Regional Cerebral Blood Flow Changes in Chronic Alcoholic Patients Induced by Naltrexone Challenge During Detoxification

Ana M. Catafau, Alvaro Etcheberrigaray, José Perez de los Cobos, Montserrat Estorch, Josep Guardia, Albert Flotats, Lluís Bernà, Carina Marí, Miquel Casas and Ignasi Carrió

Nuclear Medicine Department and Addictive Behavior Unit, Hospital de Sant Pau, Barcelona; and Departamento de Psiquiatría y Medicina Legal, Universitat Autónoma de Barcelona, Barcelona, Spain

The recent introduction of the opioid antagonist naltrexone for alcohol-dependence therapy has been mainly based on behavioral animal models that provide evidence of the involvement of the endogenous opioid system in alcohol drinking and dependence. However, the neurophysiological mechanisms of the effect of naltrexone in alcoholic patients remain unknown. This study investigates the effects of a naltrexone challenge on regional cerebral blood flow (rCBF) in chronic alcoholic patients during detoxification. **Methods:** Sixteen alcoholic inpatients underwent two ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) brain SPECTs: a basal SPECT on day 10 of abstinence and a second SPECT on day 12 of abstinence after oral administration of 150 mg naltrexone. Region-to-cerebellar ratios were obtained for the orbitary frontal, prefrontal, lateral temporal and mesial temporal regions, basal ganglia and thalamus in each hemisphere. A percentage of rCBF change between both SPECTs was calculated for each region as 100 × (naltrexone − baseline)/baseline. Values from 13 brain SPECTs of age-matched normal volunteers including test-retest measurements were used for statistical comparison. **Results:** In baseline conditions, alcoholics showed lower rCBF than controls in left orbitofrontal cortex (84.0 ± 5.1 versus 89.8 ± 5.0, $P < 0.01$) and prefrontal cortex (left hemisphere: 87.4 ± 5.2 versus 96.2 ± 3.6, $P < 0.001$; right hemisphere: 87.0 ± 4.9 versus 95.8 ± 4.2, $P < 0.001$). After naltrexone, a significant rCBF decrease was found versus test-retest values in left basal ganglia (−3.3% ± 4.0% versus 1.5% ± 4.1%, $P < 0.05$), right basal ganglia (−4.2% ± 4.9% versus 0.6% ± 2.7%, $P < 0.01$) and left mesial temporal region (−4.5% ± 6.8% versus 2.2% ± 2.9%, $P < 0.01$). **Conclusion:** The rCBF decrease detected by SPECT after naltrexone challenge in structures rich in opioid receptors, such as the basal ganglia and the left mesial temporal region, may reflect a naltrexone-induced decreased metabolic activity in these areas. These results support the involvement of the opioid system in alcohol dependence. Furthermore, the localization of naltrexone-induced rCBF changes in mesial temporal structures and in basal ganglia supports the implication of emotional memory and obsessive-compulsive phenomena in craving.

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For correspondence or reprints contact: Ana M. Catafau, MD, Servicio de Medicina Nuclear, Hospital de Sant Pau, Sant Antoni M. Claret, 167, 08025 Barcelona, Spain.

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Naltrexone is an opioid antagonist used in the treatment of opioid dependence that has recently been introduced for alcohol-dependence therapy. It has been demonstrated that naltrexone attenuates alcohol craving (*1*), which has been related to the loss of control over consumption and to the compulsion to self-administer alcohol in addicted patients (*2*). Naltrexone decreases and/or postpones relapse when associated with appropriate psychotherapy (*3*). The introduction of naltrexone for the treatment of alcohol dependence has been mainly based on behavioral animal models that provide evidence of the involvement of the endogenous opioid system in alcohol drinking and dependence (*1*). Along this line, small doses of morphine increase intake of alcoholic beverages and the opioid antagonists naloxone and naltrexone decrease intake of alcoholic beverages in both rats (*4*) and monkeys (*5*). In human studies, abnormalities in plasma levels of β-endorphin both in basal conditions and in response to ethanol have been reported in subjects genetically at high risk for alcoholism (*6*). However, the underlying neurophysiological mechanisms of the effect of naltrexone in alcoholic patients remain unknown.

