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Changes in brain oxygen and glucose induced by oxycodone: relationships with brain temperature and peripheral vascular tone

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Abstract

Oxycodone is a semi-synthetic opioid drug that is used to alleviate acute and chronic pain. However, oxycodone is often abused and, when taken at high doses, can induce powerful CNS depression that manifests in respiratory abnormalities, hypotension, coma, and death. Here, we employed several measurement techniques to examine the effects of intravenous oxycodone at a wide range of doses on various metabolism-related parameters in awake, freely-moving rats. High-speed amperometry was used to assess how oxycodone affects oxygen and glucose levels in the nucleus accumbens (NAc). These measurements were supplemented by recordings of locomotor activity and temperature in the NAc, temporal muscle, and skin. At low doses, which are known to maintain self-administration behavior (0.15–0.3 mg/kg), oxycodone transiently decreased locomotor activity, induced modest brain and body hyperthermia, and monotonically increased NAc oxygen and glucose levels. While locomotor inhibition became stronger with higher oxycodone doses (0.6–1.2 mg/kg), NAc oxygen and glucose transiently decreased and subsequently increased. High-dose oxycodone induced similar biphasic down-up changes in brain and body temperature, with the initial decreases followed by increases. While cerebral vasodilation induced by neural activation appears to be the underlying mechanism for the correlative increases in brain oxygen and glucose levels, respiratory depression and the subsequent drop in blood oxygen likely mediate the brain hypoxia induced by large-dose oxycodone injections. The initial inhibitory effects induced by large-dose oxycodone injections could be attributed to rapid and profound CNS depression—the most dangerous health complication linked to opioid overdose in humans.

Graphical abstract

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Keywords

opiates; brain and body hyperthermia; metabolic brain activation; vasoconstriction; vasodilation; nucleus accumbens; rats

1. Introduction

Oxycodone is a semi-synthetic μ -opioid agonist clinically used as an analgesic drug since 1917. In the past, like other opioid drugs, oxycodone was prescribed sparingly, and mainly to alleviate severe short-term pain. However, changes in United States government recommendations and aggressive marketing by pharmaceutical companies led to a dramatic increase in the last 25 years of oxycodone prescriptions for long-term use in patients with chronic pain. Oxycodone is often combined with other pain-relieving drugs like acetaminophen (Percocet) or used as an extended-release formulation (OxyContin). Currently, oxycodone is the second most prescribed opioid drug and the second most commonly used illegal drug after marijuana (National Drug Threat Assessment, 2017).

In addition to its pain-relieving effects, oxycodone has strong addictive potential, predisposing individuals for its repeated, non-medical use. This addictive behavior is driven by both the immediate positive psycho-emotional effects of this drug (euphoria) and its negative withdrawal effects (Koob and Volkow, 2016). Like other opioid drugs, the euphoric effects of oxycodone exhibit tolerance following repeated use, and the likelihood of withdrawal effects also increases since it takes a larger amount of the drug to achieve the desired subjective effects. Although oxycodone is typically taken orally when used as a therapeutic drug in the United States, more aggressive, intravenous (iv) delivery is often employed by drug users (Havens et al., 2007; Rosenblum et al., 2007; Katz et al., 2008), especially in countries where this formulation is approved by government regulations.

Despite the alarming progression of medical and non-medical use of oxycodone during recent years, our knowledge on its effects as an addictive drug remains very limited. While it is usually believed that oxycodone has weaker effects and thus is less dangerous than heroin, both drugs are equally reinforcing in rat self-administration models, with approximately two-fold higher optimal doses for oxycodone vs. heroin (150 µg/kg vs. 60 µg/kg, respectively), but with comparable lever-pressing rates and breakpoint values (Wade et al., 2015). Similarly to heroin, oxycodone overdose can result in serious health complications, but the estimates of potentially lethal doses in humans and the LD50 in animals for different administration routes varies widely or remains unknown (Ordonez Gallego et al., 2007). Oxycodone also shares similar physiological and behavioral effects with heroin, including the ability to induce respiratory depression that results in acute brain hypoxia (Jaffe et al., 1997). This effect appears to be the most dangerous health complication during oxycodone overdose and could lead to death.

Recently, by using oxygen sensors coupled with high-speed amperometry, we showed that iv heroin, a representative opioid drug of abuse, induces dose-dependent oxygen decreases in the nucleus accumbens (NAc) of awake, freely moving rats (Solis et al., 2017b). At a low dose (100 µg/kg) optimal for self-administration in rats, the hypoxic effect was rapid, appearing within the first minute of drug administration, strong with a 30% drop from baseline, but relatively transient in its duration. At higher heroin doses, within the range injected by experienced drug users, this effect greatly increased in magnitude and duration, suggesting robust brain hypoxia. By employing oxygen recording in the subcutaneous space, a highly vascularized area with no metabolic activity of its own, we confirmed that the heroin-induced drop in brain oxygen results from a decrease in blood oxygen levels due to respiratory depression.

