Opioid Receptor Imaging with Positron Emission Tomography and $[^{18}F]$Cyclofoxy in Long-Term, Methadone-Treated Former Heroin Addicts

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ABSTRACT

Stabilized methadone-maintained former heroin addicts (MTPs) treated with effective doses of methadone have markedly reduced drug craving; reduction or elimination of heroin use; normalized stress-responsive hypothalamic-pituitary-adrenal, reproductive, and gastrointestinal function; and marked improvement in immune function and normal responses to pain, all of which are physiological indices modulated in part by endogenous and exogenous opioids directed at the mu and, in some cases, the kappa-opioid systems. This study was performed to explore opioid receptor binding in MTPs. Fourteen normal, healthy volunteers and 14 long-term MTPs in treatment for 2 to 27 years and receiving 30 to 90 mg/day of methadone were studied with positron emission tomography using tracer amounts of $[^{18}F]$cyclofoxy, an opioid antagonist that labels mu and kappa opioid receptors. Imaging was performed in the morning, 22 h after the last dose of methadone in patients, and concurrent plasma levels of methadone were determined. Five brain regions of specific interest for addiction and pain research (thalamus, amygdala, caudate, anterior cingulate cortex, and putamen) were among the six regions of highest $[^{18}F]$cyclofoxy binding. Specific binding of $[^{18}F]$cyclofoxy was lower by 19 to 32% in these regions in MTPs compared with those in normal volunteers. The degree to which specific binding was lower in caudate and putamen correlated with methadone plasma levels ($P < .01$ and $P < .05$, respectively), suggesting that these lower levels of binding may be related to receptor occupancy with methadone and that significant numbers of opioid receptors may be available to function in their normal physiological roles.

We have found that well stabilized, methadone-maintained, former heroin addicts (MTPs) treated with effective dosages, with no ongoing polydrug or alcohol abuse, have markedly reduced or eliminated drug craving and normalized stress-responsive hypothalamic-pituitary-adrenal axis function and also reproductive, biology-related hypothalamic-pituitary-gonadal axis function (Kreek, 1973a, 1978, 1987, 1992a, 1996a,b; Kreek et al., 1981, 1984; Kreek and Koob, 1998). In contrast, profound alterations in both the stress-responsive and the reproductive axes have been documented in active heroin addicts during cycles of short-acting opiate abuse, primarily of heroin (which has a half-life of only 3 min in humans) and its major metabolite, morphine (which has a half-life of 4–6 h) (Kreek, 1973a, 1978, 1987, 1996a,b; Kreek et al., 1981, 1984; Kreek and Koob, 1998). Many studies have shown that both these functional systems are modulated by the mu opioid receptor-directed endogenous opioid ligands in normal, healthy humans (Kreek, 1987, 1996b; Kreek and Koob, 1998; Schlugger et al., 1998). Immune function, which may also be modulated in part by the endogenous opioid system and is abnormal during cycles of heroin addiction, becomes normal during long-term methadone treatment (Novick et al., 1989). The subjective responses to acute and chronic pain are similar in methadone-maintained patients and non-opioid-dependent persons; acute and chronic pain in maintenance patients similarly responds to treatment with short-acting, primarily mu opioid receptor-directed analgesic agents such as morphine, hydromorphone, and fentanyl (Ho and Dole, 1979).

We have hypothesized that although a proportion of mu opioid receptors would be occupied by methadone at all times during stabilized, long-term methadone maintenance with

ABBREVIATIONS: MTP, methadone-maintained former heroin addicts; PET, positron emission tomography; ROI, region of interest; RUH, Rockefeller University Hospital; NIH, National Institutes of Health.
moderate to high doses of methadone, significant numbers of mu receptors remain unoccupied and thus available for action by the endogenous opioid ligands in critical brain regions. These unoccupied receptors are also available for action by exogenous opioid ligands commonly used for the relief of pain. The half-life of methadone in the racemic (d,l or S,R) form commonly used in treatment is 24 h in humans, and additional studies using stable isotope technology have shown that the half-life of the active (l,R) enantiomer of methadone in humans is 36 to 48 h (Inturrisi and Verebely, 1972; Kreek, 1973b; Rubenstein et al., 1978; Kreek et al., 1979). We would predict that a significant proportion of mu opioid receptors would be occupied by this ligand in steady state during treatment. We also hypothesized that if in long-term, stabilized, methadone maintenance patients, the occupancy of mu opioid receptors by methadone uses only a portion of available receptors, then this would allow the documented gradual normalization of those aspects of physiology that are under modulation by mu opioid receptor-directed endogenous ligands. Furthermore, these unoccupied receptors may bind endogenous opioids to allow normal responsiveness to pain and stressors as well as to exogenous opioids used in analgesia.

