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METABOLIC DISPOSITION OF 8-TETRAHYDROCANNABINOL AND ITS ACTIVE 1/0903-0261502.00/0
IBOLISM AND DISPOSITION OF A⁸-TETRAHYDROCANNABINOL AND ITS ACTIVE
METABOLIC DISPOSITION OF A⁸-TETRAHYDROCANNABINOL AND 11-OXO-A⁸-
METABOLITES, 11-HYDROXY-A⁸-TETRAHYDROCANNABINOL AND 11-OXO-A⁸-**IMMOOLOGY And Experimental Therapeutics
ITION OF A⁸-TETRAHYDROCANNABINOL AN
IYDROXY-A⁸-TETRAHYDROCANNABINOL AN
TETRAHYDROCANNABINOL, IN MICE TETRAHYDROCANNABINOL, IN MICE
KAZUHITO WATANABE, IKUO YAMAMOTO, KAZUTA OGURI, AND HIDETOSHI YOSHIMURA**

MAMOTO, KAZUTA OGURI
I.Y.) and Faculty of Pharmaceu
(Received October 13, 1980)

SCHOOL OF A READ IS A READ ON THE CORRECT ON A READ ON A READ ON A READ TO SHIMURA
School of Pharmacy, Hokuriku University (K. W., I. Y.) and Faculty of Pharmaceutical Sciences, Kyushu University (K.O., H. Y.)

ABSTRACT:

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**Metabolic disposition of Δ^s-tetrahydrocannabinol (Δ^s-THC), 11-hy- than
droxy-Δ^s-THC (11-OH-Δ^s-THC), and 11-oxo-Δ^s-THC was studied in these
mouse blood, liver, and brain. After administration of thes ABSTRACT:**
Metabolic disposition of Δ⁸-tetrahydrocannabinol (Δ⁸-THC), 11-h
droxy-Δ⁸-THC (11-OH-Δ⁸-THC), and 11-oxo-Δ⁸-THC was studied
mouse blood, liver, and brain. After administration of these cann
binoids at **binding at a dose of deterministic at a dose of A°-tetrahydrocannabinoi (** Δ^6 **-THC), 11-hy-
droxy-** Δ^6 **-THC (11-OH-** Δ^6 **-THC), and 11-oxo-** Δ^6 **-THC was studied in thes
mouse blood, liver, and brain. After administrati Metabolic disposition of** Δ^n **-tetrahydrocannabinol (** Δ^n **-THC), 11-hy-** thadroxy- Δ^0 -THC (11-OH- Δ^0 -THC), and 11-oxo- Δ^0 -THC was studied in the mouse blood, liver, and brain. After administration of these canna droxy-Δ°-THC (11-OH-Δ°-THC), and 11-oxo-Δ°-THC was studied in
mouse blood, liver, and brain. After administration of these canna-
binoids at a dose of 10 mg/kg iv, the concentration in blood
declined biphasically. The bio mouse blood, liver, and brain. After administration of these canna-
binoids at a dose of 10 mg/kg iv, the concentration in blood fou
declined biphasically. The biological half-lives of the slower phases mili
were 32, 12, binoids at a dose of 10 mg/kg iv, the concentration in blood
declined biphasically. The biological half-lives of the slower phases
were 32, 12, and 6 min, respectively, for Δ^ε-THC, 11-OH-Δ^ε-THC,
and 11-oxo-Δ^ε-THC. 1 **oxo-8-THC in brain were, however, however, however, however, hadded the fraction brain than is** Δ^8 **-THC. The peak levels of 11-OH- and 11-oxo-** Δ^8 **-THC in brain than is** Δ^8 **-THC. The peak levels of 11-OH- and 11-oxo**and 11-oxo- Δ^6 -THC. 11-OH- and 11-oxo- Δ^6 -THC were also eliminated oxo- Δ^8 -THC. The results suggest that 11-OH- Δ^6 -THC may play an faster from brain than is Δ^6 -THC. The peak levels of 11-OH- and 11-
oxo- $\$ **and 11-οxo-Δ"-THC. 11-OH- and 11-οxo-Δ"-THC were also eliminated**
faster from brain than is Δ"-THC. The peak levels of 11-OH- and 11- is
oxo-Δ"-THC in brain were, however, higher (10.64 and 4.25 μg/g, ε
respectively) t **faster from brain than is Δ°-THC. The peak levels of 11-OH- and 11-** impoxo-Δ^a-THC in brain were, however, higher (10.64 and 4.25 μg/g, add respectively) than that of Δ^a-THC (3.48 μg/g) at 0.5 min after the iv metinj

than is **8-THC, and explain the greater pharmacological activity of** than is ∆^s-THC, and explain the greater pharmacological activity of
these metabolites, as reported previously. It was also interesting to
note that a much higher level of 11-OH-∆^s-THC (3.27 _{M3}/g) was than is ∆^s-THC, and explain the greater pharmacological activity of
these metabolites, as reported previously. It was also interesting to
note that a much higher level of 11-OH-∆^s-THC (3.27 µg/g) was
found in brain tha than is Δ^s-THC, and explain the greater pharmacological activity of
these metabolites, as reported previously. It was also interesting to
note that a much higher level of 11-OH-Δ^s-THC (3.27 μg/g) was
found in brain th these metabolites, as reported previously. It was also interesting to note that a much higher level of 11-OH- Δ^2 -THC (3.27 μ g/g) was
found in brain than in liver (0.74 μ g/g) and blood (0.29 μ g/ml) at 15
min af these metabolites, as reported previously. It was also interesting to
note that a much higher level of 11-OH-Δ⁸-THC (3.27 μg/g) was
found in brain than in liver (0.74 μg/g) and blood (0.29 μg/ml) at 15
min after the inj note that a much higher level of 11-0H-Δ"-THC (3.27 μg/g) was
found in brain than in liver (0.74 μg/g) and blood (0.29 μg/ml) at 15
min after the injection of 11-oxo-Δ⁸-THC (10 mg/kg, iv). In this case
the levels of 11found in brain than in liver (0.74 µg/g) and blood (0.29 µg/ml) at 15
min after the injection of 11-oxo- Δ^2 -THC (10 mg/kg, iv). In this case
the levels of 11-OH- Δ^2 -THC were always higher than those of 11-
oxo- Δ^2 min after the injection of 11-oxo-A"-THC (10 mg/kg, iv). In this case
the levels of 11-OH-A"-THC were always higher than those of 11-
oxo-A"-THC. The results suggest that 11-OH-A"-THC may play an
important role in the phar oxo-A⁸-THC. The results suggest that 11-OH-A⁸-THC may play an important role in the pharmacological effects of 11-oxo- Δ^2 -THC. In additional experiments, SKF 525-A (25 mg/kg, ip) inhibited the metabolism of 11-OH- Δ^2 -THC to 11-oxo- Δ^2 -THC, supporting the previous suggestion additional experiments, SKF 525-A (25 mg/kg, ip) inhibited the