The present study was designed to gain more knowledge on the central and peripheral effects of iv oxycodone within a wide range of doses from small, presumably ineffective or low effective to large, presumably dangerous in awake, freely moving rats. Since brain hypoxia appears to be the most dangerous effect of opioid drugs, we first examined oxycodone-induced changes in NAc oxygen levels using oxygen sensors coupled with high-speed amperometry. Second, our oxygen recordings were supplemented by direct monitoring of NAc glucose, another critical metabolic parameter, using enzyme-based glucose biosensors coupled with high-speed amperometry. Third, to elucidate the behavioral and physiological effects of this drug, we examined oxycodone-induced changes in locomotor activity and temperature at three distinct sites: the NAc, temporal muscle, and skin. While brain temperature by itself is an important parameter that reflects neural activity and affects neural functions (Kiyatkin, 2010), the three-point thermorecording technique allowed us to assess oxycodone-induced changes in metabolic brain activity and the tone of peripheral blood vessels. These data were used to examine how these global physiological effects of oxycodone are related to changes in NAc glucose and oxygen. Like our previous work, we chose the NAc, a deep, ventrally located structure critically involved in sensorimotor integration (Mogenson et al., 1980; Wise, 1989) as a representative area to obtain oxygen, glucose, and brain temperature recordings.

2. Materials and Methods

2.1. Subjects

31 adult male Long-Evans rats (Charles River Laboratories) weighing 460 ± 40 g at the time of surgery were used in this study. Rats were individually housed in a climate-controlled animal colony maintained on a 12-12 light-dark cycle (lights on at 6:00) with food and water available *ad libitum*. All procedures were approved by the NIDA-IRP Animal Care and Use Committee and complied with the Guide for the Care and Use of Laboratory Animals (NIH, Publication 865-23). Maximal care was taken to minimize the number of experimental animals and any possible discomfort or suffering at all stages of the study.

2.2. Overview of the study

This study describes the results of three experiments conducted in awake, freely moving rats. In the first two experiments, we employed substrate-selective sensors coupled with amperometry to examine how iv oxycodone affects extracellular levels of oxygen and glucose in the NAc. In the third experiment, we used the three-point thermorecording technique to examine how iv oxycodone affects temperature in the NAc, temporal muscle, and skin. These data allowed us to examine the effects of oxycodone on metabolic brain activity and skin vascular tone and explore how oxycodone-induced changes in these parameters are related to changes in NAc oxygen and glucose.

2.3. Surgical preparations

Surgical procedures for electrochemical experiments have been described in detail elsewhere (Kiyatkin and Lenoir, 2012; Solis et al., 2017c; Solis et al., 2018). In brief, under general anesthesia (Equithesin, a mixture of sodium pentobarbital and chloral hydrate), each rat was unilaterally implanted with a BASi guide cannula (Bioanalytical Systems, West Lafayette, IN, USA) into which an electrochemical sensor was later inserted. Target coordinates of the recordings in the right NAc shell were: AP +1.2 mm, ML ± 0.8 mm, and DV +7.6 mm from the skull surface, according to coordinates of the rat brain atlas (Paxinos and Watson, 1998). The guide cannula was secured with dental acrylic in a head mount anchored to the skull. During the same surgical procedure, rats were also implanted with a chronic jugular catheter, which ran subcutaneously to the head mount and was secured to the same head assembly. Rats were allowed a minimum of 5 days of post-operative recovery and at least 3 daily habituation sessions (~6 h each) to the recording environment with no water or food available, which is the same environment during experimental sessions. Jugular catheters were flushed daily with 0.2 ml heparinized saline to maintain patency.

Surgical procedures for thermorecording experiments have been described in detail elsewhere (Kiyatkin et al., 2013; Bola and Kiyatkin, 2017). In brief, under the same general anesthesia protocol, rats were implanted with a jugular catheter and three copper-constantan thermocouple electrodes in the NAc shell (AP +1.2mm, M-L: ± 0.8 mm, DV +7.4 mm), temporal muscle, and subcutaneously along the nasal ridge with the tip ~15 mm anterior to bregma. The probes were secured with dental cement to the three stainless steel screws threaded into the skull. As shown in our previous studies [see Kiyatkin, 2010 for review], by simultaneously recording temperatures from these three locations, it is possible to assess the

effect of a physiological or drug stimulus on intra-brain heat production due to metabolic brain activation and heat loss or retention due to changes in skin vascular tone (vasoconstriction/vasodilation).

2.4. Electrochemical detection of oxygen and glucose

In experiments assessing oxygen, we used commercially produced oxygen sensors (Model 7002-02; Pinnacle Technology, Inc., Lawrence, KS, USA). These sensors consist of an epoxy-sheathed disc electrode that is grounded to a fine surface using a diamond-lapping disc. These sensors are prepared from Pt-Ir wire 180 μm in diameter, with a sensing area of 0.025 mm^2 at the sensor's tip. The active electrode is incorporated with an integrated Ag/AgCl reference electrode. Dissolved oxygen is reduced on the active surface of these sensors, which is held at a stable potential of -0.6 V vs. the reference electrode, producing an amperometric current. The current from the sensor is relayed to a computer via a potentiostat (Model 3104, Pinnacle Technology) and recorded at 1-s intervals, using the PAL software utility (Version 1.5.0, Pinnacle Technology).

Oxygen sensors were calibrated at 37°C by the manufacturer (Pinnacle Technology) according to a standard protocol described elsewhere (Bolger et al., 2011). The sensors produced incremental current changes with increases in oxygen concentrations within the wide range of previously reported brain oxygen concentrations ($0\text{--}50\text{ }\mu\text{M}$). Substrate sensitivity of oxygen sensors varied from 1.35 to $1.52\text{ nA}/\mu\text{M}$ (mean= $1.41\text{ nA}/\mu\text{M}$). Oxygen sensors were also tested by the manufacturer for their selectivity toward other electroactive substances, including dopamine ($0.4\text{ }\mu\text{M}$) and ascorbate ($250\text{ }\mu\text{M}$), none of which had significant effects on reduction currents.