Brain SPECT has been shown to be useful in detecting changes in human cerebral function as a response to the administration of several psychoactive drugs (*7–9*). It is well known that brain perfusion SPECT studies can detect regional cerebral blood flow (rCBF) increases as a response to vasodilatory drugs such as acetazolamide (*10*). In a similar manner, the tight coupling of neuronal metabolism and rCBF in most conditions makes brain SPECT a feasible technique for studying the effects of drugs without direct vascular action on the central nervous system. Therefore, the blockade of opioid neuroreceptors induced by naltrexone may lead to neuronal metabolic changes that can be reflected in the rCBF. In this study, we investigated the effects on

rCBF of a naltrexone challenge in alcohol-dependent patients.

METHODS

Subjects

Sixteen inpatients were recruited from the detoxification unit of our hospital with the following characteristics: right-handed men, mean age 39 y, range 28–52 y. All had *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis of alcohol dependence and fit criteria for Cloninger type 2 alcohol dependence (all patients had onset of alcoholism before 25 y of age and 13 out of 16 had an alcoholic biological father). Patients had not used other psychoactive drugs in the last year as assessed by a urine test at the time of admission. Although all patients had high transaminase levels, these were inferior to two-fold normal values, which is a condition for naltrexone treatment (*11*). All patients were heavy drinkers; the mean alcohol intake in the preceding year was 204 ± 90.5 g/d (range 120–400 g/d). The mean time of alcohol abuse was 22.6 ± 7.6 y (range 14–37 y). Patients received decreasing doses of benzodiazepines during the first 8 d of detoxification, and no withdrawal symptoms were present at the time of the SPECT study.

Thirteen normal right-handed volunteers (5 women, 8 men), mean age 28 y (range 26–42 y) without history of alcoholism or other drug abuse were recruited for comparison. Subjects were asked not to drink alcohol or xanthines or to smoke during the week before the SPECT study. Informed consent to participate in the study was obtained from all patients.

SPECT Procedure

All patients and controls underwent two ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO; Nycomed Amersham, Madrid, Spain) SPECTs 48 h apart. Controls underwent both SPECTs in the same baseline conditions to obtain both normal relative rCBF ratios and the normal intrasubject variability of tracer uptake (test-retest values). Alcoholic patients underwent the first SPECT study on day 10 of abstinence in baseline conditions. The second SPECT was performed on day 12 of abstinence, 24 h after the oral administration of 150 mg naltrexone.

SPECTs were performed using a dual-head system (Elscint-Helix, Haifa, Israel) fitted with parallel-hole, low-energy, high-resolution collimators. Acquisition was started 20 min after the intravenous injection of 740 MBq (20 mCi) ^{99m}Tc-HMPAO. A complete 360° circular orbit, mode step and shoot (20 s image every 3°) was used. Images were acquired in a 128 × 128 matrix, and the final pixel size was 2.96 mm. The full width at half maximum (FWHM) in the transaxial plane was 9 mm. Filtered backprojection was used for reconstruction by applying a Metz filter. Attenuation correction of the reconstructed data was applied using the Chang method, with a coefficient factor of 0.075. The SPECT data were realigned to obtain within-subject correlated slices. Two-pixel-thick oblique, coronal, sagittal and temporal slices were obtained. Oblique slices were taken in the fronto-occipital direction, and temporal slices were parallel to the long axis of the temporal lobe (Fig. 1).

Semiquantitative analysis was performed to obtain region-to-cerebellar ratios for each hemisphere, as previously described (*12*). Irregular regions of interest (ROIs) stored in the computer as a template were placed by the same investigator, who was blind to clinical data. Oblique slices were used to place ROIs corresponding to cerebellum, orbitofrontal and prefrontal cortex, basal ganglia and thalamus. Temporal slices were used to place the lateral and mesial temporal ROIs (Fig. 1). Mean counts per pixel on two consecutive slices were averaged for each region to take in the maximum extension possible for each region and to minimize problems due to partial volume effect. All indices were corrected for the injected dose.

