



STUDIES ON [³H]CP-55940 BINDING IN THE HUMAN CENTRAL NERVOUS SYSTEM: REGIONAL SPECIFIC CHANGES IN DENSITY OF CANNABINOID-1 RECEPTORS ASSOCIATED WITH SCHIZOPHRENIA AND CANNABIS USE

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Abstract—A number of studies suggested that cannabis use can cause or exacerbate psychoses and may increase the risk of developing schizophrenia. These findings suggest that changes in the cannabinoid system of the brain may be involved in the pathology of schizophrenia. To determine whether changes in the cannabinoid system were present in the brains of subjects with schizophrenia, we used *in situ* radioligand binding and autoradiography to measure the binding of [³H]CP-55940 to the cannabinoid-1 receptor in the dorsolateral prefrontal cortex (Brodmann's area 9), caudate–putamen and areas of the temporal lobe from schizophrenic and control subjects, some of whom had ingested cannabis close to death. There was an increase in the density of [³H]CP-55940 binding to cannabinoid-1 receptors in the dorsolateral prefrontal cortex from subjects with schizophrenia (mean $\pm$ S.E.M.: 142 ± 9.9 vs 119 ± 6.6 fmol/mg estimated tissue equivalents; $P < 0.05$) that was independent of recent cannabis ingestion. There was an increase in the density of cannabinoid-1 receptors in the caudate–putamen from subjects who had recently ingested cannabis (151 ± 9.0 vs 123 ± 7.2 fmol/mg estimated tissue equivalents; $P < 0.05$) that was independent of diagnoses.

These data indicate that there are changes in cannabinoid-1 receptors in the dorsolateral prefrontal cortex that may prove to be associated with the pathology of schizophrenia. By contrast, changes in the density of cannabinoid-1 receptors may occur in the caudate–putamen in response to cannabis ingestion. © 2001 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Key words: cannabinoid-1 receptor, postmortem, human brain, dorsolateral prefrontal cortex, hippocampus, caudate–putamen.

It is still not clear whether the use of cannabis causes or exacerbates psychoses. It has been argued that there is no convincing evidence to associate cannabis use with the onset or worsening of psychoses, whilst others have suggested that cannabis use aggravates existing psychoses.¹¹ A longitudinal follow-up study of Swedish conscripts has shown that the incidence of schizophrenia was up to six-fold higher in subjects who had reported high cannabis use at conscription compared to conscripts who had not used cannabis.³ Furthermore, a WHO study has shown that cannabis use early in the onset of schizophrenia is a predictor of poor outcome.¹² Both studies tend to support the argument that cannabis use may be

a factor that can precipitate or perpetuate the symptoms of schizophrenia.^{17,22}

Cannabis affects the cannabinoid system of the brain, which has been shown to be modulated by “endogenous cannabinoids” or “endocannabinoids”.⁶ Endocannabinoids have been shown to act through two seven-transmembrane-domain, G-protein-linked receptors termed the cannabinoid-1 (CB₁) and cannabinoid-2 (CB₂) receptors. It has recently been reported that the concentrations of two endocannabinoids, anandamide and palmitoylethanolamide, are increased in the cerebrospinal fluid from subjects with schizophrenia.¹⁶ This finding provides the first evidence that changes in the endogenous cannabinoid system could be involved in the pathology of schizophrenia.

In order to further investigate the potential involvement of the endogenous cannabinoid system in the pathology of schizophrenia, we have measured the density of CB₁ receptors in the dorsolateral prefrontal cortex (DLPFC: Brodmann's area 9), caudate–putamen (CP) and areas within the temporal lobe obtained post-mortem from schizophrenic and non-schizophrenic (control) subjects. The CB₁ receptor was measured as a marker of the endogenous cannabinoid system because it is reactive to cannabis use¹⁸ and, unlike endocannabinoids,¹⁶ is stable postmortem. The CB₁ receptor was

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Abbreviations: ANCOVA, analysis of covariance; CA, cornu Ammonis; CB₁ receptor, cannabinoid-1 receptor; CB₂ receptor, cannabinoid-2 receptor; CP, caudate–putamen; DGL, dentate granule cell layer; DLPFC, dorsolateral prefrontal cortex; DML, dentate molecular layer; DPL, dentate polymorphic layer; ETE, estimated tissue equivalents; PMI, postmortem interval; SUB, subiculum; THC, Δ^9 (-)-tetrahydrocannabinol.