In an extensive series of double blind studies, it was shown that adequate doses of methadone fully protected against any perception of superimposed short-acting opiates, including objective and subjective potentially priming effects and any adverse reactions (Dole et al., 1966; Kreek, 1992). However, we have also shown that if very large amounts of heroin are superimposed, narcotic-like, including euphorogenic, effects can be produced by exceeding the degree of tolerance and cross-tolerance to other opioids achieved during steady-state, moderate- to high-dose (60–150 mg/day) methadone treatment (Dole et al., 1966; Kreek, 1992).

Therefore, we conducted a study using positron emission tomography (PET) with $^{[18F]}$cyclofoxy as the radioligand, an opioid antagonist with mu and kappa opioid receptor-directed binding (Pert et al., 1984; Burke et al., 1985; Channing et al., 1985; Rothman and McLean, 1988; Theodore et al., 1992; Carson et al., 1993; Cohen et al., 1997). The purposes of this study were 1) to extend earlier PET studies in young and middle-aged healthy volunteers with no history of substance abuse by mapping the extent of opioid receptor binding throughout the human brain, including five regions of special interest for research in addictive diseases that are also related to pain and analgesia (caudate, putamen, amygdala, anterior cingulate cortex, and thalamus) and 2) to conduct PET studies in long-term, stabilized, methadone-maintained former heroin addicts to determine the possible changes in the binding of $^{[18F]}$cyclofoxy assumed to be attributable to occupancy by methadone and to determine whether there are any regional variations in changes of opioid receptor binding.

Materials and Methods

Twenty-eight subjects were studied: 14 normal, healthy volunteers (7 males) with a mean age of 38 years (23–65 years) and 14 long-term, methadone-treated patients (8 males), all former heroin addicts, with a mean age of 37 years (20–60 years). Each subject in this second group met the requirements of the federal regulations for entry into long-acting opioid agonist treatment with methadone, or l-α-acetylmethadol, i.e., at least 1 year of multiple, daily self-administrations of a short-acting opiate, primarily heroin, with the development of tolerance and physical dependence. These subjects were maintained on methadone administered orally each day at doses ranging from 30 to 90 mg/day, with a mean dose of 62 mg/day. Their duration of methadone-maintenance treatment ranged from 2 to 27 years, with a mean of 7.6 years.

Subjects were initially evaluated in the Rockefeller University Hospital (RUH), a National Institutes of Health (NIH) General Clinical Research Center. Each subject signed a written informed consent at the RUH General Clinical Research Center. Later, each subject signed a separate informed consent form at the NIH Clinical Center. Study protocol and informed consents were approved by the appropriate institutional review boards and radiation safety committees at both institutions.

Potential study subjects were first seen in the outpatient clinic on two or more occasions for evaluation and explanations of the entire study procedure. Subjects were admitted to the RUH General Clinical Research Center for at least 1 day for baseline neuroendocrine re-evaluation immediately before going to the NIH Clinical Center. They were then accompanied to Bethesda, MD, the location of the NIH Clinical Center, by a Rockefeller University physician or nurse for 1) an initial outpatient visit, 2) a magnetic resonance imaging scan to rule out any gross structural abnormality of the brain, and 3) PET imaging using $^{[18F]}$cyclofoxy, which was performed in the morning for all subjects 22 ± 1 h after the last dose of methadone in the methadone-maintained patients. All studies were performed within 2 days on an outpatient basis at the NIH Clinical Center.

Cyclofoxy, an opioid antagonist originally synthesized and developed by the laboratory group of Dr. Kenner Rice (National Institute for Diabetes, Digestive and Kidney Diseases, NIH), made imaging of opioid receptors possible (Pert et al., 1984; Burke et al., 1985; Channing et al., 1985). On each study day, $^{[18F]}$cyclofoxy was synthesized in the NIH-CC PET Department. A Scanditronix scanner (model PC2048-15B; Scanditronix, Uppsala, Sweden), which provides 15 simultaneous slices with 6- to 7-mm axial and transverse resolution, was used for PET imaging. Subjects were positioned so that transverse slices were acquired along the canthomeatal line.

