the present study show that, as with amphetamine[12-14], the ability to stimulate release and inhibit uptake of DA resides primarily in the (+)-isomer.

It is concluded that, in vitro, the optical isomers of monofluorinated amphetamine behave in much the same way as those of the parent amphetamine with regard to interaction with transport of the neurotransmitter DA. Studies are now underway to investigate the effects of these new compounds in vivo on brain DA and DA-mediated behaviour.

1 Financial support for this project was supplied by the Medical Research Council of Canada, the Alberta Mental Health Research Fund and the Special Services and Research Committee, University of Alberta Hospital.

2 Acknowledgments. Skilled technical assistance was provided by Ms L. Hiob. The authors also wish to thank Dr W.G. Dewhurst, Department of Psychiatry, and Dr D.F. LeGatt, for their advice and comments.

3 R.M. Pinder, R.W. Brimblecombe and D.M. Green, J. med. Chem. *12*, 322 (1969).
4 L.R. Meyersen and R.W. Fuller, Res. Commun. chem. Path. Pharmac. *21*, 581 (1978).
5 R.W. Fuller, Ann. N.Y. Acad. Sci. *305*, 147 (1978).
6 R.T. Coutts, A. Benderly and A.L.C. Mak, J. Fluorine Chem. *16*, 277 (1980).
7 R.T. Coutts, G.B. Baker, A. Benderly and H.R. McKim, Res. Commun. chem. Path. Pharmac. *24*, 201 (1979).
8 M. Raiteri, A. Bertollini, F. Angelini and G. Levi, Eur. J. Pharmac. *34*, 189 (1975).
9 I.L. Martin, G.B. Baker and P.R. Mitchell, Neuropharmacology *17*, 421 (1978).
10 R.E. Heikkila, H. Orlansky and G. Cohen, Biochem. Pharmac. *24*, 847 (1975).
11 P.A. Baumann and L. Maître, Nature, Lond. *264*, 789 (1976).
12 R.M. Ferris, F.L.M. Tang and R.A. Maxwell, J. Pharmac. exp. Ther. *181*, 407 (1972).
13 P.F. Von Voigtlander and K.E. Moore, J. Pharmac. exp. Ther. *184*, 242 (1973).
14 C.C. Chieuh and K.E. Moore, Res. Commun. chem. Path. Pharmac. *7*, 189 (1974).

Tolerance to, and symmetrical cross-tolerance between, cannabinol and Δ^9-tetrahydrocannabinol[1]

Barbara Schneiderman Fish and P. Consroe

Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson (Arizona 85721, USA), 14 May 1980

Summary. Tolerance to, and symmetrical cross-tolerance between, cannabinol and Δ^9-tetrahydrocannabinol (THC) occurs in rabbits which uniquely exhibit behavioral convulsions with THC.

It is well established that Δ^9-tetrahydrocannabinol (THC) is the major psychoactive ingredient in marijuana[2], and that, following chronic administration, tolerance to many of its effects occur in both laboratory animals[3-5] and humans[6]. However, the activity in humans of acute cannabinol (CBN), another major constituent of marijuana, is equivocal[7-10]. Although data on chronic effects are lacking, acute CBN is active, albeit much less potent than THC, in laboratory animals[11-13], including tetrahydrocannabinol seizure susceptible (THC-SS) rabbits[14]. The THC-SS rabbits are unique in that they exhibit a selective response following low dose, i.v., injection of THC but not following noncannabinoid psychoactive drugs[14]. In the present study, the chronic effects of CBN and THC, and their subsequent interactive effects in THC-SS rabbits were investigated.