measured in preference to the CB₂ receptor because it is the most prevalent of the cannabinoid receptors in the human brain²³ and is thought to be the receptor which mediates the CNS effects of cannabis.⁶ Finally, in an attempt to delineate between changes due to pathological processes and changes due to the use of cannabis, we measured CB₁ receptor density in brain tissue from subjects with a history of cannabis use and detectable levels of $\Delta^9(-)$ -tetrahydrocannabinol (THC) in blood and subjects with no history of cannabis use and no THC in blood. THC is the major active constituent of cannabis and detectable levels in the blood would indicate that cannabis had been ingested within at least five days of death.¹⁵

EXPERIMENTAL PROCEDURES

Materials

[³H]CP-55940 (165 Ci/mmol) was obtained from NEN Life Sciences Products (Boston, MA, USA) and ³H-microscales were obtained from Amersham Australia Pty. (Sydney, Australia). BAS-TR[®] plates were obtained from Fuji Photo Film Co. (Tokyo, Japan). HU-210 was obtained from Tocris Cookson (Bristol, UK). All other chemicals were obtained from Sigma Aldrich Pty. (Castle Hill, New South Wales, Australia).

Tissue collection and diagnostic evaluation

Having obtained ethical approval from the North-Western Health Care Human Ethics Committee, the DLPFC, CP and temporal lobe from the left brain hemisphere were collected at autopsy from 14 subjects with a provisional diagnosis of schizophrenia suggested in a police report of death to the Coroner (Table 1) and from 14 subjects with no known history of psychiatric illness (controls). All tissue was collected at the Victorian Institute of Forensic Medicine, where a neuropathological examination was carried out by a Forensic Neuropathologist. The control subjects were matched for sex and were of a similar age to the schizophrenic subjects.

To minimise variation because of anatomical variation, all tissue blocks were prepared by standardised procedures. Thus, the DLPFC was taken from the dorsolateral region of a slice of tissue between 2 and 3 cm from the frontal pole to include equal amounts of the superior frontal gyrus and the middle frontal gyrus on either side of the superior frontal sulcus. Blocks of the CP were taken from a rostral region so as to include the nucleus accumbens and exclude the globus pallidus (pars lateralis). Finally, blocks of the hippocampus were taken from the mid-region of the hippocampal formation, where the entorhinal cortex has been replaced by the parahippocampal gyrus and the lateral geniculate body appears dorsomedial to the hippocampus. The blocked tissue was rapidly frozen to -70°C and stored at this temperature until required.

Where death did not involve suicide, tissue was collected from subjects whose death was witnessed and the postmortem interval (PMI) was the time from death to autopsy. With suicides, tissue was only taken from individuals who had been seen alive up to 5 h before being found dead. In those cases, the PMI was the interval between the donor being found dead and autopsy plus half the time between the donor last being seen alive and being found dead. In all cases, the cadavers were refrigerated within 5 h of being found.

The provisional diagnosis of schizophrenia was confirmed by a senior psychologist and senior psychiatrist after an extensive case history review using the Diagnostic Instrument for Brain Studies,¹⁰ a structured instrument for the collection of clinical, pharmacological and other relevant information from case histories. In this study, the diagnosis of schizophrenia was made according to DSM-IV criteria.² In addition to the DSM-IV diagnosis of schizophrenia, there were two schizophrenic

subjects who would fulfil the DSM-IV criteria for cannabis abuse at death (4 and 5) and two subjects that would have fulfilled those criteria during their lifetime (2 and 3), but not at death. Two of the schizophrenic subjects (6 and 10) would fulfil the DSM-IV criteria for alcohol abuse. There was no evidence to suggest that any of the schizophrenic subjects would fulfil the DSM-IV criteria for the abuse of other substances and there was no evidence that any of the control subjects would have fulfilled any of the DSM-IV criteria for the abuse of any substance.

Duration of illness was calculated as the time from first hospital admission to death. In addition, information on the type and amount of antipsychotic drugs prescribed close to death was obtained from the case history, and the final recorded dose of antipsychotic drug was converted to chlorpromazine equivalents.⁸ Toxicology reports were examined to identify which subjects had detectable levels of THC in the blood and case histories were carefully examined for any suggestion of cannabis use.