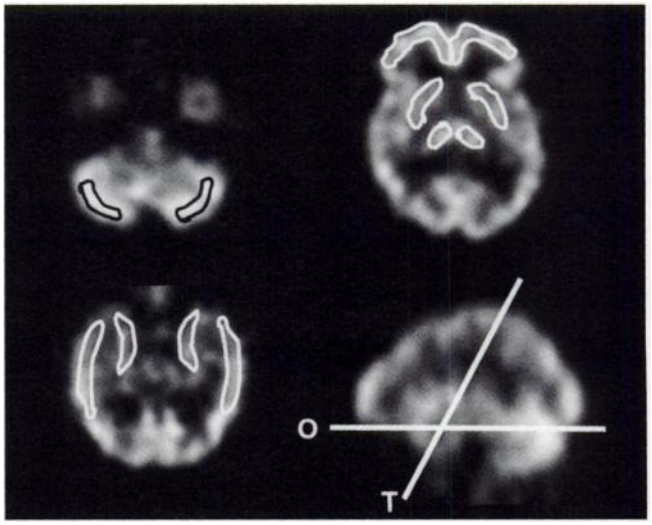

FIGURE 1. Representative template of ROIs used to obtain mean counts per pixel on cerebellum, orbitofrontal and prefrontal cortex, basal ganglia and thalamus (ROIs placed on orbitofrontal slices [O]), as well as mesial and lateral temporal regions (ROIs placed on temporal slices [T]).

Intra- and interobserver variation with respect to the quantitative method is expressed in Table 1 as the within (CVI) and between (CVB) assay coefficients of variation for each ratio. All ratios were obtained twice by two independent observers on separate days on 10 subjects. The coefficients of variation were calculated as CVI = $100 \times \alpha/\sqrt{r}$, where $\alpha = \sqrt{\sigma^2 \bar{x}}$ (r = number of measurements, in this case, 2; σ^2 = mean of variances of both measurements; and $\bar{x}$ = mean of the means of both measurements) and CVB = CV $\bar{x}$, where CV $\bar{x}$ = coefficient of variation of the means of each assay measurement (*12,13*).

In alcoholic patients, a percentage of rCBF change between the baseline and the postnaltrexone scans was calculated for each

TABLE 1
Within and Between Assay Coefficient of Variation (CVI and CVB, Respectively) Calculated for Each Region in 10 Subjects

Cerebral region	CVI	CVB
Right orbitary frontal	0.35	0.49
Left orbitary frontal	0.27	0.68
Right prefrontal	0.35	0.61
Left prefrontal	0.22	0.37
Right lateral temporal	0.39	1.04
Left lateral temporal	0.44	0.84
Right mesial temporal	0.44	0.57
Left mesial temporal	0.44	0.64
Right basal ganglia	0.38	0.32
Left basal ganglia	0.35	0.33
Right thalamus	0.31	0.39
Left thalamus	0.26	0.78

region using the formula 100 × (naltrexone − baseline)/baseline (*14*).

In a similar manner, test-retest values for each region were calculated from the SPECTs obtained in normal subjects (100 × (second SPECT − first SPECT)/first SPECT).

Statistical Analysis

Baseline rCBF ratios were compared between alcoholic patients and normal subjects. The percentage of rCBF change between the resting and postnaltrexone scans of alcoholic patients was compared to the test-retest measurements obtained in normal subjects. Results are expressed as mean ± SD for each cerebral region. The Mann-Whitney *U* test was used, and the level of significance was $P < 0.05$.

RESULTS

The within and between assay coefficients of variation calculated for each region-to-cerebellar ratio were inferior to 0.44 and 1.04, respectively (Table 1).

When comparing baseline perfusion patterns between alcoholics and controls, we found a significant frontal rCBF impairment in alcoholics. The left orbitofrontal-to-cerebellar ratio was significantly lower in alcoholics (84.0 ± 5.1) than in controls (89.8 ± 5.0, $P < 0.01$), and the prefrontal-to-cerebellar ratio was significantly lower in alcoholics than in controls in both hemispheres (left hemisphere: 87.4 ± 5.2 versus 96.2 ± 3.6, $P < 0.001$; right hemisphere: 87.0 ± 4.9 versus 95.8 ± 4.2, $P < 0.001$). No significant rCBF differences were found in the remaining cerebral regions studied.