Materials and methods. Rabbits, weighing 1.3–3.8 kg, selected from our closed stock of THC-SS rabbits, were implanted with a cannula in the external jugular vein under pentobarbital anesthesia so that drugs could be repeatedly and conveniently administered. 6 rabbits were studied since the THC-SS rabbits, bred exclusively in our closed colony (Uaz:NZW), were limited in number. 7 days were allowed for recovery before testing. THC and CBN were prepared in a vehicle of a 10% polysorbate (Tween)-80 and 90% distilled water solution. During testing, individual rabbits were observed, for behavioral convulsions, through a 1-way

Development of behavioral convulsant tolerance to THC (A) and CBN (B) and cross-tolerance between the 2 cannabinoids (A and B) in THC seizure susceptible rabbits[a]

Rabbit identification number	Days of drug administration 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
A																					
358	0.1	0.1	0.1	0.1	0.1	0.1*	0.5	0.5	0.5	0.5	0.5	0.5	0.5*	15* CBN							0.1
351	0.1	0.1*	0.5	0.5	0.5	0.5	0.5	0.5	0.5*	15* CBN							0.1				
354	0.1	0.1	0.1*	0.5	0.5*	15* CBN							0.1*		0.5						
B																					
319	15	15	15*	20	20	20	20	20	20	20	20*	0.1* THC							15		
320	15	15	15	15	15	15*	20	20	20	20*	0.1* THC							15			
321	15	15	15	15*	20*	25*	30	30*	0.1* THC							15					

[a] Asterisks indicate no convulsion occurred; convulsions occurred on all other days of i.v. CBN (15, 20, 25 or 30 mg/kg) and THC (0.1, 0.5 mg/kg) administration.

vision mirror in a sound attenuated chamber measuring 82 cm^2 by 70 cm high. Daily injections of THC (0.1 mg/kg to 3 rabbits) or CBN (15 mg/kg to 3 rabbits) were continued until no convulsions occurred. The following, and subsequent days, if necessary, the dose of cannabinoid was increased until a convulsion was again elicited. This higher dose was given daily until the convulsions ceased. On the next day, the animal received an injection of the cannabinoid (0.1 mg/kg THC or 15 mg/kg CBN) that had not been previously administered. 1 week later the original dose of cannabinoid was given. If a convulsion was not elicited, a higher dose was injected.

Results. As shown in the table, A, although there was some individual variation, all rabbits exhibited tolerance to the convulsant effects of THC. The tolerance was first exhibited following repeated administration of 0.1 mg/kg THC. An increase in dose to 0.5 mg/kg was sufficient to reinstate the convulsive behaviors and tolerance developed after daily administration of this dose. On the day following occurrence of tolerance to the higher dose of THC, a dose of CBN (15 mg/kg), shown previously to reliably elicit convulsions in our rabbit population[14], was given. In all 3 rabbits, no convulsions were precipitated, indicating that cross-tolerance occurred from THC to CBN. 1 week after CBN administration each subject was injected with 0.1 mg/kg THC. In 2 out of 3 animals a convulsion occurred, indicating that tolerance had been lost. The 3rd rabbit required 0.5 mg/kg prior to exhibiting a loss of tolerance. The table, B, illustrates the results of repeated dosing with CBN. Tolerance occurred to the 15 mg/kg dose of CBN and this could be reversed by higher doses of CBN (20 or 30 mg/kg). After daily administration, tolerance occurred to the higher CBN dose. Subsequent injection of a convulsive dose of THC (0.1 mg/kg) did not evoke a convulsion, indicating a cross-tolerance from CBN to THC. CBN (15 mg/kg) again elicited convulsions when administered after a 1-week drug-free interval.