For monitoring brain glucose, we used commercially produced glucose oxidase-based biosensors (Model 7002; Pinnacle Technology). These sensors are prepared from Pt-Ir wire that is $180\text{ }\mu\text{m}$ in diameter and has a sensing cavity that is $\sim 1\text{ mm}$ in length, on its tip. The active electrode is incorporated with an integrated Ag/AgCl reference electrode. On the active surface, glucose oxidase converts glucose to glucono-1,5-lactone and hydrogen peroxide (H_2O_2), which is detected as an amperometric oxidation current generated by a $+0.6\text{ V}$ applied potential (Hu and Wilson, 1997). The potential contribution of ascorbic acid to the measured current is competitively reduced by co-localizing ascorbic acid oxidase enzymes on the active surface of the sensor. This enzyme converts ascorbic acid to non-electroactive dehydroascorbate and water. In addition, a negatively charged Nafion polymer layer under the enzyme layer serves to exclude endogenous anionic compounds (Hu and Wilson, 1997).

Glucose sensors were calibrated immediately before and after each *in vivo* experiment. *In vitro* calibrations were conducted in PBS (pH 7.3) by incrementally increasing the concentration of glucose (Sigma-Aldrich) from 0 to 0.5 , 1.0 , and 1.5 mM followed by a single addition of ascorbate ($250\text{ }\mu\text{M}$). Within this physiological range of glucose levels (Fellows and Boutelle, 1993; McNay and Gold, 2001), the glucose sensors used in this study produced incremental linear current increases. Mean sensitivity to glucose was $5.54\pm 0.50\text{ nA}/0.5\text{ mM}$ at $22\text{--}23^\circ\text{C}$ and $10.87\pm 0.97/0.5\text{ mM nA}$ at 37°C . Glucose sensors showed low sensitivity to ascorbate ($0.03\pm 0.02\text{ nA}/250\text{ }\mu\text{M}$ at $22\text{--}23^\circ\text{C}$) and, as shown previously, were

only minimally sensitive to dopamine at its physiological levels (5-50 pA/10-100 nM). Glucose sensors remained equally sensitive to glucose and selective against ascorbate during post-recording *in vitro* calibrations.

2.5. Experimental procedures

All *in vivo* electrochemical procedures were performed in an electrically insulated chamber (38 × 47 × 47 cm) located in a larger open-faced cabinet and illuminated continuously with a dim 20 W light bulb. Ambient temperature was maintained within 22-23°C and a room wide air filter fan provided background noise. The bottom of the cage was covered with wood chip bedding, which remained in place during the habituation and recording sessions for each individual rat.

At the beginning of each experimental session, rats were minimally anesthetized (<2 min) with isoflurane and the sensor was inserted into the NAc through the guide cannula. The rat was then placed in the testing chamber and the sensor was connected to the potentiostat via an electrically shielded flexible cable and a multi-channel electrical swivel. The injection port of the jugular catheter on the head mount was connected to a plastic catheter extension that allowed drug delivery from outside the cage, thus minimizing detection of iv drug injections by the rat. Testing began a minimum of 120 min after insertion of the sensor when the baseline currents stabilized.

In the first two experiments (n=13), we examined changes in oxygen and glucose in the NAc induced by iv oxycodone (oxycodone HCl; obtained from the NIDA-IRP Pharmacy) at 0.15, 0.3, and 0.6 mg/kg doses (dissolved in 0.15, 0.3 and 0.6 ml of saline and injected over 10, 20 and 40 s) over the course of 8-10 h recording sessions. Time intervals between injections were 90-150 min, typically enough for the restoration of pre-stimulus current baselines. In 8 additional rats, we examined the effects of oxycodone on NAc glucose and oxygen delivered at a high dose (1.2 mg/kg in 0.3-0.4 ml saline over 30-40 s). At the end of each session, rats were anesthetized with iv Equithesin, disconnected from the potentiostat, and the biosensors were carefully removed and re-calibrated. Typically, rats underwent only one recording session and upon completion they were euthanized by decapitation under deep isoflurane anesthesia. The rat brains were then removed, stored in 10% formalin, and sectioned for verification of sensor placement using a rat stereotaxic atlas (Paxinos and Watson, 1998) and assessed for possible brain tissue damage. In several rats, electrochemical recordings with oxygen sensors were repeated two to four days later.

The doses of oxycodone to be tested were based on existing data on rat self-administration of this drug and the possible dose range used by humans. Specifically, our minimal dose of 0.15 mg/kg (or 10 mg/70 kg) is near optimal for rat self-administration (Wade et al., 2015) and within the range of intake for drug-naïve individuals or people with limited drug experience. The larger doses (0.3, 0.6 and 1.2 mg/kg or 20, 40 and 80 mg/70 kg) are higher than those optimal for maintaining self-administration in rats but within the possible consumption range for experienced drug users.

The experimental protocol for the thermorecording experiments was similar to that of the electrochemical experiments, with some exceptions due to multi-session recordings. One

subgroup of rats (n=6) was recorded during two sessions (with one free day in between) and received 3 iv injections of oxycodone at 0.15, 0.3 and 0.6 mg/kg doses (in ascending order) during each session. A second group of rats (n=4) was recorded during two sessions (with one free day in between) and received one injection of oxycodone at the 1.2 mg/kg dose. In these experiments, we also measured locomotor activity using 4 infrared motion detectors (Med Associates) as previously described (Brown and Kiyatkin, 2004).