 σ - Δ ⁸-THC are distributed more readily from blood to brain in mice

The metabolism of Δ ⁸-THC¹ or Δ ⁹-THC, the active componen

marihuana, has been investigated by a number of groups (1–5) The metabolism of Δ^8 -THC¹ or Δ^8 -THC, the active component of marihuana, has been investigated by a number of groups (1–5).
They suggested that the oxidation at 11-position (fig. 1) is very The metabolism of Δ^8 -THC¹ or Δ^9 -THC, the active component in of marihuana, has been investigated by a number of groups (1–5). Further oxidation at 11-position (fig. 1) is very disimportant, because it is a major The metabolism of Δ^8 -THC¹ or Δ^9 -THC, the active component in of marihuana, has been investigated by a number of groups (1–5). Furthey suggested that the oxidation at 11-position (fig. 1) is very distimportant, b Incertations of Δ -1 HC of Δ -1 HC, the active component
of marihuana, has been investigated by a number of groups (1-5).
They suggested that the oxidation at 11-position (fig. 1) is very
important, because it is a ma of marinuana, has been investigated by a number of groups $(1-5)$. They suggested that the oxidation at 11-position (fig. 1) is very dimportant, because it is a major metabolite pathway of THC in mammals (6-10). The 11-hy They suggested that the oxidation at 11-position (rig. 1) is very
important, because it is a major metabolic pathway of THC in
mammals (6–10). The 11-hydroxy metabolite was first identified
as a major metabolite of THC, an mportant, oecause it is a major metabolic pathway of $1 \text{R} \text{C}$ m
mammals (6–10). The 11-hydroxy metabolite was first identified
as a major metabolite of THC, and the pharmacological activity
of this metabolite was the as a major metabolite of THC, and the pharmacological activity
of this metabolite was then demonstrated by several workers (11-
ments. The animals were allowed to take food and water *ad lib.*, and room
16). Recently, we rapid in onset than those of Δ^8 -THC (17, 18). These results suggest that the metabolites may be more active than the parent comof this inetabolite was then demonstrated by several workers (114). Recently, we also reported that the pharmacological effects of 11-OH- and 11-oxo- Δ^8 -THC were greater in potency and more rapid in onset than those of 10). Recently, we also reported that the pharmacological effects of
11-OH- and 11-oxo- Δ^8 -THC were greater in potency and more
rapid in onset than those of Δ^8 -THC (17, 18). These results suggest
that the metabolite **Example 11-OH-** and 11-OXO- Δ -1 HC were greater in potency and more

rapid in onset than those of Δ^8 -THC (17, 18). These results suggest

that the metabolites may be more active than the parent com-

pound. In conn rapid in onset than those of Δ -1 HC (17, 16). These results suggest
that the metabolites may be more active than the parent com-
pound. In connection with these pharmacological findings, Schou
et al. (19) reported that that the metabolites may be more active than the parent com-
pound. In connection with these pharmacological findings, Schou
et al. (19) reported that the penetration of 11-OH- Δ^2 -THC into
brain was faster than that of et al. (19) reported that the penetration of 11-OH- Δ^9 -THC into
body weight. Cannabinoids were injected between 9 and 12 a.m. in all
brain was faster than that of Δ^9 -THC after intracarotid injection
in rats. Perezer al. (19) reported that the penetration of 11-OH- Δ^2 -THC into brain was faster than that of Δ^2 -THC after intracarotid injection
in rats. Perez-Reyes *et al.* (20) also found that the brain levels of
11-OH- Δ^2 brain was faster than that of Δ -1 Fic. after infractation injection
in rats. Perez-Reyes *et al.* (20) also found that the brain levels of
11-OH- Δ^9 -THC were four times higher than those of Δ^9 -THC is
mice. On t In rats. Ferez-Reyes et al. (20) also found that the brain levels of $[1-OH-A^9-THC]$ were four times higher than those of Δ^9-THC in basis shorter than that of Δ^9-THC in man, although both compounds were equally potent (1 IT-OH- Δ - I HC were four times inguer than those of Δ - I HC in
mice. On the contrary, the duration of effect of 11-OH- Δ ⁹-THC
was shorter than that of Δ ⁹-THC in man, although both com-
pounds were equally mice. On the contrary, the duration
was shorter than that of Δ^9 -THC
pounds were equally potent (15).
OH- Δ^9 -THC is metabolized or elimi
system more quickly than Δ^9 -THC.
It is thus of interest to study the It is thus of interest to study the penetration and retention in
Al-A⁹-THC is metabolized or eliminated from the central nervous and
tem more quickly than Δ^9 -THC.
It is thus of interest to study the penetration and

brain of mice of those active metabolized or eliminated from the central nervous
system more quickly than Δ^9 -THC.
It is thus of interest to study the penetration and retention in
brain of mice of those active metaboli Bystem more quickly than Δ -1 FrC.
It is thus of interest to study the penetration and retention in
brain of mice of those active metabolites in comparison with those
of Δ^8 -THC for understanding of the pharmacologi It is thus of interest to study the penetration and retention in
brain of mice of those active metabolites in comparison with those
of Δ^8 -THC for understanding of the pharmacological activity of
 Δ^8 -THC. In the pre brain of mice of those active metabolities in comparison with those
of Δ^8 -THC for understanding of the pharmacological activity of
 Δ^8 -THC. In the present paper, we wish to report the detailed
metabolic disposition etabolic disposition of Δ^8 -THC, 11-OH- Δ^8 -THC, 11-oxo-HC, and Δ^8 -THC-11-oic acid in mouse blood, brain, and liverty are: THC, tetrahydrocannabinol; 11-OH-THC, 11-hydrox-trahydrocannabinol; ECD, electron-capture

Abbreviations used are: THC, tetrahydrocannabinol; 11-OH-THC, 11-hydrocannabinol; ECD, electron-capture detector.
Send reprint requests to: Dr. H. Yoshimura, Faculty of Pharmaceutical reprint requests to: Dr. H. Yoshimura, THC, and Δ^o -THC-11-oic acid in mouse bloot

'Abbreviations used are: THC, tetrahydrocannabinol;

ytetrahydrocannabinol; ECD, electron-capture detector.

of Δ^a -THC, is mediated by the microsomal mono-oxygenase system.
in order to understand the pharmacological effect of Δ^b -THC.
Furthermore, the effect of SKF 525-A on the metabolism and in order to understand the pharmacological effect of Δ^8 -THC.
Furthermore, the effect of SKF 525-A on the metabolism and distribution of these active intermediates was studied. in order to understand the pharmacological effect of Furthermore, the effect of SKF 525-A on the metal distribution of these active intermediates was studied. d the pharmacological
ct of SKF 525-A on the
ctive intermediates was :
Materials and Methods
ning 20–25 g were used the

OH- Δ^8 -THC is metabolized or eliminated from the central nervous
system more quickly than Δ^8 -THC.
It is thus of interest to study the penetration and retention in
brain of mice of those active metabolites in compar Irthermore, the errect of SKF 323-A on the metabolism and stribution of these active intermediates was studied.
 Materials and Methods

Male ddN mice weighing 20-25 g were used throughout the experiants. The animals were distribution of these active intermediates was studied.