Mean test-retest variability in normal controls for each region ranged from −2.2% ± 4.4% (left thalamus) to 3.0% ± 5.4% (right lateral temporal). Alcoholic patients showed a significant rCBF decrease versus test-retest values after naltrexone challenge in the left mesial temporal region (−4.5% ± 6.8% versus 2.2% ± 2.9%, $P < 0.01$) and bilaterally in basal ganglia (−3.3% ± 4.0% versus 1.5% ± 4.1%, $P < 0.05$, and −4.2% ± 4.9% versus 0.6% ± 2.7%, $P < 0.01$, for left and right hemispheres, respectively) (Fig. 2). Mean test-retest values and percentages of change after naltrexone challenge for each cerebral region studied are presented in Table 2. No significant differences in the percentage of change after naltrexone challenge were found in the remaining cerebral regions studied.

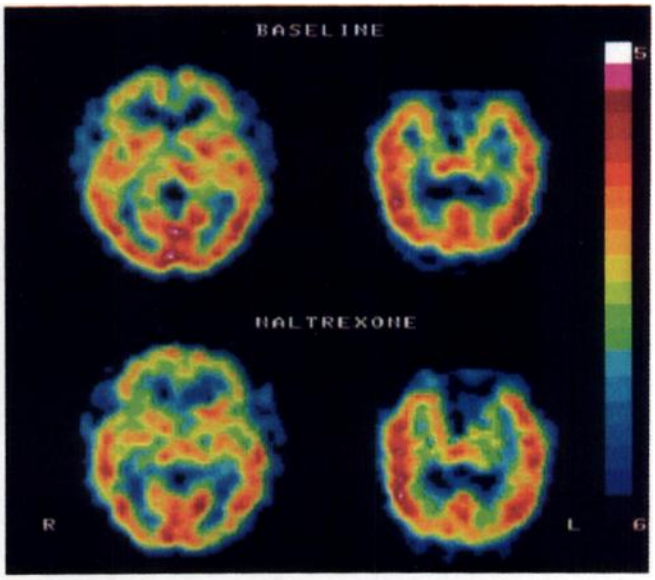

FIGURE 2. Oblique and temporal SPECT slices in an alcoholic patient. Baseline scan shows bilateral frontal hypoperfusion. In postnaltrexone scan, rCBF decrease is seen in left mesial temporal region and in basal ganglia compared to baseline images.

DISCUSSION

Alcoholic patients showed a frontal rCBF impairment in baseline conditions at day 10 of abstinence during the detoxification process. A single dose of naltrexone (150 mg orally) induced a significant decrease in basal ganglia and left mesial temporal rCBF.

Several PET and SPECT studies have reported metabolic and rCBF abnormalities in different cerebral regions of alcoholic patients without neurological impairment (*15–17*). Although results vary, the frontal metabolic and rCBF impairment, involving the orbitofrontal and the prefrontal cortex, is the most replicated finding and may affect up to 65%–67% of patients (*15,17*). This frontal impairment is independent from the degree of cerebral atrophy (*15*) and relates to the frontal neuropsychological impairment (*15,17*). Our results also show an orbitofrontal and prefrontal perfusion impairment in chronic alcoholic patients during detoxification.

In this study, alcoholic patients were studied at day 10 of abstinence and no withdrawal symptoms were present at that time. Metabolic and rCBF abnormalities due to alcohol withdrawal may subside after abstinence. However, recovery does not seem to appear before 2 wk of abstinence. We previously reported no significant rCBF changes between the day of admission (with positive alcoholemia) and the 10th d of alcohol abstinence in chronic alcoholic patients without withdrawal syndrome, but an rCBF improvement after 2 mo of abstinence was observed (*15*). Studying a similar patient population by PET, Volkow et al. (*16*) reported that most of the recovery in brain metabolism occurred within 16–30 d of alcohol detoxification. Therefore, no rCBF changes related to withdrawal were expected between 10–12 d of abstinence.

