Chronic \(\mu\)-Opioid Receptor Stimulation in Humans Decreases Muscle Sympathetic Nerve Activity

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**Background**—Opioid-addicted patients undergoing detoxification provide a unique opportunity to assess the effects of chronic opioid receptor stimulation on the sympathetic nervous system. We tested the hypothesis that chronic oral methadone intake decreases resting efferent sympathetic nerve activity to muscle (MSA). Furthermore, we assessed whether this effect is reversed by \(\mu\)-opioid receptor blockade during antagonist-supported detoxification under general anesthesia.

**Methods and Results**—Fifteen young patients (30±1 years old, mean±SEM) with a long history of mono-opioid addiction and under oral methadone substitution therapy (65±10 mg/d for 21±6 months) were selected. Peroneal MSA (microneurography) and catecholamine plasma concentrations (high-performance liquid chromatography) were assessed in the awake state and compared with those of age-matched healthy control subjects. The effects of \(\mu\)-opioid receptor blockade by naloxone (12.4 mg IV) were determined during propofol anesthesia. Compared with healthy volunteers, resting MSA (4±2 versus 22±2 bursts/min, \(P<0.0001\)) and antecubital venous norepinephrine plasma concentration (100±64 versus 256±48 pg/mL, \(P=0.01\)) were markedly decreased in addicted patients despite similar arterial blood pressure and heart rate. Opioid receptor blockade markedly increased MSA (5±2 to 24±3 bursts/min) and norepinephrine (49±12 to 305±48 pg/mL) and epinephrine (13±2 to 482±67 pg/mL) arterial plasma concentrations as well as mean arterial pressure (82±4 to 108±3 mm Hg) and heart rate (70±3 to 86±4 beats/min).

**Conclusions**—Chronic \(\mu\)-opioid receptor stimulation by methadone decreases resting MSA in humans. (*Circulation. 2001; 103:850-855.)*

**Key Words:** anesthesia ■ nervous system, autonomic ■ catecholamines ■ circulation ■ heart failure ■ hemodynamics ■ norepinephrine ■ pharmacology

The central and peripheral sympathetic system and the heart and vasculature contain \(\mu\)-opioid receptors, but their contribution to circulatory regulation, particularly in chronic states of opioid receptor stimulation, is not well defined.\(^1\)\(^2\) Acute administration of \(\mu\)-opioid receptor agonists provides little insight in this respect, because any effects are blurred by respiratory depression, an altered state of consciousness, or even anesthesia.\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) Furthermore, under resting conditions, \(\mu\)-opioid receptor blockade by naloxone, which attenuates the effects of endogenous opioids, does not change muscle sympathetic activity (MSA), arterial baroreflex gain, or catecholamine plasma concentrations in healthy volunteers.\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)

Conversely, naloxone potentiates the increase in MSA during exercise and in response to lower-body negative pressure, indicating inhibition of MSA by endogenous opioids when the sympathetic nervous system is activated.\(^15\)\(^17\)\(^18\) Moreover, during sympathetic activation in experimental congestive heart failure (CHF), \(\mu\)-opioid receptor blockade attenuates both decreased adrenergic inotropic responsiveness and baroreflex sensitivity, whereas cardiac function is improved.\(^19\)\(^20\)\(^21\) Finally, in contrast to subjects with physiological endogenous opioid activity, naloxone administration in patients with CHF prevents an attenuated inotropic response to adrenergic stimulation.\(^22\)\(^23\) Thus, opioid effects on sympathetic cardiovascular control may depend on the duration of opioid receptor stimulation and/or degree of resting sympathetic activity.

Patients addicted to opioids consume and are adapted to otherwise lethal opioid dosages, with respiratory regulation adapted to chronic opioid receptor agonist stimulation.\(^24\) Under these unique conditions, the effects of chronic opioid receptor stimulation on sympathetic nervous system and cardiovascular regulation can be studied both under resting conditions and after opioid receptor blockade, unmasking opioid effects. Therefore, in patients addicted to opioids alone for almost 10 years, we tested the hypothesis that chronic opioid receptor stimulation decreases resting efferent sympa-
thetic nerve activity to muscle. In addition, we assessed the effects when opioids are acutely displaced from their receptors.