Materials and Methods

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ments. The animals were allowed to take food and water *ad lib.*, and room

t **Materials and Methods**
Male ddN mice weighing 20–25 g were used throughout the experi-
ments. The animals were allowed to take food and water *ad lib.*, and room
temperature was set at 22-24°C. Δ^8 -THC, 11-OH- Δ^8 -T Male ddN mice weighing 20-25 g were used throughout the experiments. The animals were allowed to take food and water *ad lib.*, and room temperature was set at 22-24°C. Δ^6 -THC, 11-OH- Δ^6 -THC, 11-oxo- Δ^6 -THC, and Male ddN mice weighing 20-25 g were used throughout the experiments. The animals were allowed to take food and water *ad lib.*, and room temperature was set at 22-24°C. Δ^6 -THC, 11-OH- Δ^6 -THC, 11-oxo- Δ^6 -THC, and temperature was set at 22-24°C. Δ^8 -THC, 11-OH- Δ^8 -THC, 11-oxo- Δ^8 -THC, and Δ^8 -THC-11-oic acid were prepared by the methods reported previously (17). Each of the cannabinoids except for Δ^8 -THC-11-oic acid temperature was set at 22-24°C. Δ^8 -THC, 11-OH- Δ^8 -THC, 11-oxo- Δ^8 -THC, and Δ^8 -THC-11-oic acid were prepared by the methods reported previously (17). Each of the cannabinoids except for Δ^8 -THC-11-oic acid THC, and Δ^8 -THC-11-oic acid were prepared by the methods reported
previously (17). Each of the cannabinoids except for Δ^8 -THC-11-oic acid
was suspended in saline containing 1% Tween 80 and injected iv into mice
(1 previously (17). Each of the cannabinoids except for Δ^8 -THC-11-oic acid was suspended in saline containing 1% Tween 80 and injected iv into mice (1, 5, and 10 mg/kg) through the tail vein, over a period of 3 sec. Each was suspended in saline containing 1% Tween 80 and injected iv into mice (1, 5, and 10 mg/kg) through the tail vein, over a period of 3 sec. Each group consisted of four mice and the injection volume was 0.1 ml/10 g of bod (1, 5, and 10 mg/kg) through the tail vein, over a period of 3 sec. Each
group consisted of four mice and the injection volume was $0.1 \text{ mI}/10 \text{ g}$ of
body weight. Cannabinoids were injected between 9 and 12 a.m. in all group consisted of four mice and the injection volume was 0.1 ml/10 g of body weight. Cannabinoids were injected between 9 and 12 a.m. in all experiments. SKF 525-A, a generous gift of Smith Kline & French Labs. (Philadelp body weight. Cannabinoids were injected between 9 and 12 a.m. in all experiments. SKF 525-A, a generous gift of Smith Kline & French Labs. (Philadelphia, Pa.), was administered at a dose of 25 mg/kg ip 30 min before the in experiments. SKF 525-A, a generous gift of Smith Kline & French Labs.
(Philadelphia, Pa.), was administered at a dose of 25 mg/kg ip 30 min
before the injection of cannabinoids. Mice were killed by cervical fracture
at 0. (Philadelphia, Pa.), was administered at a dose of 25 mg/kg ip 30 minus before the injection of cannabinoids. Mice were killed by cervical fractuat 0.5, 1, 5, 15, 30, and 60 min after the injection. Blood was quick collec before the injection of cannabinoids. Mice were killed by cervical fractuat 0.5, 1, 5, 15, 30, and 60 min after the injection. Blood was quickle collected by cardiac puncture and brain and liver were then removed. Δ THC at 0.5, 1, 5, 15, 30, and 60 min after the injection. Blood was quickly collected by cardiac puncture and brain and liver were then removed. Δ^6 -THC and its metabolites were quantitated by ECD-gas chromatography, after collected by cardiac puncture and brain and liver were then removed. $\Delta^{\hat{e}}$ -
THC and its metabolites were quantitated by ECD-gas chromatography,
after extraction with acetone, purification by thin-layer chromatography THC and its metabolites were quantitated by ECD-gas chromatography,
after extraction with acetone, purification by thin-layer chromatography,
and conversion to the corresponding heptafluorobutyrates as described
previousl after extraction with acetone, purification by thin-layer chromatography, and conversion to the corresponding heptafluorobuty
rates as described previously (21). Gas chromatograms were recorded with a Shimadzu model GC-6A and conversion to the corresponding heptafluorobutyrates as described
previously (21). Gas chromatograms were recorded with a Shimadzu
model GC-6A gas chromatograph equipped with a ⁶⁵Ni-ECD at 195°C. A
glass column, 1.0 previously (21). Gas chromatograms were recorded with a Shimadzu model GC-6A gas chromatograph equipped with a ${}^{68}\text{Ni-ECD}$ at 195°C. A glass column, 1.0 m × 3 mm, packed with 1% XE-60 on Chromosorb W, 60–80 mesh, was u model GC-6A gas chromatograph equipped with a 68 Ni-ECD at 195°C. A glass column, 1.0 m × 3 mm, packed with 1% XE-60 on Chromosorb W, 60–80 mesh, was used. Nitrogen was used as the carrier gas with a flow rate of 60 ml glass column, 1.0 m × 3 mm, packed with 1% XE-60 on Chromosorb W, 60–80 mesh, was used. Nitrogen was used as the carrier gas with a flow rate of 60 ml/min. The retention times of the heptafluorobutyrates of Δ^8 -THC, 11 60–80 mesh, was under a following a state of 60 ml/min.
THC, 11-OH- Δ^{6} -T
ester were 2.3, 4.2
described above.