Effect of a Single Administration of Opioid Antagonists

The pharmacological duration of naltrexone is actually longer than might be predicted by plasma kinetics. Pharmacokinetic studies have demonstrated a plasma half-life of 4 h for naltrexone and of 12 h for its major active metabolite, 6-β-naltrexol (*18*). However, after a 150-mg dose, antagonism of injected opioids has been shown to be at its maximum from 24 to 48 h but to be still present at 72 h (*19*). Furthermore, the percentage of blockade of ^{11}C-carfentanil induced by a single oral dose of 50 mg naltrexone has been reported to rise up to 91% at 48 h and to decrease monoexponentially with an average half-time of 72 h (*20*).

TABLE 2
Test-Retest Values and Percentage of Change After Naltrexone Challenge for the Cerebral Regions Studied

Cerebral region	Test-retest (controls, n = 13)	% Change after naltrexone (alcoholics, n = 16)
Right orbitary frontal	2.1 ± 4.0	1.0 ± 6.3
Left orbitary frontal	1.0 ± 3.5	0.7 ± 6.6
Right prefrontal	1.2 ± 2.4	0.5 ± 5.6
Left prefrontal	0.8 ± 4.9	−0.2 ± 5.9
Right lateral temporal	3.0 ± 5.4	0.0 ± 6.2
Left lateral temporal	2.4 ± 7.2	1.9 ± 6.7
Right mesial temporal	2.6 ± 6.0	0.3 ± 6.7
Left mesial temporal	2.2 ± 2.9	−4.5 ± 6.8*
Right basal ganglia	0.6 ± 2.7	−4.2 ± 4.9*
Left basal ganglia	1.5 ± 4.1	−3.3 ± 4.0*
Right thalamus	−0.7 ± 3.7	0.3 ± 9.1
Left thalamus	−2.2 ± 4.4	0.6 ± 9.2

Values are mean ± SD.
*Mann-Whitney *U* test, $P < 0.05$.

Therefore, the largest SPECT changes should be expected between 24 and 48 h after naltrexone challenge.

Using ^{99m}Tc-HMPAO brain SPECT, researchers have studied the effect of the acute administration of opioid antagonists naloxone and naltrexone in opiate-dependent patients (*21,22*) and in healthy volunteers after an acute intake of ethanol (*23*) but not in chronic alcoholic patients. Van Dyck et al. (*21*) studied 11 opiate-dependent patients with naltrexone-precipitated withdrawal from buprenorphine. They found no significant effect of naltrexone (25 mg orally) on rCBF ratios, but they found a significant negative correlation between severity of withdrawal and anterior cingulate rCBF after naltrexone. In a different study, the same group administered a single dose of naloxone (0.8 mg subcutaneously) to 10 methadone-maintained patients undergoing opiate withdrawal (*22*), and they found decreased whole-brain count density and lower right temporal cortex rCBF ratio, compared to the effect of naloxone in controls. In that study, the small magnitude of the changes reported (the highest regional difference found was 2.4%) was remarkable. Apart from methodological differences, the higher naltrexone dose used in our study may explain the larger rCBF changes found, because cerebral metabolic abnormalities related to opiate withdrawal in rats seem to be dependent on the dose of naloxone used to precipitate withdrawal (*24*). Finally, Tiihonen et al. (*23*) studied the effect of both intravenous placebo and intravenous naloxone (0.004 mg/kg) administered to six healthy men before an acute ethanol intake. Although the ethanol intake after placebo resulted in a right prefrontal rCBF increase, no significant rCBF change was found after naloxone, indicating that naloxone blocked the ethanol-induced rCBF changes and suggesting that these changes are mediated through the endogenous opioid system.

Although the effect of naltrexone on rCBF of normal subjects in baseline conditions is still unknown, no or few changes should be expected. Krystal et al. (*22*) reported slightly decreased right parietal cortex and increased right temporal cortex and left basal ganglia activity ratios in their controls after naloxone administration. In addition, no effect of naloxone on cerebral glucose utilization in nonopiate-dependent rats has been reported (*25*).