Methods

Subjects

The study protocol was approved by the local ethics committee and is consistent with the Helsinki declarations. Subjects were enrolled on a voluntary basis and gave written informed consent.

Patients Chronically Addicted to Opioids

Fifteen patients (3 women and 12 men; age, 30 ± 1 years, mean ± SEM; range, 20 to 37 years) were enrolled from a methadone outpatient care unit to undergo rapid detoxification during general anesthesia. All had a long history of opioid addiction (9 ± 2 years; range, 2 to 26 years) and received oral methadone substitution therapy (65 ± 10 mg/d; range, 10 to 150 mg/d, for 21 ± 6 months; range, 1 to 60 months) to prevent heroin intake. Methadone therapy resulted in high urinary methadone concentrations (3273 ± 324 ng/mL). Other than methadone, the patients reported not having consumed other drugs. This was confirmed by weekly urine toxicology screens (sensitive for opioids, methadone, benzodiazepines, cocaine, amphetamine/methamphetamine, barbiturates, tetrahydrocannabinol, and tricyclic antidepressants), with the last test made on the day before study and detoxification. Patients did not suffer from other overt disease. Six patients, however, had serological evidence of having been exposed to the hepatitis B or C virus in the past but did not show current clinical or laboratory signs of abnormal liver function or active infection.

The last dose of methadone was given 24 hours before naloxone treatment. A small dose of flunitrazepam (0.5 mg PO; Rohypnol, Roche) was administered only on patient demand before transfer to our intensive care unit at 7:00 AM.

Healthy Volunteers

Six unmedicated healthy normotensive volunteers (who participated in an unrelated study performed at the same time) were matched by sex, age, and body mass index to 6 addicted patients not receiving premedication. As a result of matching, both groups were similar in sex (6 men each), age (control subjects, 29 ± 2 versus patients, 29 ± 3 years), and body mass index (control subjects, 22.0 ± 0.8 versus patients, 21.8 ± 0.6 kg/m²). None of the subjects were taking prescription or nonprescription drugs.

After an overnight fast, all subjects were studied in the supine resting position in the morning.

Measurements

Muscle Sympathetic Activity

Multunit postganglionic MSA was recorded by microneurography in the peroneal nerve at the fibular head as previously described. The nerve signal was amplified (×50 000), filtered (bandpass, 500 to 2000 Hz), and fed through a discriminator for further noise reduction and audio monitoring (662C-3 Nerve Traffic Analysis System, University of Iowa, Bioengineering). A mean voltage (integrated) signal was obtained by passing the original signal through a resistance-capacitance circuit. MSA recording sites were accepted when burst amplitude was ≥2x baseline noise and reproducible responses were obtained to challenges (apnea, 1 to 2 µg/kg IV sodium nitroprusside).

MSA bursts were counted and expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats), the latter also accounting for differences or changes in heart rate. Furthermore, the area under the curve of each burst was calculated as an estimate for the number of activated sympathetic fibers, indicating the strength of a single burst. MSA total activity was calculated as the sum of burst areas and expressed in arbitrary units per minute.

Cardiovascular Variables

Heart rate was determined from the ECG (lead II; Sirecust 1281, Siemens). In opioid-addicted patients, radial arterial and central venous pressures were measured electromanometrically. In healthy volunteers, arterial blood pressure was measured by the volume-clamp method with a plethysmographic cuff placed around the middle phalanx of the third finger (Finapres 2300, Ohmeda) after determination of resting blood pressure by oscillometry in the ipsilateral upper arm. Compared with intra-arterial measurements, the volume-clamp method has been shown to provide reliable measurements of beat-by-beat changes in arterial blood pressure during a variety of test conditions.

Catecholamine Plasma Concentrations

Norepinephrine and epinephrine plasma concentrations were determined with a Beckmann System Gold high-performance liquid chromatograph (HPLC) and electrochemical detection (Chromsystems No. 41 000). A catecholamine-detection kit (Chromsystems Catalog No. 5000) included a probe preparation system, HPLC column, and all necessary chemicals and buffers. The lower detection limit was 10 pg/mL for both epinephrine and norepinephrine, with a coefficient of variation of 6.2% for norepinephrine and 6.8% for epinephrine, respectively.