Results

er were 2.3, 4.2, 5.8, and 6.8 min, respectively, under the conditions

Elimination of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-Oxo- Δ^8 -THC

om Blood. After iv injection of Δ^8 -THC, 11-OH- Δ^8 -THC, or 11-**Results**
Elimination of Δ^6 **-THC, 11-OH-** Δ^6 **-THC, and 11-Oxo-** Δ^6 **-THC
from Blood. After iv injection of** Δ^6 **-THC, 11-OH-** Δ^6 **-THC, or 11-
oxo-** Δ^6 **-THC at doses of 10 mg/kg, the concentration of these Results**
Climination of Δ^8 **-THC, 11-OH-** Δ^8 **-THC, and 11-Oxo-** Δ^8 **-THC
from Blood. After iv injection of** Δ^8 **-THC, 11-OH-** Δ^8 **-THC, or 11-
oxo-** Δ^8 **-THC at doses of 10 mg/kg, the concentration of these**

vetrahydrocannabinol; ECD, electron-capture detector.

Send reprint requests to: Dr. H. Yoshimura, Faculty of Pharmaceutical

Sciences. Kyushu University. Fukuoka 812. Japan.

WATANABI
compounds in blood declined rapidly within the first few minutes
and slowly thereafter (fig. 2). The half-life of the rapid phase was WATANABE
compounds in blood declined rapidly within the first few minutes
and slowly thereafter (fig. 2). The half-life of the rapid phase was C
about 0.5 min for all these cannabinoids, whereas those of the a WATANABE *I*
compounds in blood declined rapidly within the first few minutes
and slowly thereafter (fig. 2). The half-life of the rapid phase was O
about 0.5 min for all these cannabinoids, whereas those of the ab
slow ph compounds in blood declined rapidly within the first few minutes
and slowly thereafter (fig. 2). The half-life of the rapid phase was O
about 0.5 min for all these cannabinoids, whereas those of the als
low phase were 32, compounds in olood declined rapidly within the first rew infinites
and slowly thereafter (fig. 2). The half-life of the rapid phase was
about 0.5 min for all these cannabinoids, whereas those of the
about 0.5 min for all and slowly therefailed (iig. 2). The hand-life of the rapid phase w
about 0.5 min for all these cannabinoids, whereas those of the
slow phase were 32, 12, and 6 min, respectively, for Δ^8 -THC, 1
OH- Δ^8 -THC, and 11-o about 0.5 him for an these cannaomed
slow phase were 32, 12, and 6 min, resp
OH-Δ⁸-THC, and 11-oxo-Δ⁸-THC. The
elimination rate from blood of mice dec
Δ⁸-THC > 11-OH-Δ⁸-THC > Δ⁸-THC.

(1), Δ^8 -THC; (2), 11-OH- Δ^8 -THC; (3), 11-oxo- Δ^8 -THC; (4), Δ^8 -THC-11-
oic acid.

FT AL.
Penetration and Retention of Δ⁸-THC, 11-OH-Δ⁸-THC, and 11-
κο-Δ⁸-THC in Brain. In the same group of animals used in the ET AL.
Penetration and Retention of Δ^8 **-THC, 11-OH-** Δ^8 **-THC, and 11-
Oxo-** Δ^8 **-THC in Brain. In the same group of animals used in the
above experiments, the contents of unchanged cannabinoids in** ET AL.

Penetration and Retention of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-

Oxo- Δ^8 -THC in Brain. In the same group of animals used in the

above experiments, the contents of unchanged cannabinoids in

the brain were a **Penetration and Retention of** Δ^6 **-THC, 11-OH-** Δ^6 **-THC, and 11-Oxo-** Δ^6 **-THC in Brain. In the same group of animals used in the above experiments, the contents of unchanged cannabinoids in the brain were also determi** injections. As indicated in table 1, i8-THC, ll-OH-8-THC, and DAV-A8-THC in Brain. In the same group of animals used in the
above experiments, the contents of unchanged cannabinoids in
the brain were also determined at the same time intervals after the
injections. As indicated in ta above experiments, the contents of unchanged cannaomolos in
the brain were also determined at the same time intervals after the
injections. As indicated in table 1, Δ^8 -THC, 11-OH- Δ^8 -THC, and
11-oxo- Δ^8 -THC pene injections. As indicated in table 1, Δ^8 -THC, 11-OH- Δ^8 -THC, and
11-oxo- Δ^8 -THC penetrated the brain rapidly, and their peak levels
were attained within 0.5 min after the iv injection. It is very
interesting to n three times higher than those is Δ^2 -THC, in-Ori- Δ^2 -THC, and 11 -oxo- Δ^8 -THC penetrated the brain rapidly, and their peak levels
were attained within 0.5 min after the iv injection. It is very
interesting to no were attained within 0.5 min after the iv injection. It is very
interesting to note that the brain levels of 11-OH- Δ^8 -THC were
three times higher than those of Δ^8 -THC, whereas the blood levels
of 11-OH- Δ^8 -THC The attained within 0.9 mm after the tv injection. It is very deresting to note that the brain levels of $11-OH-\Delta^8-THC$ were times higher than those of Δ^8-THC , whereas the blood levels 11-OH- Δ^8-THC were lower than those

three times higher than those of Δ^8 -THC, whereas the blood levels
of 11-OH- Δ^8 -THC were lower than those of Δ^8 -THC.
Table 2 shows the brain/blood ratio of the concentration of
cannabinoids at several time inter three times inglier than those of Δ -1 FrC, whereas the blood levels
of 11-OH- Δ ⁸-THC were lower than those of Δ ⁸-THC.
Table 2 shows the brain/blood ratio of the concentration of
cannabinoids at several time i Table 2 shows the brain/blood ratio of the concentration of cannabinoids at several time intervals after the iv injection. The result indicates that the ratios rose markedly with time because of a slower elimination of th rative 2 shows a cannabinoids at sensult indicates that
a slower elimination of Δ
Penetration of Δ miability at several time intervals after the *N* injection. The
sult indicates that the ratios rose markedly with time because of
slower elimination of these cannabinoids from the brain than
ose from blood.
Penetration o

those from blood.
 Penetration of Δ^8 **-THC, 11-OH-** Δ^8 **-THC, and 11-Oxo-** Δ^8 **-THC

into Brain at Different Doses.** Higher levels of 11-OH- Δ^8 -THC in

brain were also found 5 min after the iv injection of doses of and 11-Oxo- Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-Oxo- Δ^8 -THC
into Brain at Different Doses. Higher levels of 11-OH- Δ^8 -THC in
brain were also found 5 min after the iv injection of doses of 1, 5,
and 10 mg/kg as compa **FERENTATION OF A -1 FIC., 11-OFI-A -1 FIC., and 11-OXO-A -1 FIC.**

Into Brain at Different Doses. Higher levels of 11-OH- Δ^8 -THC in

brain were also found 5 min after the iv injection of doses of 1, 5,

and 10 mg/kg a muo brain at Durerent Doses. Figher levels of 11-OH- Δ -1 FIC in brain were also found 5 min after the iv injection of doses of 1, 5, and 10 mg/kg as compared with those of Δ^8 -THC and 11-Oxo- Δ^8 -THC (fig. 3). On orain were also a
and 10 mg/kg as
THC (fig. 3). O
THC was lower
same experimen
Disposition of THC (fig. 3). On the other hand, the blood level of 11 -oxo- Δ^8 -THC was lower than those of Δ^8 -THC and 11 -OH- Δ^8 -THC in the same experiment.