In situ radioligand binding

[³H]CP-55940 binding was measured using a method modified from a previous study,²³ except that we utilised the CB₁ receptor-preferring agonist HU-210⁷ as the displacing agent to improve the selectivity of [³H]CP-55940 binding for the CB₁ receptor. Thus, frozen tissue sections (20 μm) were air dried for 1 h prior to exposure to [³H]CP-55940 (10 nM) for 4 h at room temperature in 50 mM Tris-HCl buffer containing 1% bovine serum albumin at pH 7.4. These incubations were carried out either in the absence (three sections: total binding) or in the presence (two sections: non-specific binding) of HU-210 (10^{-6} M). Following this incubation, all sections were washed twice for 10 min in assay buffer at 4°C and then rinsed for 10 s in distilled water at 4°C . Bound radioactivity was imaged as described below. The concentration of [³H]CP-55940 used in this study was calculated from preliminary data showing that the K_d for that radioligand binding to human CP was approximately 2.5 nM (data not shown).

Image analysis

All washed tissue sections were fixed by being placed at room temperature, overnight, in a desiccator containing paraformaldehyde powder. The fixed sections were then apposed to BAS-TR2025[®] imaging plates along with a ³H-microscale[™] until images of appropriate intensity were obtained. The plates were then read in a BAS 5000 high-resolution phosphorimager and the phosphorescences of the resulting images were measured using AIS imaging software and expressed as photo-stimulated luminescence. The photo-stimulated luminescence levels were calibrated against a standard curve generated using the ³H-microscales, allowing [³H]CP-55940 binding to be expressed as d.p.m./mg estimated tissue equivalents (ETE). The specific binding of [³H]CP-55940 was calculated by subtracting the non-specific binding from the total binding for each brain region for each subject. Given that the concentration of [³H]CP-55940 was approximately $4 \times K_d$ for its binding to the CB₁ receptor,⁹ this represents a single-point saturation analysis. Assuming that there is no large change in the affinity of radioligand binding in one of the diagnostic groups, such an analysis of the specific binding of a radioligand gives a good estimate of the density of binding sites on the tissue sections.¹⁹

Statistical analysis

The Kolmogorov-Smirnov test was applied to each data set to test for parametric or non-parametric distributions. Two-way ANOVA was used to identify differences in radioligand binding within a brain region between diagnostic cohorts that were due to either diagnosis or the presence of THC in blood. Because data were not available on all subjects for all regions, separate analyses of results for the hippocampal formation are reported. ANOVA across regions within the two cohorts was carried out using a one-way unstacked ANOVA. Where there were significant

differences relating to either diagnosis or drug effects, analysis of covariance (ANCOVA) was used to ensure there were no significant effects associated with the confounding variables age, PMI and brain pH. Relationships between radioactive ligand binding and confounding measures were analysed using Pearson single product-moment correlation coefficients calculated using an assumed straight-line model.

RESULTS

There were no significant neuropathological abnormalities found in the brains from subjects included in this study. All data in this study were normally distributed and therefore analysed using parametric analyses. There were no significant differences in the density of [³H]CP-55940 binding between the laminae of the DLPFC. The density of [³H]CP-55940 did not vary significantly across the CP. Therefore, we took an integrated measure of [³H]CP-55940 binding across the laminae of the DLPFC and across the CP.

Tissue was obtained from 14 subjects with schizophrenia, five (four male, one female) of whom had a history of cannabis use and THC in their blood at death and nine (seven males, two females) who had no history of cannabis use and no THC in their blood at death (Table 1). Tissue was also obtained from 14 control subjects, four (all males) of whom had a history of cannabis use and THC in their blood, with the remainder (eight males, two females) having no history of cannabis use or THC in their blood (Table 1). Using two-way ANOVA to take into account variation due to THC or diagnoses, there were no significant differences in age (all subjects: interaction $P=0.99$, drug $P=0.19$, diagnosis $P=0.12$; hippocampal formation only: interaction $P=0.72$, drug $P=0.10$, diagnosis $P=0.06$), PMI (all subjects: interaction $P=0.12$, drug $P=0.24$, diagnosis $P=0.71$; hippocampal formation: interaction $P=0.37$, drug $P=0.32$, diagnosis $P=0.33$) or brain pH (all subjects: interaction $P=0.51$, drug $P=0.44$, diagnosis $P=0.46$; hippocampal formation: interaction $P=0.37$, drug $P=0.32$, diagnosis $P=0.33$) between the schizophrenic and control subjects.