In this study, we did not test the effects of saline on oxygen and glucose levels as well as temperature parameters. As shown previously, iv saline injection conducted from outside of the chamber via the catheter extension has negligible effects on locomotor activity, cortical EEG, brain temperatures as well as NAc glutamate levels (Kiyatkin and Lenoir, 2011; Wakabayashi and Kiyatkin, 2014).

2.6. Data analysis

Electrochemical data were sampled at 1 Hz (i.e. mean current over 1 s) using the PAL software utility (Version 1.5.0, Pinnacle Technology) and analyzed with two time resolutions, with slow (1-min) and rapid (10-s) quantification bins. Electrochemical data were first analyzed as raw currents. Because each of the individual sensors differed slightly in background currents and substrate sensitivity *in vitro*, currents were then transformed into concentrations and represented as relative concentration changes, setting the pre-stimulus baseline current as 0. Basal electrochemical currents and their concentration equivalents were used to estimate basal levels of oxygen and glucose in the NAc. One-way repeated measure ANOVAs (followed by Fisher LSD post-hoc tests) were used to evaluate the statistical significance of drug-induced changes in oxygen and glucose. To assess the magnitude of drug-induced changes in oxygen and glucose, data were additionally analyzed as percent change from baseline, where the baseline was represented as 100%.

Temperature data were sampled with 10-s time resolution and analyzed in terms of absolute changes in each recording location (i.e. NAc, temporal muscle, skin), relative changes with respect to baseline, as well as NAc-Muscle and Skin-Muscle temperature differentials. Since the brain and temporal muscle receive arterial blood from the same common carotid artery and are equally exposed to blood-delivered heat from the body, NAc-Muscle temperature differentials show the source of heat production, providing a measure of drug-induced metabolic brain activation. Skin temperature is determined by the state of peripheral vessels, but it also depends on the temperature of arterial blood inflow. Therefore, Skin-Muscle temperature differential serves as an accurate measure of peripheral vascular tone, another important determinant of brain temperature changes (Kiyatkin, 2010). We used one-way ANOVA with repeated measures, followed by Fisher's LSD post-hoc test to evaluate the effects of oxycodone on the different dependent measures.

We also assessed the effects of oxycodone on locomotor activity, which was collected and analyzed with 1-min time resolution. Because of low and highly variable locomotor activity in rats preceding oxycodone injections, these data are shown as the change in mean activity with respect to averaged baseline activity assessed for 10 min preceding drug injections.

We also used time-dependent correlation analyses to examine the relationship between oxygen, glucose, and several temperature parameters. All statistical analyses were conducted using GraphPad Prism software.

3. Results

Data presented in this report were obtained from 31 rats, in which the locations of temperature and electrochemical sensors in the medial NAc shell were verified histologically.

3.1. Changes in NAc oxygen and glucose: slow time-course analyses

When analyzed with 1-min time resolution, oxycodone significantly increased NAc glucose levels and the effect was dose-dependent ($F_{7,196}=9.91$, $F_{8,240}=14.43$, $F_{7,658}=15.83$ and $F_{6,756}=18.06$ for 0.15, 0.3, 0.6 and 1.2 mg/kg, respectively; $p<0.001$ for each dose) (Fig. 1A). With respect to basal glucose levels (mean, 744 ± 67 μM ; SD, 377 μM), the glucose increase assessed by its peak magnitude was 10, 15, 40 and 73%, respectively. While the glucose response was monophasic at the two lower doses, it became two-phasic at the two larger doses, with the appearance of a rapid but transient decrease immediately after the injection. At the largest dose, this transient decrease began during the first minute from injection onset, peaked at 2 min (~ 300 μM drop or 41% vs. pre-injection baseline), and returned to baseline 7 min post-injection, after which it began to increase.

Oxycodone also increased NAc oxygen levels, but the effect was weaker in magnitude and more gradual than that for NAc glucose (Fig. 1B). Relative to basal oxygen levels (15.88 ± 1.81 μM , SD 7.87 μM), the increase assessed by its maximal amplitude was $\sim 15\%$ at each dose tested. There was no effect on oxygen at the 0.15 mg/kg dose ($p=0.79$), but a significant effect was seen for each of the higher doses ($F_{19,1691}=3.50$, $F_{15,1710}=7.62$ and $F_{11,1518}=18.64$ for 0.3, 0.6 and 1.2 mg/kg, respectively; $p<0.001$ for each dose). Although oxygen increased at each of these doses, for the two larger doses, the increase was preceded by a significant decrease, which was clearly larger for the 1.2 mg/kg than 0.6 mg/kg dose. This post-injection decrease was relatively short in duration but much larger in magnitude (mean 7.4 μM or 47% drop from baseline) than the subsequent increase.

Next, we examined the relationships between oxycodone-induced changes in NAc oxygen and glucose (Fig. 1C). For this analysis, changes in both parameters were expressed as a percent relative to the pre-injection baseline (=100% red symbol). Filled cyan values correspond to the ascending curve of the glucose increase and subsequent values (white symbols) correspond to the return of glucose to baseline. Changes in glucose and oxygen strongly correlated with each other at each dose ($r=0.929$, 0.979, 0.914 and 0.819 for 0.15, 0.3, 0.6 and 1.2 mg/kg, respectively; $p<0.001$ for each dose). The correlation was direct, i.e., increases in oxygen correlated with increases in glucose and decreases in oxygen correlated with decreases in glucose. At the two lowest doses, both parameters increased after oxycodone injection, but at the two higher doses the correlation was more complex, showing an initial drop in both parameters followed by their increase.