Disposition of Δ^8 -THC and Its Metabolites in Liver, Blood, and
 T_{ABTE} 2

Each value represents the mean for four mice.

injection at different doses of Δ^8 -THC and its metabolites. **Each point represents the mean** $\log A$ **.** Thus and blood levels of unchanged compounds at 5 min after the injection at different doses of Δ^8 -THC and its metabolites.
Each point represents the mean \pm SE for four mice. FIG. 3. *Brain and blood levels a*
injection at different dos
Each point represents the mea
OH- Δ^8 -THC; **B**, 11-oxo- Δ^8 -THC

₋₉
Each poi
OH-Δ⁸-TH
TABLE 1
*TC, 11-OH-*Δ⁸-*TH*

	injected		тнс	тнс	oic Acid
		µg/g			
Liver	Δ^8 -THC	1.31 ± 0.13	3.62 ± 0.26	0.07 ± 0.01	3.82 ± 0.22
	11 -OH- Δ ⁸ -THC		4.58 ± 1.65	0.14 ± 0.01	6.46 ± 0.56
	11 -Oxo- Δ^8 -THC		0.74 ± 0.07	0.46 ± 0.05	12.00 ± 2.22
		μ g/ml			
Blood	Δ^8 -THC	1.19 ± 0.10	0.28 ± 0.04	< 0.01	0.68 ± 0.02
	11 -OH- Δ ⁸ -THC		0.87 ± 0.10	0.01 ± 0.00	1.26 ± 0.22
	11 -Oxo- Δ^8 -THC		0.29 ± 0.04	0.13 ± 0.02	1.93 ± 0.25
		μ g/g			
Brain	Δ^8 -THC	2.95 ± 0.15	0.89 ± 0.06	< 0.01	0.25 ± 0.03
	11 -OH- Δ ⁸ -THC		8.39 ± 0.75	0.03 ± 0.03	0.48 ± 0.04
	11 -Oxo- Δ^8 -THC		3.27 ± 0.23	2.99 ± 0.29	0.87 ± 0.09

TABLE 4
Effect of SKF 525-A on the metabolic disposition of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-oxo- Δ^8 -THC in mouse liver and brain
specialized 15 min ofter the injection of connectionishs (10 ms (ke, in). The sexult Animals were killed 15 min after the injection of cannabinoids (10 mg/kg, iv). The results are expressed as means \pm SE for four mice. *N. D.*, not detected. If SKF 525-A on the metabolic disposition of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-oxo- Δ^8 -THC in mouse liver and brain

15 min after the injection of cannabinoids (10 mg/kg, iv). The results are expressed as means \pm

* Significantly different ($p < 0.05$) from respective control (Student's t-test).

^{**} Significantly different ($p < 0.01$) from respective control (Student's t-test).

** Significantly different ($p < 0.01$) from respective control (Student's t-tes
Brain. As summarized in table 3, 15 min after the iv injection of a
 Δ^8 -THC (10 mg/kg), a higher level of its metabolite, 11-OH- Δ^8 -**Brain.** As summarized in table 3, 15 min after the iv injection of Δ^8 -THC (10 mg/kg), a higher level of its metabolite, 11-OH- Δ^8 -THC, was found in the liver as compared with the level in the **Brain.** As summarized in table 3, 15 min after the iv injection of af Δ^8 -THC (10 mg/kg), a higher level of its metabolite, 11-OH- Δ^8 -
THC, was found in the liver as compared with the level in the Tibrain and blood **Brain.** As summarized in table 3, 15 min after the iv injection of Δ^8 -THC (10 mg/kg), a higher level of its metabolite, 11-OH- Δ^8 -THC, was found in the liver as compared with the level in the brain and blood. 11-O Δ^8 -THC (10 mg/kg), a higher level of its metabolite, 11-OH- Δ^8 - the liver and blood (table 3). Furthermore, the level of 11-OH- Δ^8 -THC, was found in the liver as compared with the level in the THC (3.27 μ g/g) THC, was found in the liver as compared with the level in the brain and blood. 11-Oxo- Δ^8 -THC was also found as a metabolite of Δ^8 -THC and 11-OH- Δ^8 -THC, but the content was very low in the liver in contrast to brain and blood. 11-Oxo- Δ^8 -THC was also found as a metabolite
of Δ^8 -THC and 11-OH- Δ^8 -THC, but the content was very low in
the liver in contrast to a high level of Δ^8 -THC-11-oic acid. Table
3 further shows orain and blood. 11-Oxo-A⁻-1 HC was also found as a metabolite
of Δ^8 -THC and 11-OH- Δ^8 -THC, but the content was very low in
the liver in contrast to a high level of Δ^8 -THC-11-oic acid. Table 1
3 further shows or Δ -1 HC and 11-OH- Δ -1 HC, but the content was very low in
the liver in contrast to a high level of Δ^8 -THC-11-oic acid. Table 7
3 further shows that 11-oxo- Δ^8 -THC was partially reduced to 11-
OH- Δ^8 -TH mice. H- Δ^8 -THC, although a main metabolic route of 11-oxo- Δ^8 -THC
H- Δ^8 -THC, although a main metabolic route of 11-oxo- Δ^8 -THC
peared to be oxidation to Δ^8 -THC-11-oic acid in the liver of
ice.
As shown above, t