Data Recording and Processing

Analog variables (MSA, ECG, vascular pressures) were recorded on a thermoray recorder (TA-11, Gould Instruments) and stored on tape (RD-125T DAT-Recorder, TEAC). Signals were simultaneously fed into a personal computer and digitized (sampling frequency: 200 Hz, DT2821, Data Translation). All analyses were performed with computer support (offline) with a dedicated program (Professor G. Wallin/T. Karlsson, Göteborg, Sweden).

Study Protocol

MSA and cardiovascular variables (averages of 5-minute periods) were determined in the awake state in both opioid-addicted patients and healthy volunteers. Antecubital venous blood was collected via indwelling catheters for determination of catecholamine plasma concentrations.

After a 30-minute resting period, anesthesia was induced in opioid-addicted patients by 2 to 4 mg/kg propofol (Klimofol, Ivamed) and 0.1 mg/kg cisatracurium (Nimbex, Glaxo-Wellcome). After intubation, patients were mechanically ventilated (FIO 2 , 0.21 to 0.3; positive end-expiratory pressure, 3 mm Hg). Anesthesia was maintained by propofol infusion (167 ± 8 µg · kg⁻¹ · min⁻¹) as previously described. Ringer’s lactate was infused to keep central venous pressure at baseline values (7 ± 2 mm Hg). Normocarbia was established and repeatedly confirmed by arterial blood gas analysis.

After steady-state conditions had been achieved, µ-opioid receptor blockade was started by 0.4 mg naloxtone IV (Curamed). Four additional naloxtone boluses of increasing dosage (0.8, 1.6, 3.2, and 6.4 mg) were injected at 15-minute intervals. Accordingly, a total of 12.4 mg naloxtone was given over 60 minutes.

MSA and cardiovascular variables (averages of 5-minute periods) were determined in the awake state, during anesthesia before opioid receptor blockade, and before each naloxtone bolus, ie, at 15, 30, 45, 60, and 75 minutes. Simultaneously, radial arterial blood was collected for determination of catecholamine plasma concentrations.

Statistical Analysis

Data are expressed as mean ± SEM. Differences in means of variables between patients and healthy volunteers were assessed by unpaired t tests. Differences in means of variables over time in opioid-addicted patients during detoxification were determined by 1-way repeated-measures ANOVA followed by the Duncan multiple range post hoc test.

The following a priori null hypotheses were tested: There is no difference in means of variables (1) in the awake state between opioid-addicted patients and healthy volunteers before detoxification and (2) after induction of anesthesia before administration of...
naloxone (a) compared with observations during \( \mu \)-opioid receptor blockade and (b) compared with observations in the awake state. A null hypothesis was rejected with an \( \alpha \)-error of <0.05.

**Results**

Complete recordings of MSA were achieved in 10 of 15 patients. Six of these patients had not requested benzodiazepine premedication and were compared with healthy matched control subjects in the awake state. MSA data during \( \mu \)-opioid receptor blockade are based on 10 patients, and other data are presented from all 15 patients.

**Effects of Chronic \( \mu \)-Opioid Receptor Stimulation on Resting MSA**

Recordings from all unpremedicated patients and matched control subjects are shown in Figure 1. Patients with chronic \( \mu \)-opioid receptor stimulation showed a markedly decreased resting MSA (patients, 4±2 versus volunteers, 22±2 bursts/min, \( P < 0.0001; \) Figure 2) despite similar heart rates (patients, 66±4 versus volunteers, 66±6 beats/min; \( P = 0.9 \)) and mean arterial pressures (patients, 89±4 versus volunteers, 88±5 mm Hg, \( P = 0.9 \)).

Norepinephrine plasma concentration was lower (\( P = 0.01 \)) in opioid addicts. Epinephrine concentration was slightly but significantly (\( P = 0.001 \)) higher in patients with chronic \( \mu \)-opioid receptor stimulation (Figure 2).

**Effects of \( \mu \)-Opioid Receptor Blockade in Opioid-Addicted Patients**

Reversal of chronic \( \mu \)-opioid receptor stimulation by naloxone during propofol anesthesia markedly increased MSA and arterial pressure (Figure 3).

On average, \( \mu \)-opioid receptor blockade evoked a significant and dose-dependent increase in MSA (by 380%) from 5±2 bursts/min during anesthesia before naloxone to 24±3 bursts/min (MSA burst incidence, 12±3 to 29±5 bursts/100 heartbeats). Maximum effects were observed after a total dose of 2.8 mg naloxone, and MSA was not increased further by additional naloxone (Figure 4).