Before the study began, a physician placed an intra-arterial line in the radial artery of one arm and an intravenous line in the antecubital fossa of the other arm of the subject. A molded thermoplastic face mask was made for each subject to maintain head position throughout the PET study. $^{[18F]}$Cyclofoxy (approximately 4 mCi i.v.) was injected over 1 min. $^{[18F]}$Cyclofoxy was prepared with a sufficiently high specific activity to contain less than 8 μCi of total cyclofoxy to prevent precipitating any opioid withdrawal symptoms in the methadone-maintained patients and to prevent demonstrable changes in receptor occupancy in any study subject. Twenty-three scan frames were obtained over 90 min at predetermined time intervals (Cohen et al., 1997). Thus, cyclofoxy, which is administered by bolus, approaches equilibrium over the time of the 90-min scans. Arterial blood samples were taken at predetermined time points to measure the plasma input function. Metabolite analysis was performed at 13 time points by extraction of plasma with ethyl acetate and radiolabel counting (Carson et al., 1993). Protein binding of $^{[18F]}$cyclofoxy measured by ultrafiltration was found to be similar in the control and patient groups (unbound fractions for controls, 63.9 ± 3.2%; MTP, 63.4 ± 4.1%). Blood samples were also taken to measure plasma levels of methadone before the beginning of the study and at 30, 60, and 90 min. The daily dose of methadone was administered to maintenance patients after the study was completed approximately 24 h after the last dose.

The total binding of $^{[18F]}$cyclofoxy was determined in 14 brain regions of interest (ROIs), which were identified on the reconstructed PET images (Table 1). The procedure for data analysis for this study is based on previous $^{[18F]}$cyclofoxy studies in baboons and in humans (Theodore et al., 1992; Carson et al., 1993; Cohen et al., 1997). The time series of cyclofoxy images were first corrected for subject motion (Woods et al., 1992). Each image obtained 10 min after injection was matched to an image obtained by summing images from 0 to 10 min.
Circular ROIs (37 pixels, 2 mm/pixel) were placed on the summed images (Cohen et al., 1997). A sample ROI using the methods of this study has been published previously (Cohen et al., 1997). Time-activity curves were obtained from the motion-corrected images. Then data were fitted to a model with one tissue compartment and three parameters, \( K_1 \), \( K_2 \), and \( V_t \), to define tissue uptake (\( K_t \), clearance (\( k_t \)), and vascular volume (volume of blood, \( V_b \)), respectively. Although this model is simplified, it is adequate to describe the kinetics of cyclofoxy in humans (Theodore et al., 1992).

The primary parameter of interest in this analysis is the total tissue volume of distribution, \( V_t \), which is calculated from the fitted parameters. We define \( V_t \) as the ratio at true equilibrium of tissue concentration to metabolite-corrected plasma radioactivity. For this model, \( V_t \) is calculated as \( K_t/k_{g_0} \), i.e., the one-tissue-compartment model estimate of the total tracer volume of distribution. \( V_t \) measures total tracer bound, i.e., free tracer, nonspecifically bound tracer, and specifically bound tracer. In a region with little or no specific binding such as the occipital cortex, \( V_t \) measures only free and nonspecifically bound tracer. Published data of opioid receptor density in human brain post mortem have shown modest kappa opioid receptor density but little to no mu opioid receptor density in specific subregions of the occipital cortex (Hiller and Fan, 1996).

Assuming that nonspecific binding is uniform throughout the brain, we define the specific volume of distribution, \( V_s \), of an ROI as the ROI volume minus each individual’s value was plotted against plasma levels of methadone. The level of significance was .05, with Bonferroni correction for multiple comparisons.

To investigate the relationship between the circulating plasma levels of methadone and the degree of lowering in comparison with normal volunteers of specific cyclofoxy binding in the six ROIs with greatest specific cyclofoxy binding, regression analysis with correlation was used. For each ROI of the 12 MTPs for whom mean plasma methadone levels across the 90-min period of scanning were available, the mean value of the specific binding of the control group minus each individual’s value was plotted against plasma levels of methadone.

**Results**

The total binding for normal, healthy subjects and long-term, stabilized MTP subjects is presented (Table 1). The specific binding in healthy volunteers in all brain regions studied is compared with that in the long-term MTPs (Fig. 1 and Table 1).