ori- Δ -1 HC, annough a main metabolic route of 11-oxo- Δ -1 F
appeared to be oxidation to Δ^8 -THC-11-oic acid in the liver
mice.
As shown above, the elimination of 11-OH- and 11-oxo-4
THC is faster than that of $\Delta^$ appeared to be oxidation to Δ -1 HC-11-oic actd in the liver of mice.
As shown above, the elimination of 11-OH- and 11-oxo- Δ^8 -THC is faster than that of Δ^8 -THC. A small amount of 11-oxo- Δ^8 -THC (0.01 μ g/m As shown above, the elimination of 11-OH- and 11-oxo- Δ^8 -
THC is faster than that of Δ^8 -THC. A small amount of 11-oxo- Δ^8 -THC (0.01 μ g/ml) was found in the blood of mice 15 min after the iv injection of 11-OH As shown above, the elimination of 11-OH- and 11-OXO- Δ^2 -THC is faster than that of Δ^8 -THC. A small amount of 11-OXO- Δ^8 -THC (0.01 μ g/ml) was found in the blood of mice 15 min after the iv injection of 11-OH-

st).
after the iv injection of 11-oxo-Δ⁸-THC (10 mg/kg) than those in
the liver and blood (table 3). Furthermore, the level of 11-OH-Δ⁸after the iv injection of 11-oxo- Δ^8 -THC (10 mg/kg) than those in
the liver and blood (table 3). Furthermore, the level of 11-OH- Δ^8 -
THC (3.27 μ g/g) was significantly higher as compared with that after the iv injection of 11-oxo- Δ^8 -THC (10 mg/kg) than those in
the liver and blood (table 3). Furthermore, the level of 11-OH- Δ^8 -
THC (3.27 μ g/g) was significantly higher as compared with that
of Δ^8 -THC-1 after the iv injection of 11-oxo- Δ^8 -THC (10 mg/kg) than those in
the liver and blood (table 3). Furthermore, the level of 11-OH- Δ^8 -
THC (3.27 μ g/g) was significantly higher as compared with that
of Δ^8 -THC-1 arier the iv injection of 11-oxo- Δ^2 -1 HC (10 mg/kg) than those in
the liver and blood (table 3). Furthermore, the level of 11-OH- Δ^8 -
THC (3.27 μ g/g) was significantly higher as compared with that
of Δ^8 -THCthe liver and blood (table
THC $(3.27 \mu g/g)$ was sig
of Δ^8 -THC-11-oic acid (0
 Δ^8 -THC-11-oic acid was
THC in liver and blood.
Effect of SKF 525-A on

THC is faster than that of Δ^8 -THC. A small amount of 11-oxo-
 Δ^8 -THC in the liver was also increased significantly. Table
 Δ^8 -THC (0.01 µg/ml) was found in the blood of mice 15 min after 4 further shows that S Effect of SKF 525-A on the Metabolism of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-Oxo- Δ^8 -THC at the 11-Position. Pretreatment of mice with SKF 525-A (25 mg/kg, ip) resulted in a significant Δ -1 HC-11-oic acid was a predominant metabolite of 11-oxo- Δ ⁻.
THC in liver and blood.
Effect of SKF 525-A on the Metabolism of Δ^8 -THC, 11-OH- Δ^8 .
THC, and 11-Oxo- Δ^8 -THC at the 11-Position. Pretreatment I HC in liver and blood.

Effect of SKF 525-A on the Metabolism of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-Oxo- Δ^8 -THC at the 11-Position. Pretreatment of mice with SKF 525-A (25 mg/kg, ip) resulted in a significant incre Effect of SAF 525-A on the Metabolism of Δ^{-1} HC, 11-OH- Δ^{-1}
THC, and 11-Oxo- Δ^{8} -THC at the 11-Position. Pretreatment of
mice with SKF 525-A (25 mg/kg, ip) resulted in a significant
increase of unchanged Δ^{8} 1 **HC, and 11-OX0-** Δ -1 **HC** at the 11-Position. Pretreatment of mice with SKF 525-A (25 mg/kg, ip) resulted in a significant increase of unchanged Δ^8 -THC in the brain and liver at 15 min after the iv injection of mice with SKF 525-A (25 mg/kg, ip) resulted in a significant
increase of unchanged Δ^8 -THC in the brain and liver at 15 min
after the iv injection of Δ^8 -THC (table 4). In addition, the level of
11-OH- Δ^8 -THC in Increase of unchanged Δ -1 HC in the brain and liver at 15 mm
after the iv injection of Δ^8 -THC (table 4). In addition, the level of
11-OH- Δ^8 -THC in the liver was also increased significantly. Table
4 further sho atter the tv injection of Δ -1 HC (table 4). In addition, the level of 11-OH- Δ^8 -THC in the liver was also increased significantly. Table 4 further shows that SKF 525-A inhibited the conversion of 11-OH- Δ^8 -THC t 11-OH- Δ -1 HC in the liver was also increased
4 further shows that SKF 525-A inhibited ti
OH- Δ^8 -THC to Δ^8 -THC-11-oic acid, as jud
level of Δ^8 -THC-11-oic acid in the brain an
OH- Δ^8 -THC administration tha