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**Figure 1.** Thirty-second recordings from 6 unpremedicated opioid-addicted patients and healthy matched volunteers demonstrating markedly decreased resting MSA in awake state during chronic \( \mu \)-opioid receptor stimulation. Bursts accepted for analysis are indicated by dots.

**Figure 2.** Average resting MSA and catecholamine plasma concentrations in 6 unpremedicated opioid-addicted patients and 6 healthy matched control subjects. Chronic \( \mu \)-opioid receptor stimulation was associated with a marked parallel decrease in both MSA and norepinephrine plasma concentration.

**Figure 3.** Recording from 1 patient with chronic \( \mu \)-opioid receptor stimulation of resting MSA in awake state (left), during propofol anesthesia (middle), and after \( \mu \)-opioid receptor blockade (right). Bursts accepted for analysis are indicated by dots. Starting from a low MSA both in awake state (left) and during anesthesia (middle), resting MSA is markedly augmented by \( \mu \)-opioid receptor blockade (right).
In parallel to the observed MSA increase, arterial norepinephrine plasma concentration increased to a maximum of 305.6 pg/mL, and epinephrine increased to 492.67 pg/mL (Figure 5).

Sympathetic activation by $\mu$-opioid receptor blockade was associated with significant increases in systolic arterial pressure (116.5 to 153.2 mm Hg), diastolic arterial pressure (63.3 to 83.3 mm Hg), and heart rate (70.3 to 86.4 beats/min).

No complications were observed, and all patients were transferred to the ward the next morning.

Discussion

In humans addicted to opioids for almost 10 years, MSA and norepinephrine plasma concentration at rest were decreased compared with those of healthy control subjects despite similar arterial blood pressure and heart rate. $\mu$-Opioid receptor blockade by naloxone increased MSA and catecholamine plasma concentrations even beyond awake values despite maintained propofol anesthesia that unmasked the effects of chronic $\mu$-opioid receptor stimulation.

Critique of Methods

A particular strength of this study is that we assessed patients addicted exclusively to opioids for many years, ruling out drug interactions.

Results describing opioid effects on resting MSA are based on 6 unpremedicated addicted patients and 6 healthy volunteers. For assessment of effects of $\mu$-opioid receptor blockade, a larger sample was available by pooling data from unpremedicated patients and patients requesting a small dose of flunitrazepam in the morning, because no significant differences were observed between patients receiving premedication and those who did not.

Mean MSA at rest in our volunteer control group corresponds very well to values obtained in larger cohorts of similar age. Thus, despite a small sample size, results provide valid information comparing opioid-addicted patients with healthy individuals.

Certainly, it would have been of interest to assess the effects of opioid receptor blockade in awake addicted patients. However, opioid receptor blockade in addicts cannot be performed without additional medications, because a severe withdrawal syndrome would immediately be precipitated. Therefore, anesthesia with propofol has been proposed for detoxification when opioid receptors are acutely blocked.

Propofol anesthesia decreased MSA by 70%. A similar effect was determined in our addicted patients. Because propofol was administered by a constant high-dose infusion throughout the observational period, the observed increase in MSA evoked by opioid receptor blockade may be considered to be even more pronounced in the awake state.
Interpretation of Results

Although the effects of endogenous opioids on heart and circulation have gained substantial importance, in particular in patients with CHF, only very limited data addressing potential cardiovascular effects of chronic opioid receptor stimulation are available. In patients with CHF and in animal models of CHF, plasma concentrations of endogenous opioid peptides are significantly increased.19–23 Moreover, naloxone administration during CHF prevents attenuation of the inotropic response to adrenergic stimulation, antagonizes baroreflex depression, and improves cardiac output.19–23 Thus, chronic opioid receptor stimulation by endogenous ligands may dampen excessive sympathetic stimulation of the cardiovascular system.35 Accordingly, during chronic opioid receptor agonist stimulation, antagonist administration may unmask these effects on cardiovascular control.

Previously, the effects of chronic opioid receptor stimulation on cardiovascular regulation have not been assessed in humans.

