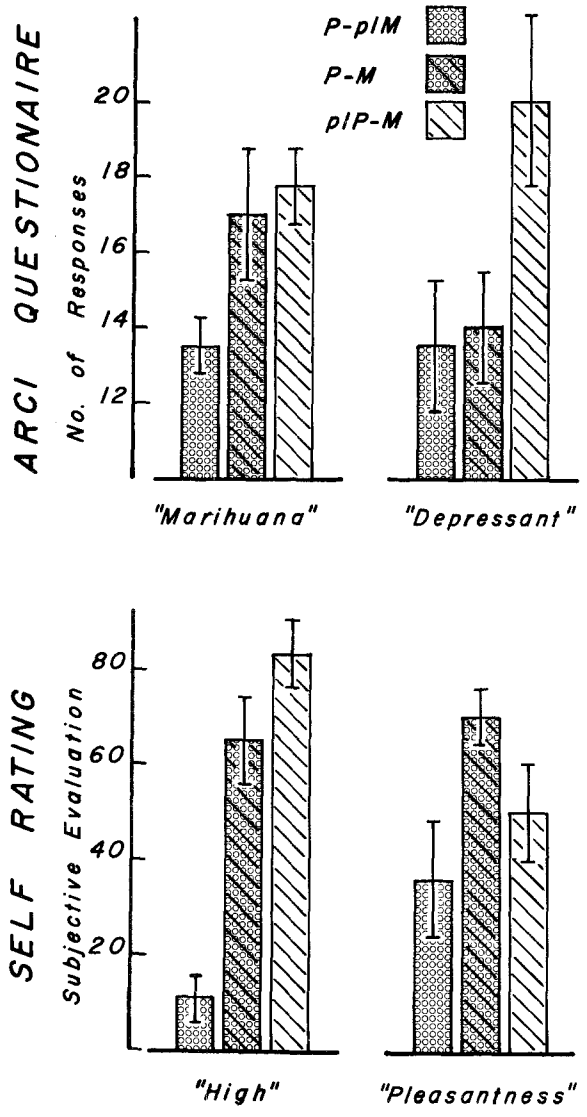

Fig. 2. Subjective effects. The rating and questionnaire were obtained approximately one and a half hour after the end of smoking