3.2. Immediate changes in NAc oxygen and glucose: rapid time-course analyses

Since the oxycodone-induced changes in glucose and oxygen shown in Fig. 1 were very rapid, to capture these dynamics, the data were analyzed with 10-s temporal resolution for the first 15 minutes following oxycodone injection (Fig. 2). By using shorter quantification bins, we showed that glucose levels began to increase within 80-100 s at the two lower doses (Fig. 2A; 0.15 and 0.3 mg/kg). At the two larger doses, we observed a two-phasic glucose response, with a rapid, transient drop immediately after the injection (onset latency of 50 and 40 s for 0.6 and 1.2 mg/kg, respectively) and a stronger and more prolonged increase thereafter.

Changes in oxygen generally mimicked those of glucose, with no changes at the 0.15 mg/kg dose, a weak and more delayed increase at 0.3 mg/kg, and rapid decreases immediately after injection at the 0.6 and 1.2 mg/kg doses (Fig. 2B). The latency to oxygen decrease (40 and 30 s for 0.6 and 1.2 mg/kg, respectively) was similar to that of glucose increase.

For more precise analysis of the initial changes in glucose and oxygen, we examined their correlative relationships from the onset of oxycodone injection to the end of the glucose response (Fig. 2C and D). This analysis was conducted for the two larger drug doses. Changes in oxygen and glucose tightly and directly correlated for both drug doses ($r=0.931$ and 0.866 for 0.6 and 1.2 mg/kg, respectively; $p<0.001$); they simultaneously decreased for 80 s after the injection onset (cyan symbols; $r=0.779$ and $r=0.991$) and then simultaneously increased for 42 (0.6 mg/kg) or 80 min (for 1.2 mg/kg) until the glucose increase peaked (magenta symbols; $r=0.987$ and 0.987).

3.3. Temperature and behavioral effects of oxycodone

Oxycodone induced significant temperature responses at each dose tested (Fig. 3A). At the lowest dose (0.15 mg/kg), oxycodone moderately increased NAc and muscle temperature ($F_{14,1274}=24.2$ and 26.1 , respectively; $p<0.0001$). These increases were generally parallel, became significant at 5-6 min after injection onset, peaked at ~30 min (~1.0°C) and returned to baseline at ~70 min post-injection. Oxycodone also increased skin temperature ($F_{14,1274}=5.2$; $p<0.0001$), but this increase was much weaker (~0.5°C at peak response) and was preceded by a transient temperature decrease within the first 10 min post-injection.

Although changes in brain and muscle temperatures were parallel, their difference, the NAc-Muscle differential, slightly increased for ~40 min post-injection with a peak at 20-25 min ($F_{14,854}=1.73$; $p<0.001$; Fig. 3B). Due to the different temperature dynamics seen in the temporal muscle and skin, the Skin-Muscle differential rapidly and strongly decreased for ~50 min post-injection ($F_{14,1274}=10.4$, $p<0.001$). This change occurred very rapidly and peaked at ~26 min, a time-point corresponding to the peak increases in brain and muscle temperatures. Consistent with the known behavioral effects of opioid drugs, locomotor activity dropped immediately after the injection, remained at low levels for ~10min, and then slightly increased above baseline from ~20 to 60 min post-injection (Fig. 3C).

At higher doses (0.3 and 0.6 mg/kg), oxycodone induced similar temperature and locomotor responses, but their changes were stronger and more prolonged (Fig. 3). The dose dependence was evident for increases in NAc and muscle temperature, locomotor inhibition,

and decreases in skin-muscle differentials, but the increase in NAc-muscle differentials remained weak, being significant only at the 0.3 mg/kg dose ($F_{14,854}=1.69$; $p<0.01$).

Oxycodone injected at the largest dose (1.2 mg/kg) also increased NAc, muscle and skin temperature, but the temperature increase at all sites was preceded by a clear temperature decrease within the first 40 min post-injection (Fig. 3A, C). At this dose, the NAc-muscle differentials showed a two-phase increase ($F_{7,427}=3.60$; $p<0.0001$), the skin-muscle differential displayed a weaker decrease than those observed at the lower doses, and this decrease was preceded by a slight increase in this parameter within ~20 min post-injection. The effect on locomotion was also maximal, with a total block of activity lasting 40-50 min.

To determine the contribution of the two primary mechanisms, intra-brain heat production and heat loss, to brain temperature increases induced by oxycodone, we used time-dependent correlations that show how the changes in one parameter depend on changes in another parameter within the duration of the drug effect (Fig. 4). Oxycodone-induced increases in NAc temperatures strongly correlated with decreases in skin-muscle temperature differentials ($r=-0.860$, -0.845 , and -0.903 for 0.15, 0.3 and 0.6 mg/kg doses; $p<0.001$), suggesting skin vasoconstriction as a primary contributor to the drug-induced temperature increases. In contrast, changes in NAc temperature did not correlate with NAc-muscle differentials ($r=0.266$, 0.192 , and 0.268 for 0.15, 0.3 and 0.6 mg/kg doses) indicative of no or a minor role of metabolic activation in mediating NAc temperature increase. At the largest dose (1.2mg/kg), the correlation was more complex, weaker for NAc temperature and skin-muscle differentials($r=-0.545$, $p<0.01$) but stronger for NAc-muscle differentials ($r=-0.349$).