Analysis of the density of [³H]CP-55940 binding using two-way ANOVA showed that there was an increase in the density of radioligand binding in the DLPFC from subjects with schizophrenia compared to controls (Fig. 1A, Table 2: interaction $P=0.45$, drug $P=0.08$, diagnosis $P<0.05$). In the CP, there was a significant increase in the density of [³H]CP-55940 binding in tissue from those subjects who had THC in their blood (Fig. 1B, Table 2: interaction $P=0.75$, drug $P<0.05$, diagnosis $P=0.96$) that was independent of diagnosis. There were no significant differences in the density of [³H]CP-55940 binding in the subiculum (SUB), cornu Ammonis (CA) 1–3, the dentate polymorphic layer (DPL), the dentate granule cell layer (DGL) or the dentate molecular layer (DML) with either diagnosis or the ingestion of cannabis close to death (Fig. 1A, B).

In the tissue from the schizophrenic (d.f. = 8,103, $F=5.770$, $P<0.0001$) and control (d.f. = 8,117, $F=13.40$, $P<0.001$) subjects, there were significant differences in the density of [³H]CP-55940 binding

between brain regions (Table 2). In the schizophrenic subjects, this was due to higher binding in the DGL compared to the CP ($P<0.001$), CA3 ($P<0.001$), DLPFC ($P<0.001$), DPL ($P<0.001$) and SUB ($P<0.05$). In the control subjects, binding was higher in the DGL compared to CA3 ($P<0.001$), the DLPFC ($P<0.001$), DPL ($P<0.001$), CP ($P<0.001$), SUB ($P<0.001$), CA2 ($P<0.001$), CA1 ($P<0.01$) and DML ($P<0.05$). Binding was also higher in the DML from control subjects compared to that in CA3 ($P<0.001$), the DLPFC ($P<0.001$), DPL ($P<0.001$) and CP ($P<0.01$), and in the SUB when compared to CA3 ($P<0.01$), the DLPFC ($P<0.001$), DPL ($P<0.001$) and CP ($P<0.01$). Finally, binding was higher in CA2 than in CA3 ($P<0.05$), the DLPFC ($P<0.05$) and DPL ($P<0.05$).

There were no significant correlations between the density of [³H]CP-55940 binding in any of the groups with age, PMI, brain pH, the final recorded antipsychotic drug dose or levels of THC in the blood. Moreover, ANCOVA showed that the increase in the [³H]CP-55940 binding to the DLPFC between the diagnostic groups (d.f. = 1,27, $F=5.48$, $P=0.03$) was not dependent on the covariates (d.f. = 3,27, $F=2.43$, $P=0.09$) of age ($P=0.08$), PMI ($P=0.23$) or pH ($P=0.19$). In the CP, ANCOVA showed that the increase in [³H]CP-55940 binding was associated with the presence of THC in the blood (d.f. = 1,27, $F=4.12$, $P=0.05$), which was not dependent on the covariates (d.f. = 3,27, $F=0.22$, $P=0.88$) of age ($P=0.86$), PMI ($P=0.80$) or brain pH ($P=0.50$).

DISCUSSION

This study has shown an increase in the density of [³H]CP-55940 binding in the DLPFC, but not the CP or regions within the temporal lobe, from subjects with schizophrenia which was independent of cannabis use. Under the conditions used, [³H]CP-55940 would bind predominantly to the CB₁ receptor.²³ Therefore, our data would suggest that there is an increase in the density of CB₁ receptors in the DLPFC of subjects with schizophrenia. Studies have shown an increase in levels of endogenous cannabinoids in cerebrospinal fluid from subjects with schizophrenia.¹⁶ Hence, results from our study using human brain tissue and the previous study using cerebrospinal fluid support the proposal that changes in the endogenous cannabinoid system may be involved in the pathology of schizophrenia.¹⁶ Significantly, an increase in CB₁ receptor density would, from animal studies, be predictive of low prevailing levels of endogenous cannabinoids.¹ Hence, further investigations are required to determine the overall status of the cannabinoid system in the illness. However, current data would be consistent with the hypothesis that there is an abnormality in the control of the density of the CB₁ receptor *per se* in the DLPFC from subjects with schizophrenia that may be independent of prevailing levels of endogenous cannabinoids. The consequences of changes in the cannabinoid system in the DLPFC are not yet known. However, cannabis use is known