Effect of Naltrexone in Alcoholic Patients

In our cohort of alcoholic patients, the single acute administration of naltrexone (150 mg orally) induced a significant rCBF decrease in the basal ganglia and in the left mesial temporal region. These structures are rich in opioid receptors, as reported in PET studies on the distribution of μ-opioid receptors in humans (*26*). Therefore, these rCBF changes could reflect a naltrexone-induced decrease in metabolic activity. The mesial temporal ROI designed in this study included the amygdala and hippocampus, which are structures involved in memory and emotion. There is PET evidence of increased metabolism in the amygdala of cocaine abusers when submitted to cue-induced craving (*27*), suggesting a role for memory (especially its emotional component) in craving. In our study, no craving rating scales were applied to the alcoholic patients. However, because the main therapeutic action of naltrexone in alcoholic patients is related to the attenuation of craving (*1*), the naltrexone-induced mesial temporal rCBF decrease is a striking finding. A positive correlation of the severity of cocaine craving and the μ-opioid receptor tracer ^{11}C-carfentanil binding in the amygdala and temporal cortex of cocaine-dependent patients has been published as the first PET evidence of the involvement of the endogenous opioid system in cocaine craving (*28*). Our finding of a mesial temporal rCBF decrease induced by naltrexone may be related to its μ-opioid receptor antagonism. This finding gives support to the hypothesis of the involvement of mesial temporal lobe structures in the pathophysiology of craving. There may be a relationship between the blockade of the opioid system and the inhibition of emotional memory circuits that is linked to mesial temporal lobe structures.

Based on clinical similarities between the obsessive thoughts and compulsive behaviors of alcohol-dependent subjects and those of patients with obsessive-compulsive disorder (OCD) (*29*) and based on the evidence that serotonin uptake inhibitors used in the treatment of OCD are also effective in inhibiting volitional drinking (*30*), alcohol dependence has been compared to OCD. Furthermore, a modified OCD rating scale recently has been proposed for quantification of alcohol abuse and dependence severity (*31*). There is increasing evidence that basal ganglia dysfunction underlies OCD. The association of OCD with several basal ganglia disorders and the PET and SPECT evidence of basal ganglia metabolic and perfusion abnormalities in OCD patients support such a model (*32*). In our alcoholic patients, the basal ganglia rCBF was significantly reduced after

naltrexone challenge. In a ^{99m}Tc-HMPAO SPECT study of nine alcohol-dependent subjects, a blood flow increase during alcohol craving was found in the head of the right caudate nucleus, which correlated with the experimentally induced increases in craving, thus suggesting a functional role for the limbic striatum in the mediation of the impaired control over alcohol consumption (*33*). Furthermore, Volkow et al. (*34*) found an increased metabolic activity in the basal ganglia and orbitofrontal cortex induced by δ-9-tetrahydrocannabinol (main psychoactive component of marijuana) in chronic marijuana abusers, and they suggested that the same frontostriatal dysfunction underlying OCD could lead to the loss of control and compulsive drug use. The orbitofrontal cortex and the anterior cingulate are limbic structures that have been linked to OCD and craving. These regions are part of the frontostriatal pathway and have been reported to be hyperactive on brain SPECT in OCD patients (*35*). Moreover, μ-opioid binding in these regions positively correlates to the severity of craving in cocaine abusers (*28*). Interestingly, a negative correlation between severity of withdrawal and anterior cingulate rCBF after naltrexone in opiate-dependent patients has been assessed by SPECT (*21*). In the current study, no rCBF changes were found in the orbitofrontal cortex, and the anterior cingulate was included in the frontal ROIs. It is not known if the baseline impaired frontal rCBF in alcoholics could be related to the lack of naltrexone rCBF-induced changes found in this region. However, the naltrexone-induced basal ganglia rCBF decrease found in this study makes it tempting to hypothesize that naltrexone inhibits the compulsion of drinking by acting through the biological basis of the obsessive-compulsive phenomena.

CONCLUSION

Brain perfusion SPECT shows a rCBF decrease in structures rich in opioid receptors such as the basal ganglia and the left mesial temporal region after a single oral administration of naltrexone. This finding may reflect a naltrexone-induced decrease in the metabolic activity of these regions. The target cerebral regions that present changes in activity after naltrexone in alcoholic patients may participate in alcohol dependence, thus supporting the involvement of the opioid system in such a compulsive habit. Furthermore, the localization of naltrexone-induced rCBF changes in mesial temporal structures and in basal ganglia supports the implication of emotional memory and obsessive-compulsive phenomena in craving.

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