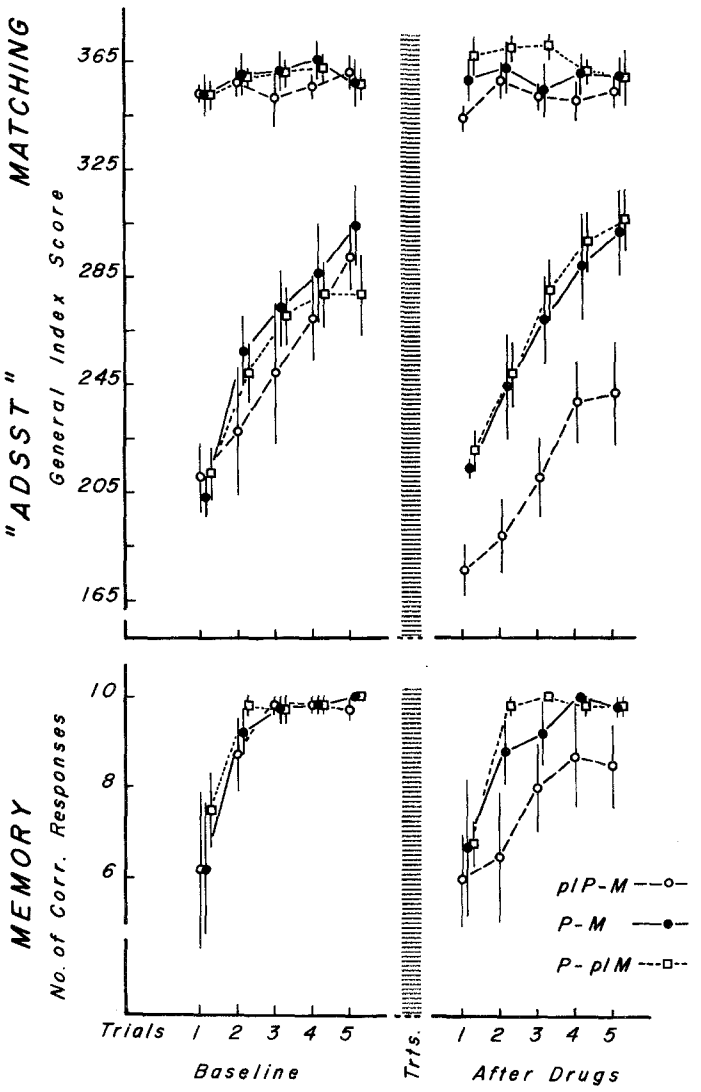

Fig. 3. Psychomotor performance. The effect of *plP-M* stands out on the learning tests

Propranolol-placebo marihuana (*P-plM*). A single oral dose of 120 mg of propranolol, followed by the smoking of placebo marihuana, was effective in producing the classical cardiovascular signs of beta-adrenergic blockade (Nies and Shand, 1975). None of the psychomotor tasks were affected. This would support the reports (Dunleavy et al., 1971; Lader and Tyrer, 1972; Mendelson et al., 1974) that propranolol, in clinical doses, does not show any CNS action. The subjective effects are worth noting: although the cardiovascular signs of beta blockade were unmistakable, the subjects reported no concern nor discomfort. The ratings for the "high" and "pleasantness" are not different from those obtained after placebo marihuana alone (Vachon et al., 1974). The scores on the ARCI questionnaire were identical to those obtained under a "no-drug" condition. It can be concluded that the dose of propranolol was effective: while it had a clear cardiovascular effect, it did not show any manifest central nervous system action nor did it block the psycho-social aspect of the marihuana experience.

Placebo propranolol and marihuana (*plP-M*). The dose of Δ^9-THC, approximately 10 mg, was lower than that which we used before. Nevertheless, the active marihuana cigarette preceded by the placebo propranolol pill, was adequate to induce the cardiovascular changes which are expected after marihuana smoking: definite tachycardia, elevated systolic blood pressure and conjunctival reddening. The psychomotor tests offer a replication and an extension of our previous findings (Vachon et al., 1974). As before, we observed a significant decrease of the learning curve

on the ADSST. This occurred without significant change in the motor speed required for this task, as reflected in the matching task, nor any change in the level of attention, as reflected in the CPT, even though this task had been made more difficult. Finally, the subjective ratings of "high" and "pleasantness" as well as the scores on the "Marihuana" and "Depressant" scales of the ARCI were typical of the acute marihuana intoxication. In short, the dose of marihuana used effectively produced a typical intoxication; the analysis of psychomotor performance shows an impairment predominantly of the responses requiring central information processing and integration with a selective sparing of attention.

Propranolol and marihuana (*P-M*). Propranolol pre-medication had a striking effect. At the dosages used, the cardiovascular effects of the two drugs counter-balanced one another almost completely. On the psychomotor tasks, those unaffected by either drug alone were also unaffected by the combined treatment. Propranolol prevented the marihuana impairment on the learning task. Subjectively, the marihuana "high" after propranolol pre-treatment was slightly lower than after the placebo propranolol pre-treatment; the changes in the "pleasantness" ratings were not significant. On the ARCI, the "Marihuana" scale was unaffected and the "Depressant" scale was significantly reduced. These date indicate that there was still a discernible marihuana effect; propranolol had a major protective action, at a dosage which is clinically silent (for CNS functions) when not challenged pharmacologically.

These findings support the hypothesis that the THC action in the brain may be mediated, in part, through beta-receptors and that propranolol effectively blocks these sites. As we indicated earlier, a beta-adrenergic agonistic mechanism is among the several which have been suggested for THC and propranolol is a powerful beta-blocker. However, this drug has several other actions and when metabolized by the liver it can yield several metabolites which themselves are pharmacologically active (Ishizaki et al., 1974; Saelens et al., 1974). To confirm the hypothesis suggested here will require testing the interaction of marihuana and various dosages of other beta-blocking agents. If this interaction takes place centrally, the effect of marihuana should not be affected when the pre-medication is a beta-blocking agent which does not cross the blood brain barrier, but is should be prevented by a beta-blocking agent which does.

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