Table 1. Demographic data from, and radioligand data (fmol/mg ETE) for, schizophrenic and control subjects from whom brain tissue was obtained postmortem for the study of cannabinoid-1 receptors in brain tissue obtained postmortem

ID	Sex	Age (yr)	PMI (h)	pH	DOI (yr)	FRD	THC	Cause of death	DLPFC	CP	SUB	CA1 (fmol/mg ETE)	CA2	CA3	DPL	DGL	DML
Schizophrenia																	
1	M	25	49	6.38	2	200	DET	Suicide: overdose of mixed drugs	112	194	156	210	177	120	114	249	214
2	M	22	37	6.07	3	450	DET	Pericarditis	207	150	143	214	297	102	212	369	272
3	F	35	15	6.26	7	300	75	Coronary arterial thrombosis	119	100	124	147	106	72	51	118	133
4	M	41	31	6.20	11	500	10	Suicide: combined drug toxicity	113	143	194	212	212	166	141	298	245
5	M	45	68	6.48	12	300	15	Suicide: hanging	119	177	127	171	121	98	140	256	214
6	M	38	40	5.52	15	160		Mediastinitis	106	82	92	148	102	83	66	138	124
7	M	36	38	6.04	12	200		Suicide: overdose amitryptiline	200	95	228	199	198	166	191	282	236
8	M	42	47	6.26	22	1000		Coronary arterial atheroma	141	87	126	171	107	69	40	139	119
9	F	27	41	5.85	10	750		Suicide: asphyxia	167	127	279	279	331	197	173	330	220
10	M	44	32	6.28	23	600		Ischaemic heart disease	114	167	328	379	347	275	313	433	317
11	M	48	30	6.62	24	1250		Bronchopneumonia	123	143	195	221	197	110	168	267	227
12	M	55	25	6.10	33	400		Coronary arterial atheroma	114	146	179	199	210	141	106	257	238
13	M	23	43	6.40	6	1750		Suicide: hanging	198	130							
14	F	36	45	6.28	4	160		Suicide: CO poisoning	160	116							
Analyses																	
+ THC	Mean	34	40	6.27	7.0	350											
	S.E.M.	4.4	8.9	0.07	2.0	55											
– THC	Mean	39	38	6.15	16.6	697											
All subjects	S.E.M.	3.3	2.5	0.10	3.2	184											
– THC	Mean	41	36	6.10	19.9	623											
T.L. only	S.E.M.	9.0	2.8	0.13	2.8	154											
ID	Sex	Age	PMI	pH			THC	Cause of death	DLPFC	CP	SUB	CA1 (fmol/mg ETE)	CA2	CA3	DPL	DGL	DML
Controls																	
15	M	30	27	5.86			23	Coronary arterial atheroma	114	155	126	179	131	86	100	187	152
16	M	26	24	6.42			30	Electrocution	89	132	160	186	130	86	86	174	142
17	M	25	50	6.48			85	Exsanguination	79	142	188	138	158	100	132	270	168
18	M	29	15	6.46			14	Congestive cardiac failure	100	164	271	238	195	150	182	311	216
19	F	21	58	6.03				Myocarditis	167	145	187	250	208	120	115	309	250
20	F	32	56	6.16				Coronary arterial atheroma	149	133	152	227	198	120	107	240	216
21	M	25	36	6.15				Right ventricular hypertrophy	138	186	92	156	175	126	136	218	178
22	M	42	26	6.32				Coronary arterial atheroma	111	126	195	223	171	152	172	342	260
23	M	30	24	6.46				Electrocution	119	139	201	199	214	170	211	258	260
24	M	38	46	6.42				Trauma and asphyxia	115	148	130	175	141	108	92	229	185
25	M	50	69	6.43				Ischaemic heart disease	119	127	185	201	229	126	91	277	264
26	M	23	36	6.13				Asthma	142	96	108	191	196	138	93	180	177
27	M	43	45	6.25				Drowning	131	79	146	135	155	122	98	254	217
28	M	21	51	6.58				Exsanguination	86	69	141	116	84	49	50	96	77

Table 1 (continued)