<table>
<thead>
<tr>
<th>Total [18F]Cyclofoxy Binding</th>
<th>Specific [18F]Cyclofoxy Binding</th>
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<tbody>
<tr>
<td>Normal Volunteers</td>
<td>Methadone-Treated Patients</td>
</tr>
<tr>
<td></td>
<td>ml plasma/ml tissue</td>
</tr>
<tr>
<td>Thalamus</td>
<td>20.7 ± 2.5</td>
</tr>
<tr>
<td>Amygdala</td>
<td>17.8 ± 3.6</td>
</tr>
<tr>
<td>Caudate</td>
<td>17.1 ± 2.7</td>
</tr>
<tr>
<td>Insula</td>
<td>16.4 ± 2.1</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>16.3 ± 1.9</td>
</tr>
<tr>
<td>Putamen</td>
<td>16.3 ± 2.5</td>
</tr>
<tr>
<td>Middle temporal cortex</td>
<td>14.4 ± 1.7</td>
</tr>
<tr>
<td>Middle frontal cortex</td>
<td>13.7 ± 1.6</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>12.6 ± 1.5</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>11.5 ± 1.4</td>
</tr>
<tr>
<td>Inferior temporal cortex</td>
<td>11.5 ± 1.8</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>10.9 ± 1.7</td>
</tr>
<tr>
<td>White matter</td>
<td>7.3 ± 0.7</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>6.6 ± 0.6</td>
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</tbody>
</table>

* Values are mean ± S.D.

\( n = 13. \)
term, stabilized, methadone-maintained patients and the normal, healthy volunteers are shown in Table 2. Plasma levels of methadone were at a plateau, as expected from previous studies, and within the expected therapeutic range (Fig. 2). The degree to which specific binding of $^{[18F]}$cyclofoxy was lower in MTPs in comparison with normal volunteers, although small, was significantly correlated with the mean plasma levels of methadone ($0–90$ min) in caudate ($P, .01$) and putamen ($P, .05$) and was near significant levels in anterior cingulate cortex ($P, .06$) and insula ($P, .06$) (Fig. 3).

### Discussion

To further our understanding of opioidergic function in opiate addiction and its effective treatment, specific binding of $^{[18F]}$cyclofoxy was determined by PET imaging in 14 stabilized, long-term, methadone-maintained former heroin addicts (mean age, $38$ years) and compared with binding in normal, healthy volunteers (mean age, $37$ years). The five brain regions, which were of especial interest to us from the start of the study because of their involvement in addictive diseases and pain, were found to be five of the six areas with the most cyclofoxy binding in human brain: thalamus, amygdala, caudate, anterior cingulate cortex, and putamen. In a previously reported study of patients with Alzheimer’s disease and similarly older, age-matched healthy subjects from $51$ to $75$ years of age, similar subcortical (caudate, putamen, and thalamus) and limbic and paralimbic (anterior cingulate cortex, amygdala, and insula) brain regions were found to have the highest values for cyclofoxy-specific binding (Cohen et al., $1997$). Specific binding of $^{[18F]}$cyclofoxy in these five regions of special interest in methadone-maintained former heroin addicts studied $22$ h after the last oral dose of methadone was determined to be $19$ to $32\%$ lower than that observed in normal volunteers. Furthermore, the lower specific binding in MTPs compared with normal volunteers was correlated with their plasma methadone levels.

Since the cloning of first the rodent and then the human mu opioid receptor, it has been possible to study the binding of mu, kappa, and delta opioid ligands. In all these studies, as