3.4. Relationships between oxycodone-induced changes in NAc oxygen and glucose and temperature parameters

Next, we used time-dependent correlations to examine how oxycodone-induced changes in NAc glucose and oxygen are related to drug-induced changes in NAc temperature, NAc-muscle, and skin-muscle temperature differentials (Fig. 5). This analysis was conducted for oxycodone at the 0.3 mg/kg that is the minimal dose that induces significant changes in all monitored parameters.

As shown in Fig. 5A, increases in NAc glucose occurred much more rapidly than changes in NAc temperature. Glucose values began to increase within minutes after oxycodone injection and peaked at ~10 min, when NAc temperature only began to increase. Despite the much shorter duration of glucose increases relative to NAc temperature increases, glucose levels within this time span (0-10 min) tightly correlated with NAc temperature ($r=0.936$). Then, the correlation inverted and the glucose decreased toward baseline, correlating with the NAc temperature increase until it reaches its peak ($r=-0.993$). Similarly to that for glucose, oxygen levels rapidly increased within 6 min after oxycodone injection, during which NAc temperature remained virtually unchanged, and then oxygen levels continued to increase to its peak in parallel with increases in NAc temperature (Fig. 5B).

A tight positive correlation was found between increases in NAc glucose and oxygen and NAc-muscle temperature differentials, a measure of drug-induced brain metabolic response

(Fig. 5C and D). In this case, increases in both glucose and oxygen correlated with increases in NAc-muscle differentials ($r=0.987$ and 0.877 for glucose and oxygen, respectively) until they peaked. However, increases in NAc-muscle differentials were longer in duration than increases in NAc glucose, and they peaked when glucose levels began to decrease toward baseline. Changes in NAc oxygen tightly correlated with NAc-muscle differentials, increasing in parallel until their peaks.

In contrast to the positive correlations for NAc-muscle differentials, a strong negative correlation was found for changes in both glucose and oxygen and skin-muscle temperature differentials, a measure of skin vascular tone ($r=-0.973$ and -0.906 ; Fig. 5E and F). Specifically, decreases in skin-muscle differentials correlated with increases in glucose ($r=-0.973$) until the peak glucose response. Then, glucose levels began to decrease but skin-muscle differentials continued to increase until they peaked ($r=0.926$). A simple correlation was found for NAc oxygen and skin-muscle differentials, which both decreased until their peaks.

4. Discussion

Although oxycodone is widely used for both therapeutic and recreational purposes, our knowledge about the basic physiological effects of this drug is limited. To address this issue, we examined the effects of iv oxycodone within the probable range of human consumption on three distinct metabolism-related parameters in awake, freely-moving rats. Since respiratory depression with subsequent brain hypoxia is the most dangerous complication when using large opioid doses (Yeadon and Kitchen, 1989; White and Irvine, 1999), our primary focus was on assessing the effect of oxycodone on brain oxygen levels. Our oxygen measurements were supplemented by evaluations of oxycodone-induced changes in glucose, another critical metabolic parameter, and temperatures in the brain, temporal muscle, and skin. The latter data allowed us to examine how oxycodone affects brain metabolic activity and peripheral vascular tone as well as to assess how these effects related to changes in oxygen and glucose.

4.1. Brain and body hyperthermia induced by oxycodone: underlying mechanisms

While it is generally believed that brain temperature is a tightly regulated and highly stable homeostatic parameter, most neuroactive drugs significantly affect brain temperature (Kiyatkin, 2013). Drugs with sedative potential (i.e., general anesthetics, THC, alcohol) typically decrease brain temperature, whereas psychostimulants (i.e., cocaine, amphetamine, methamphetamine, MDMA) increase temperature. Although opioid drugs have sedative effects, they do not follow this trend. For example, despite its powerful sedative effect, iv heroin within the range of human consumption moderately increases brain and body temperatures (Bola and Kiyatkin, 2017). Brain and body temperatures also strongly increase (up to 39.0-39.5%) during heroin self-administration in trained rats (Kiyatkin and Wise, 2002).

Like heroin, iv oxycodone has sedative potential and inhibits locomotor activity, but it induces brain and body hyperthermia. Within the probable range of human consumption (0.15-0.6 mg/kg or 10-40 mg/70 kg), the temperature increases in response to oxycodone

were clearly dose-dependent, moderate in amplitude (1.0-1.7°C), and exceeded the period of locomotor freezing—the typical immediate effect of opioid drugs. While hyperthermia induced by psychomotor stimulants results from increased intra-brain heat production and diminished heat loss due to peripheral vasoconstriction (Kiyatkin, 2013), the latter effect appears to be the primary factor underlying oxycodone-induced hyperthermia. Skin vasoconstriction, which was assessed in this study by evaluating changes in skin-muscle differentials, was rapid, dose-dependent, and tightly correlated with the increase in brain temperature (see Fig. 4). Oxycodone also increased the NAc-muscle differential, indicative of metabolic brain activation, but this effect was relatively weak, peaked at ~20 min, and did not correlate with the increase in brain temperature (see Fig. 4).