ID	Sex	Age	PMI	pH	THC	Cause of death	DLPFC	CP	SUB	CA1	CA2	CA3	DPL	DGL	DML
Analyses + THC	Mean	38	29	6.31											
	S.E.M.		1.2	0.14											
- THC	Mean	33	45	6.29											
	S.E.M.	3.3	4.6	0.06											

Abbreviations for demographics: PMI, postmortem interval; DOI, duration of illness; FRD, final recorded antipsychotic drug dose (chlorpromazine equivalents per day); THC, blood THC levels (ng/ml); DET, detected but below sensitivity of assay; T.L., temporal lobe.

to affect information processing and planning tasks,¹¹ functions that are regulated by the frontal cortex.⁴ It could therefore be postulated that changes in the cannabinoid system in schizophrenia are associated with the changes in cognitive function that are prominent in the illness.¹³

This study also showed a significant increase in the density of [³H]CP-55940 binding in the CP from subjects who had ingested cannabis within five days of death which was independent of the diagnosis of schizophrenia. These data would suggest that there is an increase in the CB₁ receptor in this region of the brain in subjects who had recently been exposed to cannabis. In animal studies, THC has been shown to reduce the CB₁ receptor protein in certain brain regions (the striatum, cerebellum and limbic forebrain, but not the ventral mesencephalon), but such treatment has been reported not to alter levels of mRNA for the CB₁ receptor.¹ These results are interpreted to indicate that THC causes a regionally selective down-regulation of CB₁ receptors in the rat brain. Hence, our results may seem to contradict these findings, but it is important to consider that the studies in animals are of a relatively short duration and involve the injection of THC. Hence, the difference in our findings may reflect either the outcomes of long-term cannabis use, different routes of intake or regional differences in the effects of THC in humans and rats. In humans, the reason why a change in CB₁ receptor density associated with recent cannabis should be restricted to the CP is not known. However, it is well established that the putamen is a brain region that is predominantly involved in motor control.⁵ Hence, it could be postulated that the change in CB₁ receptors in the putamen from subjects who had recently ingested cannabis is associated with the impaired motor control apparent in humans soon after ingestion of THC¹⁴ or in rats after an intraperitoneal injection of anandamide.²⁰

As in previous studies,^{9,23} in the tissue from control subjects the density of [³H]CP-55940 binding was greater in most regions of the temporal lobe studied compared to the DLPFC and CP. In the tissue from the schizophrenic subjects, the binding of [³H]CP-55940 was only different in the DGL compared to the other regions studied. This would suggest that the density of CB₁ receptors shows less variation in the brain of schizophrenic subjects. However, this phenomenon does not appear to be disease specific, as it has been reported in both alcoholism and Fahr's disease.²³

There is a number of confounding factors associated with our study. Firstly, the number of subjects in each category used in our analysis is low; therefore, our findings must be viewed as preliminary. In addition, all of the schizophrenic subjects had been treated with antipsychotic drugs, so it is possible that the changes in CB₁ receptors we have measured in schizophrenia are due to the effects of such treatment. However, our preliminary studies on the effects of antipsychotic drug treatment in rats do not suggest that such treatment increases the density of CB₁ receptors in either the cortex or striatum.²¹ These data, plus the lack of correlation