<table>
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<tr>
<th>TABLE 2 Percentage lower binding in five ROIs in MTPs compared with normal volunteers$^a$</th>
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<tbody>
<tr>
<td>Total $^{[18F]}$Cyclofoxy Binding</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Thalamus</td>
</tr>
<tr>
<td>Amygdala</td>
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<td>Caudate</td>
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<td>Anterior cingulate cortex</td>
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<td>Putamen</td>
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$^a$ Percentage lower binding = (mean of normal volunteers – individual MTP’s values). Values are mean ± S.D.
well as in recent signal transduction studies, methadone has been demonstrated to be a pure and full agonist directed specifically at the mu opioid receptor. However, the only available published data for cyclofoxy have been generated in in vitro experiments using rodent tissue and indicate that cyclofoxy binds to both mu and kappa receptors (Rothman and McLean, 1988). To date, there is only indirect evidence suggesting that cyclofoxy binds preferentially at mu receptors, such as the finding in this study of low binding in the occipital cortex, an area with little mu but significant kappa opioid receptor density in humans as well as similar in vivo findings from previous PET studies using this ligand (Hiller and Fan, 1996; Cohen et al., 1997). The methodology of our study did not permit the determination of whether these findings are consistent with an overall decrease, increase, or lack of change in opioid receptor number (with occupancy alone accounting for the lower binding), affinity, or function in MTPs compared with normal volunteers. Interestingly, there is one recent report that includes the assessment of mu opioid receptor density in human heroin addicts post mortem in comparison with healthy controls, which showed no change in opioid receptor density (Gabilondo et al., 1994). Potentially relevant preclinical studies have not yielded a consensus on the effects of chronic exposure to short-acting mu opioid receptor agonists on receptor density or binding capacity. There are no studies delivering methadone by pump, which is necessary in rodents to model the long-acting pharmacokinetic properties of methadone in humans (Zhou et al., 1996). We hypothesize that the lower binding in MTPs in comparison with normal volunteers reflects steady-state methadone occupancy of mu opioid receptors. The half-life of methadone in the racemic ($d,l$ or $S,R$) form, usually used in treatment of heroin addiction or chronic pain, is 24 h in humans, and the half-life of the active ($l,R$) enantiomer in humans is 36 to 48 h (Inturrisi and Verebely, 1972; Kreek, 1973b; Rubenstein et al., 1978; Kreek et al., 1979). The peak plasma levels of methadone occur 2 to 4 h after oral dosing, and the plasma levels return to plateau levels within 4 to 8 h after each oral dose (Inturrisi and Verebely, 1972; Kreek, 1973b; Kreek et al., 1979). In addition, we have found that the cerebrospinal fluid levels of methadone vary in relationship to plasma levels of methadone, with peak levels occurring at approximately the same time and with levels of methadone in cerebrospinal fluid approximately 10 to 20% of those in plasma at most time points studied (Rubenstein et al., 1978). Therefore, these PET studies were performed at a time that, in other studies, we have found plasma levels of methadone to be sustained at a plateau, usually approximately.

Fig. 2. Plasma levels of methadone in long-term, methadone-treatment patients sampled across the 90-min PET scan session (starting approximately 22 h after the last dose of methadone). Values for the 12 patients for whom the plasma was available are expressed as mean ± S.E.M.

![Graph](image-url)

**Fig. 3.** The amount of each methadone-treated patient’s $^{[18]}F$-cyclofoxy binding less than the mean of that region for the normal volunteers is plotted against the mean plasma methadone level across the PET scan session. The scatterplot with regression line and 95% confidence interval are shown for four of the six regions with the highest levels of specific binding. The amount by which specific binding is lower than the mean of that for the normal volunteers is significantly correlated in caudate (A) and in putamen (B), whereas the relationship fails to reach significance in the anterior cingulate cortex (C) and in insula (D) in the 12 patients for whom plasma methadone levels were available.
150 to 400 ng/ml. In this study, the plasma levels at 22 h after the last oral dose of methadone (dose range, 30–90 mg; mean dose, 62 mg) ranged from 127 to 673 ng/ml, with a mean approximately 350 ng/ml.

Many studies exploring the mechanism of action of methadone and its effectiveness have shown the disruption by chronic use of short-acting opiates such as heroin of multiple physiological processes including modulation of normal stress responsivity, actions at hypothalamic-anterior pituitary sites of release of corticotropin-releasing factor and pro-opiomelanocortin peptides (adrenocorticotropin and \( \beta \)-endorphin), control of reproductive biology, specifically by impairing luteinizing hormone release, alterations of many indices of immune and gastrointestinal function, and a variety of other physiological systems (Kreek, 1973, 1978, 1987, 1992, 1996a,b; Ho and Dole, 1979; Kreek et al., 1981, 1984; Novick et al., 1989; Kreek and Koob, 1998). The early findings of effects of short-acting opioids, in contrast to the gradual normalization during steady-dose, steady-state treatment with methadone, led to the discovery of the role of endogenous opioids in a variety of physiological processes (Kreek, 1973a, 1978, 1992, 1996b; Kreek et al., 1981, 1984). It has been demonstrated and reported that very large amounts of heroin, greater than those usually self-administered, are necessary to overcome the “blockade” provided by moderate to high (60–150 mg) doses of methadone. This is compatible with the concept that methadone is occupying some, but not all, of the available opioid receptors. However, this is not necessarily the full explanation for the blockade or for the gradual normalizations of functions under mu opioid receptor modulation during long-term treatment. The mechanisms that allow the long-acting mu opioid agonist methadone, at doses used in maintenance treatment, to block the effects of the usual self-administered doses of heroin, but that allow normalization of other physiological functions modulated by opioids as well as adequate response to opioid analgesics, have not been fully elucidated. The findings of the present study are not inconsistent with a substantial fraction of opioid receptors being available for binding both to endogenous ligands (which would presumably be related to normalized function of physiological systems known to be modulated in part by endogenous opioids) as well as to additional exogenous opioids (potentially related to the adequate response to opioid analgesia seen in MTPs).