Discussion

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Discussion oxidation oxidation
After the iv injection into mice of Δ^8 -THC, 11-OH- Δ^8 -THC, ^{of Δ^8 -THC} and 11-oxo- Δ^8 -THC, the blood levels of unchanged cannabinoids declined biphasically. Biological half-lives of Δ^8 -THC, 11-OH- Δ^8 -**Discussion**
After the iv injection into mice of Δ^8 -THC, 11-OH- Δ^8 -THC,
and 11-oxo- Δ^8 -THC, the blood levels of unchanged cannabinoids
declined biphasically. Biological half-lives of Δ^8 -THC, 11-OH- Δ^8 -
TH After the iv injection into mice of Δ^8 -THC, 11-OH- Δ^8 -THC, ^{of} *i* and 11-oxo- Δ^8 -THC, the blood levels of unchanged cannabinoids TH declined biphasically. Biological half-lives of Δ^8 -THC, 11-OH- Δ^8 -THC, After the tv injection into intee of Δ^2 -1 HC, 11-OH- Δ^2 -1 HC,
and 11-oxo- Δ^8 -THC, the blood levels of unchanged cannabinoids
declined biphasically. Biological half-lives of Δ^8 -THC, 11-OH- Δ^8 -
THC, and 11and 11-0x0- Δ -111C, the blood levels of the half-lives of Δ^8 -THC, 11-OH- Δ^8 -THC, and 11-0x0- Δ^8 -THC in the slow phase were 32, 12, and 6 min, respectively. In this connection, Lemberger *et al.* (16, 22) arep THC, and 11-oxo- Δ^8 -THC in the slow phase were 32, 12, and 6 min, respectively. In this connection, Lemberger et al. (16, 22) reported that the half-lives of Δ^8 -THC and 11-OH- Δ^8 -THC were very long in man (57 an FILE, and 11-0x0- Δ -THC in the slow phase were 32, 12, and 6
min, respectively. In this connection, Lemberger et al. (16, 22)
reported that the half-lives of Δ^8 -THC and 11-OH- Δ^8 -THC were
very long in man (57 and him, respectively. In this connection, Lemberger et al. (16, 22)
reported that the half-lives of Δ^9 -THC and 11-OH- Δ^9 -THC were
very long in man (57 and 22 hr, respectively). Interestingly, 11-
OH- Δ^8 -THC when ad teported that the han-lives of Δ -1 HC and 11-OH- Δ -1 HC were
very long in man (57 and 22 hr, respectively). Interestingly, 11-
OH- Δ ⁸-THC when administered iv into mice showed three times
higher concentration in Very long in man (57 and 22 nr, respectively). Interestingly, 11-
OH- Δ^8 -THC when administered iv into mice showed three times
higher concentration in brain as compared with Δ^8 -THC, although
the former was eliminat bigher concentration in brain as compared with Δ^8 -THC, although
the former was eliminated more rapidly from blood than the
latter. In addition, 11-OH- and 11-oxo- Δ^8 -THC showed 6-7 times
higher brain/blood ratios t the former was eliminated more rapidly from blood than the latter. In addition, 11-OH- and 11-oxo- Δ^8 -THC showed 6-7 times higher brain/blood ratios than did Δ^8 -THC at 0.5 min after their injections, suggesting tha the former was emimated more raptury from blood than the latter. In addition, 11-OH- and 11-oxo- Δ^8 -THC showed 6-7 times higher brain/blood ratios than did Δ^8 -THC at 0.5 min after their injections, suggesting that Example 1.1-011- and 11-0x0- Δ -111C showed 0-7 times
higher brain/blood ratios than did Δ^8 -THC at 0.5 min after their
injections, suggesting that both metabolites of Δ^8 -THC can pene-
trate much more readily into injections, suggesting that both metabolites of Δ^8 -THC can penetrate much more readily into brain of mice than the parent compound. The result is of interest because these metabolites are less lipophilic than Δ^8 -T injections, suggesting that both inetabolites of Δ -1 FIC can pene-
trate much more readily into brain of mice than the parent
compound. The result is of interest because these metabolites are
less lipophilic than Δ^8 compound. The result is of interest because these metabolites are
less lipophilic than Δ^8 -THC, and therefore their slower penetration
into brain is expected. In fact, Gill *et al.* (23) have reported that
octanol/wate less lipophilic than Δ^8 -THC, and therefore their slower penetration into brain is expected. In fact, Gill et al. (23) have reported that

THC might be explained by a difference in binding affinities of Δ⁸-THC and 11-OH-Δ⁸-THC were 6000 and 3500, respectively.
THC were 6000 and 3500, respectively.
THC might be explained by a difference in binding affini THC were 6000 and 3500, respectively.
THC were 6000 and 3500, respectively.
This interesting penetration rate of Δ^8 -THC and 11-OH- Δ^8 -
THC might be explained by a difference in binding affinities of
these cannabino The were coop and 5500, respectively.
This interesting penetration rate of Δ^8 -THC and 11-OH- Δ^8 -THC might be explained by a difference in binding affinities of these cannabinoids to plasma proteins. The binding of THC might be explained by a difference in binding affinities of
these cannabinoids to plasma proteins. The binding of drugs with
plasma proteins is known to influence greatly the transport of
drugs into the tissues. It is these cannabinoids to plasma proteins. The binding of drugs with plasma proteins is known to influence greatly the transport of drugs into the tissues. It is recognized that most of Δ^9 -THC in plasma binds to lipoprote mese cannaomological process. The omang of drugs with
plasma proteins is known to influence greatly the transport of
drugs into the tissues. It is recognized that most of Δ^9 -THC in
plasma binds to lipoproteins in vivo plasma proteins is known to influence greatly the transport of drugs into the tissues. It is recognized that most of Δ^9 -THC in plasma binds to lipoproteins in vivo (24, 25) as well as in vitro (26, 27). 11-OH- Δ^9 -T drugs into the ussues. It is recognized that most of 2
plasma binds to lipoproteins in vivo (24, 25) as well as in
27). 11-OH- Δ^9 -THC also binds to plasma proteins, but ti
seems to be lesser than that of Δ^9 -THC (27 In connection with the higher distribution of 11-OH-A⁸-THC in connection with the higher distribution of 11-OH-A⁸-THC in wever, be necessary to confirm the above explanation.
In connection with the higher distribution

 $2r$). 11-OH-Δ²-THC also billus to plasma proteins, but the arimity seems to be lesser than that of Δ^8 -THC (27). Further studies will, however, be necessary to confirm the above explanation.
In connection with the bowever, be necessary to confirm the above explanation.

In connection with the higher distribution of 11-OH- Δ^8 -THC

brain of mice than that of Δ^8 -THC, Christensen *et al.* report

that 11-OH- Δ^8 -THC and 11-OH-In connection with the higher distribution of 11-OH- Δ^8 -THC in
brain of mice than that of Δ^8 -THC, Christensen *et al.* reported
that 11-OH- Δ^8 -THC and 11-OH- Δ^9 -THC had twice the pharma-
cological potency as in connection with the inglier distribution of 11-OH- Δ -1 HC in
brain of mice than that of Δ^8 -THC, Christensen et al. reported
that 11-OH- Δ^8 -THC and 11-OH- Δ^9 -THC had twice the pharma-
cological potency as co brain of lines than that of Δ -1 HC, Christensen *et al.* reported to the 11-OH- Δ^8 -THC and 11-OH- Δ^9 -THC had twice the phare cological potency as compared with Δ^8 -THC and Δ^9 -THC winjected iv into mice (14 that 11-OH- Δ ⁻-1 HC and 11-OH- Δ ⁻-1 HC nad twice the pharma-
cological potency as compared with Δ ⁸-THC and Δ ⁹-THC when
injected iv into mice (14). More recently, we also found that
cataleptogenic, hypoth cological potency as compared with Δ^{-1} HC and Δ^{-1} HC when
injected iv into mice (14). More recently, we also found that
cataleptogenic, hypothermic, pentobarbital-induced sleep-pro-
longing, and anticonvulsant eff injected iv into mice (14). More recently, we also found that
cataleptogenic, hypothermic, pentobarbital-induced sleep-pro-
longing, and anticonvulsant effects of 11-OH- and 11-oxo- Δ^8 -THC
in mice were greater than tho cataleptogenic, nypothermic, pentobarbital-matted sleep-pro-
longing, and anticonvulsant effects of 11-OH- and 11-oxo- Δ^8 -THC
in mice were greater than those of Δ^8 -THC, and that the effects of
these metabolites app ionging, and anticonvulsant effects of 11-OH- and 11-OXO- Δ - I HC
in mice were greater than those of Δ^8 -THC, and that the effects of
these metabolites appeared more rapidly than those of Δ^8 -THC
(17, 18). The di these metabolites appeared more rapidly than those of Δ^8 -THC