The temperature effects of oxycodone changed qualitatively at the largest dose (1.2 mg/kg), which exceeds the typical range of self-administration in rats and corresponds to the upper limits of human consumption (80 mg/70 kg). For this dose, brain and body temperature initially decreased possibly in response to transient skin vasodilation (deduced by the increase in the skin-muscle differential) that occurred immediately after the oxycodone injection. This effect then transitioned into vasoconstriction and brain and body temperature began to increase from ~30 min post-injection, though these changes were weaker than those seen at the lower doses. This pattern of changes is similar to that of heroin, which monotonically increased brain and body temperature at lower doses (0.1-0.2 mg/kg) and displayed biphasic, down-up changes at larger doses (0.4-3.2 mg/kg) (Bola and Kiyatkin, 2017).

4.2. Oxycodone-induced rapid entry of oxygen and glucose into brain tissue and its mechanisms

Oxygen and glucose continuously enter the brain's environment from arterial blood, where their concentrations are higher than those in the extracellular space (Fellows et al., 1992; Silver and Erecinska, 1994; Attwell et al., 2010). As shown previously (Kiyatkin and Lenoir, 2012; Solis et al., 2017a), the entry of these substances into the brain tissue accelerates and their levels in the brain tissue transiently increase following distinct kinds of arousing stimulation. While neural activation and subsequent cerebral vasodilation appears to be the primary cause of physiological increases in both oxygen and glucose, the changes in these substances in the brain also depend on changes in their levels in the blood, such that their increases and decreases in the brain correspond to their increases and decreases in arterial blood.

In the present study, we showed that oxycodone increases NAc glucose levels at each dose tested and in a dose-dependent manner (see Fig. 1). However, at the two larger doses (0.6 and 1.2 mg/kg) transient glucose decreases were observed immediately following the injection. While lower in magnitude and more tonic, changes in NAc oxygen mimicked glucose responses. Similarly to glucose, oxycodone induced a monotonic oxygen increase at the 0.3 mg/kg dose, and a biphasic effect at the two larger doses tested (0.6 and 1.2 mg/kg), with a rapid, strong but transient fall in oxygen levels immediately after the injection. Importantly, the changes in glucose and oxygen showed similar onset latencies and they tightly correlated both for their increases and decreases. Although NAc oxygen levels were

much lower than those for glucose (16 μM vs. 740 μM) and its changes were also much weaker in absolute terms (1-2 μM vs. 100-500 μM), the two substances showed comparable relative changes (~60% above or below baseline; see Fig. 1C). These similarities may indicate common underlying mechanisms.

Our thermorecording experiments allowed us to examine relationships between oxycodone-induced changes in NAc oxygen and glucose, metabolic neural activation, and vascular response. Specifically, increases in both oxygen and glucose were tightly related to increases in NAc-muscle differentials (see Fig. 5), suggesting that intra-brain entry of these substances is triggered by neural activation that leads, possibly via neurovascular coupling mechanism, to local cerebral vasodilation. Although brain glucose levels could increase when its blood levels are rising (Wakabayashi and Kiyatkin, 2015), this factor seems unlikely because blood glucose levels are very stable, and our results indicate that they changed very rapidly, consistent with the idea of their mediation via neural mechanism. Similarly, brain oxygen levels could increase during respiratory activation (Solis et al., 2017a), but this effect is also unlikely for oxycodone, which inhibits respiratory activity (see below). Increases in brain oxygen and glucose also tightly correlated with decreases in the skin-muscle differential that represents peripheral vasoconstriction. Since skin vasoconstriction results in decreased blood inflow in the periphery, blood inflow to the brain increases, thus enhancing intra-brain entry of oxygen and glucose. Finally, the robust increase in glucose and delayed oxygen increase seen with the large oxycodone doses could result from the rise in CO_2 , a strong vasodilator (Schmidt and Kety, 1947; Kontos, 1981; Battisti-Charbonney et al., 2011), as a consequence of the initial drop in oxygen. Hence, the brain hypoxia that is induced by oxycodone at large doses could result in local cerebral vasodilation, which contributes to the strong increases in glucose following their transient decreases, as well as the oxygen rebound.

While oxycodone-induced increases in brain oxygen and glucose involve several mechanisms, the rapid NAc oxygen drop occurring following the injection of a large dose reflects respiratory depression, a common centrally-mediated effect of all opioid drugs (Jaffe et al., 1997). This effect occurred with short but definite onset latencies, was dose-dependent, and was relatively transient. The tight correlation found between decreases in NAc oxygen and glucose points at a causal relationship between these two effects, but the mechanisms underlying the initial glucose drop remain unclear. One possible mechanism could be deduced from our thermorecording experiment, which revealed a transient increase in skin-muscle differentials within the first 10 min after the large-dose oxycodone injection. This effect, indicative of skin vasodilation, could lead to the lowering of arterial blood pressure and cerebral blood flow resulting in the decrease in brain glucose levels. Also, since the oxidation of glucose at the glucose sensor's surface depends on the concentration of dissolved oxygen (Lourenco et al., 2017), a significant drop in oxygen (to 60% of baseline with the 1.2 mg/kg oxycodone dose) could transiently decrease glucose oxidation currents. As shown *in vitro*, the glucose oxidation current decreased 12% and ~25% when concentrations of dissolved oxygen decreased from 20 μM to 10 and 5 μM , respectively (Lourenco et al., 2017). While this oxygen-dependent decrease is weaker than that observed in our experiments, the possibility of this measurement artifact warrants further experimentation and could be viewed as a potential limitation of the measurement approach used in this study.