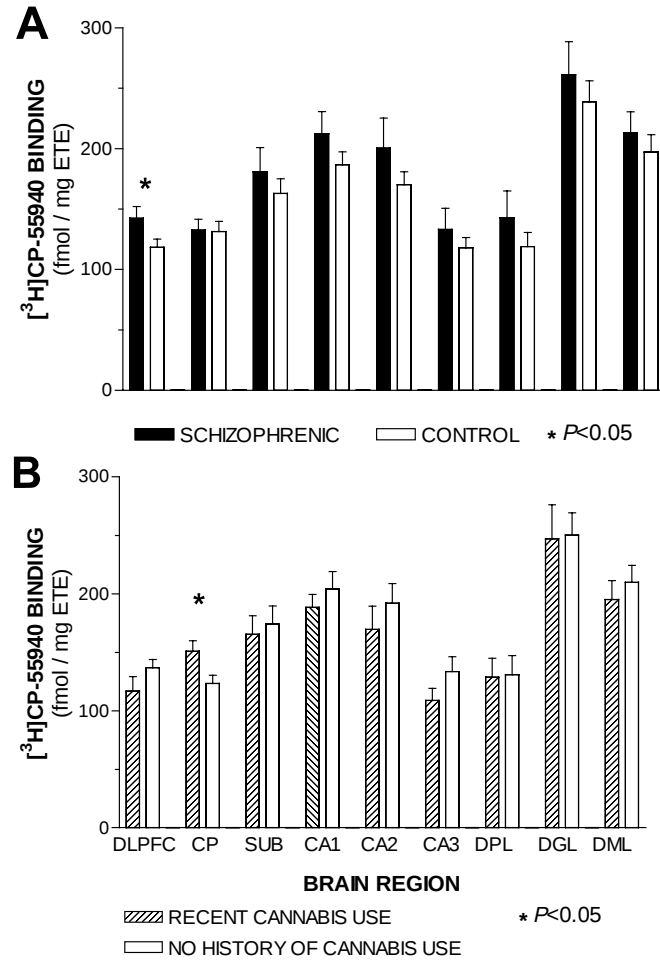


Fig. 1. The density (mean $\pm$ S.E.M.) of [3 H]CP-55940 binding in the DLPFC, CP, SUB, CA1–CA3, DPL, DGL and DML from schizophrenic and control subjects (A), and subjects (schizophrenic + controls) who had and had not recently ingested cannabis (B).

between final recorded antipsychotic drug dose and CB₁ receptor density, do not support the hypothesis that the change in CB₁ receptor density in the DLPFC from subjects with schizophrenia is an effect of such drug treatment prior to death. Thus, our data, plus data from the study of endocannabinoids in cerebrospinal fluid,¹⁶

would support the hypothesis that changes in the endogenous cannabinoid system of the brain may be involved in the pathology of schizophrenia. Moreover, our studies to date would suggest that such changes may be regionally specific and, at least, be affecting the DLPFC.

Table 2. Summary of the data on [3 H]CP-55940 binding (fmol/mg ETE: mean $\pm$ S.E.M.) in different brain regions from schizophrenic and control subjects who did, or did not, have $\Delta^9(-)$ -tetrahydrocannabinol present in plasma at death

Cohort	DLPFC	CP	SUB	CA1	CA2	CA3	DPL	DGL	DML
Schizophrenic									
All	142 $\pm$ 9.9	133 $\pm$ 9.1	181 $\pm$ 20	213 $\pm$ 18	200 $\pm$ 25	133 $\pm$ 17	143 $\pm$ 22	261 $\pm$ 27	213 $\pm$ 17
+ THC	134 $\pm$ 18	153 $\pm$ 16	149 $\pm$ 13	191 $\pm$ 14	183 $\pm$ 34	112 $\pm$ 16	132 $\pm$ 26	258 $\pm$ 41	216 $\pm$ 23
– THC	147 $\pm$ 12	121 $\pm$ 9.7	203 $\pm$ 31	228 $\pm$ 30	213 $\pm$ 36	148 $\pm$ 27	151 $\pm$ 35	264 $\pm$ 39	212 $\pm$ 26
Control									
All	119 $\pm$ 6.7	132 $\pm$ 8.5	163 $\pm$ 12	187 $\pm$ 11	170 $\pm$ 11	118 $\pm$ 8.3	119 $\pm$ 12	239 $\pm$ 17	197 $\pm$ 14
+ THC	96 $\pm$ 7.5	148 $\pm$ 7.1	186 $\pm$ 31	185 $\pm$ 21	154 $\pm$ 15	106 $\pm$ 15	125 $\pm$ 21	236 $\pm$ 33	170 $\pm$ 16
– THC	128 $\pm$ 7.2	125 $\pm$ 11	154 $\pm$ 12	187 $\pm$ 13	177 $\pm$ 13	123 $\pm$ 10	117 $\pm$ 15	240 $\pm$ 22	208 $\pm$ 18
+ THC: all	117 $\pm$ 12	151 $\pm$ 9.0	165 $\pm$ 16	188 $\pm$ 11	170 $\pm$ 20	109 $\pm$ 10	129 $\pm$ 16	248 $\pm$ 26	195 $\pm$ 16
– THC: all	137 $\pm$ 7.0	123 $\pm$ 7.2	174 $\pm$ 15	204 $\pm$ 15	192 $\pm$ 17	134 $\pm$ 13	131 $\pm$ 17	250 $\pm$ 20	210 $\pm$ 15

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