(17, 18). The difference of the pharmacological potency between
 Δ^8 -THC and 11-OH- Δ^8 -THC may therefore be attributed in part

to the higher levels (17, 18). The difference of the pharmacological potency between 7. The elimination of the pharmacological potency between
THC and 11-OH- Δ^8 -THC may therefore be attributed in part
the higher levels of 11-OH- Δ^8 -THC than of Δ^8 -THC in brains
mice.
The elimination of Δ^8 -THC

slower than were those of 11-OH- Δ^8 -THC than of Δ^8 -THC in brain of mice.
The elimination of Δ^8 -THC from brain, on the other hand, we slower than were those of both metabolites, 11-OH- and 11-ox
 Δ^8 -THC. The The elimination of Δ^8 -THC from brain, on the other hand, was
slower than were those of both metabolites, 11-OH- and 11-oxo-
 Δ^8 -THC. The result suggests that Δ^8 -THC has a higher lipophilic
property than the met The elimination of Δ^8 -THC from brain, on the other hand, was
slower than were those of both metabolites, 11-OH- and 11-oxo-
 Δ^8 -THC. The result suggests that Δ^8 -THC has a higher lipophilic
property than the met The entimation of Δ - I FIC from brain, on the other hand, was
lower than were those of both metabolites, 11-OH- and 11-oxc
 Δ ⁸-THC. The result suggests that Δ ⁸-THC has a higher lipophili
property than the met slower than were those of both metabolites, 11-OH- and 11-0x0-
 Δ^8 -THC. The result suggests that Δ^8 -THC has a higher lipophilic
property than the metabolites and is not metabolized in brain of
mice as reported by C property than the metabolites and is not metabolized in brain of mice as reported by Christensen *et al.* (14). The result also coincided with the report of Perez-Reyes *et al.* (15), who showed that Δ^9 -THC possessed property than the metaoontes and is not metaoonze
mice as reported by Christensen et al. (14). The res
cided with the report of Perez-Reyes et al. (15), who
 Δ^9 -THC possessed more long-lasting psychological a
ical effe Let us a reported by Christensen *et al.* (14). The result also consided with the report of Perez-Reyes *et al.* (15), who showed that -THC possessed more long-lasting psychological and physiolog-
al effects in man as com

clusted with the report of Petez-Reyes et al. (15), who showed that Δ^9 -THC possessed more long-lasting psychological and physiological effects in man as compared with 11-OH- Δ^9 -THC.
In addition, the present study r Δ -1 HC possessed more tong-tasting psychological and physiolog-
ical effects in man as compared with 11-OH- Δ^9 -THC.
In addition, the present study revealed that a considerable
amount of 11-OH- Δ^8 -THC was found in Lear errects in man as compared with 11-OH- Δ - 1HC.
In addition, the present study revealed that a considerable
amount of 11-OH- Δ^8 -THC was found in the brains of mice after
the injection of 11-oxo- Δ^8 -THC althou in addition, the present study reveated that a considerable 22
amount of 11-OH- Δ^8 -THC was found in the brains of mice after
the injection of 11-oxo- Δ^8 -THC although the levels in the liver
and blood were not so hig the injection of 11-oxo- Δ^8 -THC although the levels in the liver
and blood were not so high. The result obtained, therefore,
suggests that 11-OH- Δ^8 -THC may play the important role in the
pharmacological effect of 1 and blood were not so high. The result obtained, therefore,

suggests that 11-OH- Δ^8 -THC may play the important role in the 24. K. O. Fehr and H. Kalant, *Eur. J. Pharmacol.* 25, 1 (1974).

pharmacological effect of 11-oxo- Δ^8 -THC.

SKF 525-A, a known inhibitor of microsomal suggests that 11-OH- Δ - I HC may play the important fole in the pharmacological effect of 11-oxo- Δ^8 -THC.
SKF 525-A, a known inhibitor of microsomal mono-oxygenas
has been shown to inhibit the oxidation of 11-OH- Δ pharmacological effect of 11-0xo- Δ -1 ric.
SKF 525-A, a known inhibitor of microsomal mono-oxygenase
has been shown to inhibit the oxidation of 11-OH- Δ^8 -THC to 11-
oxo- Δ^8 -THC. The result indicates that the oxida Δ^8 -THC to 11-oxo- Δ^8 -THC is also mediated by the microsomal mono-oxygenase system in mice, which was reported previously in rats (28). Contrary to the result of Gill and Jones (29), the Δ^8 -THC to 11-oxo- Δ^8 -THC to 11-oxo- Δ^8 -THC to 11-oxo- Δ^8 -THC is also mediated by the microsomal Δ^8 -THC to 11-oxo- Δ^8 -THC is also mediated by the microsomal mono-oxygenase system in mice, which was repo bxo-Δ²-THC. The result matcates that the oxidation of 11-Of-
Δ⁸-THC to 11-oxo-Δ⁸-THC is also mediated by the microsomal
mono-oxygenase system in mice, which was reported previously
in rats (28). Contrary to the resu

i ET AL.
oxidation of Δ^8 -THC to 11-OH- Δ^8 -THC, inasmuch as the levels
of Δ^8 -THC became higher in all cases than those of 11-OH- Δ^8 -ET AL.
oxidation of Δ^8 -THC to 11-OH- Δ^8 -THC, inasmuch as the levels
of Δ^8 -THC became higher in all cases than those of 11-OH- Δ^8 -
THC after pretreatment with this inhibitor. ET AL.

oxidation of Δ^8 -THC to 11-OH- Δ^8 -THC, if

of Δ^8 -THC became higher in all cases that

THC after pretreatment with this inhibitor. of Δ^8 -THC became higher in all cases than those of 11-OH- Δ^8 -THC after pretreatment with this inhibitor.
Acknowledgments. The authors wish to thank Drs. I. Nishioka

THC after pretreatment with this inhibitor.
 Acknowledgments. The authors wish to thank Drs. I. Nishioka

and Y. Shoyama, Faculty of Pharmaceutical Sciences, Kyushu

University, for supplying Δ^9 -THC. Acknowledgments. The authors and Y. Shoyama, Faculty of Pha University, for supplying Δ^9 -THC. References

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