In addition, or alternatively, the lower binding in MTPs may have been attributable to an overall modest reduction of mu (and/or kappa) opioid receptors on cell surfaces during steady-dose methadone maintenance treatment. Such lower binding could be attributable either to occupancy alone and/or to methadone-induced internalization or to other mechanisms yielding actual reduction in receptor density possibly induced by chronic exposure to this long-acting, mu opioid ligand. Alternatively, lower binding could have been present on an a priori basis, such as the presence of an allelic variant of the receptor, with altered binding (Bond et al., 1998). Recent studies have suggested that methadone acts like the natural endogenous opioid peptides with respect to effecting prompt internalization of opioid receptors after cell surface receptor binding in contrast to most exogenous opioids including morphine, the major metabolite of heroin, which does not effect rapid internalization (Keith et al., 1998). The findings of this also would be compatible with a modest increase in opioid receptor density, attributable either to increased receptor presentation on cell surfaces after cycles of internalization or to actual increased production of opioid receptors, with an even higher percentage of occupancy by methadone, which in turn could account for the apparent modest lowered specific \(^{18}\)F)cyclofoxy binding observed (19–32%) during steady-state occupancy by methadone. The correlation of lower cyclofoxy binding levels with plasma methadone levels, along with all previous studies of mu opioid agonist effects on opioid receptor density in adult animals, and the recent study of mu receptor density in heroin addicts post mortem suggest that receptor occupancy with methadone represents a significant component of the lower \(^{18}\)F)cyclofoxy binding observed in MTPs.

Studying additional specific patient populations could help elucidate whether either relative down-regulation or up-regulation occurs in living humans as well as the time course of potential changes in reference to exposure to short-acting illicitly used opiates and long-acting treatment agents. Such populations might include active heroin addicts before entry into treatment as well as long-term illicit drug- and medication-free, well stabilized former addicts without any continuing drug or alcohol abuse in comparison with both normal controls and stabilized long-term MTPs. Studying such subjects presents particular challenges, however, because active heroin addicts before entry into treatment may have difficulty cooperating with the lengthy study protocol and given the approximately 80 to 90% relapse rate of heroin addicts not receiving long-acting opioid pharmacotherapy, significant numbers of truly illicit drug- and medication-free former heroin addicts are very difficult to identify for study. Studying MTPs after a medication “washout” period would also be of theoretical benefit. However, the protracted period required to ethically reduce the dose and discontinue methadone, thus avoiding the discomfort of opiate withdrawal as well as the additional time required to reach a new homeostasis in a medication-free, illicit drug-free status and the very high documented rate of relapse would outweigh the potential value of attempting such a study.

Whether either relative down-regulation or up-regulation of opioid receptors ever occurs in living adult humans could be potentially determined by studying additional specific populations. A large proportion of heroin addicts (70–90%) in many regions of the United States are also cocaine dependent, and a substantial percentage (approximately 30%) of methadone-maintained former heroin addicts remain dependent on cocaine (Borg et al., 1999). Several years ago, our laboratory showed that chronic “binge” pattern cocaine administration causes an increase in mu opioid receptor density in the rat (Unterwald et al., 1992, 1994). Subsequently, these studies were extended in humans by Zubieta et al. (1996), who found an increase of mu opioid receptor density in several specific brain regions in recently abstinent cocaine addicts using PET with \(^{11}\)C]carfentanil as the radiolabeled mu opioid receptor-directed ligand. Recently, Yuferov et al. (1999) have shown that acute binge pattern cocaine administration in a rat model significantly increases the mRNA levels of the mu opioid receptor, which may contribute to the significantly increased density of the mu opioid receptors seen after 7 and 14 days of binge pattern cocaine administration. This is the one example in which a drug of abuse or treatment agent has been shown unequivocally to increase or decrease opioid receptor density in humans as well as in rodent models. Chronic naltrexone administration has been
repeatedly shown to increase mu opioid receptor density in living adult, whole animal studies; however, no studies of its effects in humans have yet been reported. Additional PET studies in unstabilized methadone-maintained patients who continue to abuse cocaine, as contrasted with well stabilized patients receiving methadone treatment and also with “pure” cocaine abusers, would be of interest, along with studies, when possible, in long-term, drug-free former heroin addicts not receiving pharmacotherapy.

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References


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