In volunteers at rest, the effects on the sympathetic and cardiovascular systems of endogenous μ-opioid receptor agonists apparently play only a small role, if any, as demonstrated by the absence of effects evoked by μ-opioid receptor antagonists. In fact, even large doses of naloxone (10 mg IV) do not alter resting MSA, sympathetic baroreflex sensitivity, catecholamine plasma concentrations, arterial pressure, or heart rate.12–16 In contrast, naloxone potentiates the increase in MSA during exercise and in response to lower-body negative pressure, indicating an inhibition of MSA by endogenous opioids during states of sympathetic activation.15,17,18

In anesthetized animals, opioid agonists generally decrease sympathetic activity. In anesthetized dogs and cats, fentanyl (5 to 50 μg/kg IV) decreases splanchnic nerve activity and catecholamine plasma concentrations, arterial pressure, or heart rate.5,10 In contrast, naloxone potentiates the increase in MSA during exercise and in response to lower-body negative pressure, indicating an inhibition of MSA by endogenous opioids during states of sympathetic activation.15,17,18

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In awake humans, however, the effects of opioid receptor agonists are less clear, because associated respiratory depression and/or an altered state of consciousness can hardly be controlled for. Under these conditions, opioid receptor agonists even increased urine and plasma catecholamine concentrations.13,16,17,18 In contrast, fentanyl (2.5 to 5 μg/kg IV) did not change MSA when given to awake premedicated patients and unpremedicated volunteers.17,18

In contrast to the absence of sympathetic inhibition by acute opioid administration in humans, chronic μ-opioid receptor stimulation by methadone in our patients was associated with decreased MSA and norepinephrine plasma concentration compared with those of healthy control subjects. Our observations may be explained by opioid agonist effects on the activity of central sympathetic neurons, peripheral sympathetic efferent neurons, or baroreceptor afferents.

The major part of cardiovascular sympathetic premotor neurons are located in the rostral ventral medulla, caudal raphe nuclei, and in the vicinity of the fourth cerebral ventricle, with the nucleus tractus solitarius believed to be the key component for central processing of cardiovascular afferent input.19,20 Other neuronal groups, eg, located in the locus coeruleus, are capable of markedly influencing sympathetic cardiovascular function.19 Injection of morphine into the nucleus tractus solitarius in anesthetized rabbits as well as perfusion of fentanyl through the fourth cerebral ventricle in conscious dogs indicated inhibitory effects of opioid receptor agonists on central baroreflex processing.40,41 When morphine was given systemically to rats, locus coeruleus neural activity decreased.42 Thus, inhibition of several components of central sympathetic pathways may contribute to the observed effects of chronic opioid receptor stimulation on MSA in opioid-addicted patients.

Our results may also be explained by peripheral mechanisms. Opioid receptors are present on peripheral sympathetic neurons and sympathetic ganglia.43 In anesthetized dogs, basal adrenal catecholamine output is unaffected by intravenous naloxone, but systemic morphine administration decreases adrenal epinephrine release evoked by splanchnic nerve stimulation.43 Furthermore, celiac ganglionic neural discharge and superior cervical ganglionic acetylcholine release are decreased by local administration of the opioid receptor ligand methionine-enkephalin, indicating inhibition of sympathetic ganglionic transmission to multiple organ systems.44,45

The mechanism for increased epinephrine plasma concentration during chronic opioid administration in our patients remains unclear. Possibly, adrenal epinephrine release is less sensitive to the inhibitory effects of chronic opioid agonist administration or, in contrast to the decrease in MSA, shows a compensatory increase.

μ-Opioid receptor blockade in our patients reversed the inhibitory effects of chronic opioid receptor stimulation. Thus, we are able to confirm in the same patients that decreased MSA during chronic opioid administration is mediated by opioid receptor–related mechanisms. Because naloxone exerts no effects in healthy volunteers,12–14 the observed sympathetic activation after naloxone relates to opioid receptor blockade with the background of a chronically stimulated opioid receptor system and is not evoked by naloxone per se. Finally, our results raise the question why, in contrast to regulation of breathing, cardiovascular sympathetic regulatory patterns apparently do not adapt to chronic opioid receptor stimulation.

In summary, chronic μ-opioid receptor stimulation decreases MSA and norepinephrine plasma concentration despite unchanged arterial pressure and heart rate. μ-Opioid receptor blockade in patients with chronic opioid abuse unmasks these effects, resulting in markedly increased MSA.

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References


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