Discussion. In the THC-SS rabbits, tolerance developed to the behavioral convulsant effects of both THC and CBN. This was evidenced by both an abolition of response after repeated administration of the same dose and a reinstitution of convulsions subsequent to a higher dose of each cannabinoid. Tolerance to convulsions was not permanent since each cannabinoid elicited convulsions in the previously tolerant THC-SS rabbits after a 1-week drug-free interval. Reversible tolerance to the rabbit convulsions with THC reaffirms previous findings[14], and is congruent with the development of tolerance to THC effects across species[3-6]. The present findings of tolerance to CBN-induced convulsions and of symmetrical cross-tolerance between CBN and THC are novel. These data suggest a similar mechanism of action of the 2 cannabinoids which is compatible with previously reported structure-activity considerations of cannabinoids[2]. Moreover, these data support findings that CBN is capable of producing psychoactive effects in humans that are qualitatively similar to those elicited by THC. 2 human studies[9,10] have demonstrated that both CBN and THC, given by i.v. infusion, produced a psychological 'high' and tachycardia. The dose required for CBN was about 10-fold higher than that for THC. However, the results of 2 other studies indicate that humans receiving up to 400 mg/kg of oral CBN did not experience any of the mental and physical effects characteristic of an oral 10 mg dose of THC[7,8]. The discrepancies between the findings of these human studies are difficult to explain since many relevant details are absent from the reports. Nevertheless, numerous studies indicate that CBN is a less potent THC-type compound[9-13]. This suggests that a relatively high concentration of CBN in marijuana could conceivably contribute to the pharmacological effects of the plant material.

1 This research was supported by funds (grant No. DA01448) and cannabinoids from the National Institute on Drug Abuse.
2 R. Mechoulam, A. Shani, H. Edery and Y. Grundfeld, Science *169*, 611 (1970).
3 L.E. Hollister, Adv. Biosci. *22/23*, 585 (1979).
4 L. Lemberger, in: Physiologic Disposition of Drugs of Abuse, p. 337. Spectrum Publications, New York 1976.
5 A. Wikler, Ann. N.Y. Acad. Sci. *282*, 126 (1976).
6 R. Nolan and S. Cohen, Clin. Pharmac. Ther. *22*, 550 (1977).
7 L.E. Hollister, Experientia *29*, 825 (1973).
8 I.G. Karniol, I. Shirakawa, R.N. Takahashi, E. Knobel and R.E. Musty, Pharmacology *13*, 502 (1975).
9 M. Perez-Reyes, M.C. Timmous, K.H. Davis and E.M. Wall, Experientia *29*, 1368 (1973).
10 M.E. Wall, D.R. Brine and M. Perez-Reyes, in: The Pharmacology of Marijuana, p. 93. Ed. M.C. Braude and S. Szara. Raven Press, New York 1976.
11 A.L. Cragmill, Res. Commun. Psychol. Psychiat. Behav. *4*, 51 (1979).
12 J. Sanders, D.M. Jackson and G.A. Starmer, Psychopharmacology *61*, 281 (1979).
13 R.N. Takahashi and I.G. Karniol, Psychopharmacology *41*, 277 (1975).
14 P. Martin and P. Consroe, Science *194*, 965 (1976).

Electro-osmotic and iontophoretic release of noradrenaline from micropipettes[1]

P. Bevan[2], C.M. Bradshaw, R.Y.K. Pun, N.T. Slater and E. Szabadi

Department of Psychiatry, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT (England), 14 February 1980

Summary. The relative contributions of electro-osmosis and iontophoresis to the electrophoretic release of noradrenaline from micropipettes were examined. Electro-osmosis was responsible for 23.1% (±5.0%) of the total rate of release.

The technique of microelectrophoresis is used to apply minute quantities of drugs into the immediate vicinity of single neurones. Drugs are released from ionized solutions contained within glass micropipettes by the passage of currents of appropriate direction through the solutions. In most studies of central neurones, multi-barrelled micropipettes are used, consisting of several capillary tubes converging into a common tip[3]. The electrophoretic release of drugs from micropipettes involves 2 physico-chemical processes: a) the ejection of ionized drug molecules by iontophoresis, and b) the efflux of small volumes of the drug solution due to electro-osmosis. Of the two, iontophoresis is assumed to make the greater contribution to total drug release, at least in the case of well-ionized drugs[3]. We have attempted to assess the contribution of electro-osmosis to the release of noradrenaline (NA) by measuring the rate