4.3. Common features with and differences between oxycodone and heroin

Although oxycodone and heroin have important differences in their metabolism, μ -opioid receptors appear to be the primary target underlying their behavioral and physiological effects (Koob and Volkow, 2016). Rats quickly learn to self-administer heroin and oxycodone and the effective doses to maintain maximal responding for oxycodone are about two-fold larger than those for heroin (Wade et al., 2015). Oxycodone is also two- to three-fold weaker than heroin in its ability to increase brain and body temperature, and four- to six-fold weaker than heroin in producing the initial temperature drop following large-dose injections (Bola and Kiyatkin, 2017). Between-drug differences are even larger with respect to the initial oxygen drop resulting from respiratory depression (Solis et al., 2017b). For this effect, in terms of dose oxycodone was six-to-eight-fold weaker than heroin. Consistent with the known quickness of heroin's actions, its depressive effects on NAc oxygen were more rapid than those for oxycodone. Importantly, heroin, even at the low doses that are optimal for self-administration in rats (~ 0.1 mg/kg), induced a transient drop in brain oxygen (Solis et al., 2017b), but for oxycodone the drop in brain oxygen appears only at doses exceeding the dose range of self-administration (Wade et al., 2015). Therefore, although oxycodone appears less dangerous than heroin in terms of dose, both drugs share basic commonality in physiological and behavioral effects and the consequences of oxycodone intake could be equally dangerous when it is injected at higher doses.

4.4. Conclusions and Functional implications

Oxycodone is an effective medication to alleviate many types of severe pain. However, oxycodone is widely abused because of its positive psychoactive effects and eventual development of drug dependence. When abused, oxycodone is taken by different routes and at doses that exceed the typical therapeutic range. As shown in this study, iv oxycodone administered to awake, freely-moving rats at doses that maintain drug-taking behavior and are within the therapeutic range induces relatively modest physiological effects in the brain and periphery. However, these effects, particularly brain temperature, skin vascular tone, and change in brain oxygen and glucose levels became qualitatively different at higher doses that correspond to the upper limits of human consumption. In contrast to the moderate increases in brain oxygen seen at low doses, NAc oxygen levels rapidly dropped immediately following the large-dose injection, suggesting brain hypoxia. This effect, when combined with full motor inability, could result in asphyxiation leading to death. Oxycodone at a large dose also decreased brain and body temperature and induced skin vasodilation, the response pattern produced by general anesthetic drugs (Kiyatkin and Brown, 2005; Bola and Kiyatkin, 2016). While skin vasoconstriction tends to increase arterial blood pressure, skin vasodilation amplifies the centrally mediated hypotensive effect of oxycodone that could lead to coma and death. Finally, based on clinical evidence, both the central sedative effects and respiratory depression induced by oxycodone are greatly potentiated by other sedative drugs, specifically alcohol and benzodiazepines (Clarot et al., 2003; Heiskanen and Kalso, 2012), which are often used by addicted individuals in conjunction with opioid drugs. These drug interactions warrant further investigation.

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References

- Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature*. 2010; 468:232–243. [PubMed: 21068832]
- Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *J Physiol*. 2011; 589:3039–3048. [PubMed: 21521758]
- Bola RA, Kiyatkin EA. Robust brain hyperglycemia during general anesthesia: Relationships with metabolic brain inhibition and vasodilation. *Front Physiol*. 2016; 7:39. [PubMed: 26913008]
- Bola RA, Kiyatkin EA. Brain temperature effects of intravenous heroin: State dependency, environmental modulation, and the effects of dose. *Neuropharmacology*. 2017; 126:271–280. [PubMed: 28755887]
- Bolger FB, Bennett R, Lowry JP. An in vitro characterisation comparing carbon paste and Pt microelectrodes for real-time detection of brain tissue oxygen. *Analyst*. 2011; 136:4028–4035. [PubMed: 21804983]
- Brown PL, Kiyatkin EA. Brain hyperthermia induced by MDMA (ecstasy): modulation by environmental conditions. *Eur J Neurosci*. 2004; 20:51–58. [PubMed: 15245478]
- Clarot F, Goulle JP, Vaz E, Proust B. Fatal overdoses of tramadol: is benzodiazepine a risk factor of lethality? *Forensic Sci Int*. 2003; 134:57–61. [PubMed: 12842359]
- Fellows LK, Boutelle MG. Rapid changes in extracellular glucose levels and blood flow in the striatum of the freely moving rat. *Brain Res*. 1993; 604:225–231. [PubMed: 8457850]
- Fellows LK, Boutelle MG, Fillenz M. Extracellular brain glucose levels reflect local neuronal activity: a microdialysis study in awake, freely moving rats. *J Neurochem*. 1992; 59:2141–2147. [PubMed: 1431898]
- Havens JR, Walker R, Leukefeld CG. Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. *Drug Alcohol Depend*. 2007; 87:98–102. [PubMed: 16959437]
- Heiskanen T, Kalso E. Non-analgesic effects of opioids: interactions between opioids and other drugs. *Curr Pharm Des*. 2012; 18:6079–6089. [PubMed: 22747548]
- Hu Y, Wilson GS. Rapid changes in local extracellular rat brain glucose observed with an in vivo glucose sensor. *J Neurochem*. 1997; 68:1745–1752. [PubMed: 9084449]
- Jaffe, JH., Knapp, CM., Ciraulo, DA. Opiates: Clinical Aspects. In: Lowinson, JH, Ruiz, P, Millman, RB., Langrod, JG., editors. *Substance Abuse*. Third. Baltimore: Williams & Wilkins; 1997. p. 158-166.
- Katz N, Fernandez K, Chang A, Benoit C, Butler SF. Internet-based survey of nonmedical prescription opioid use in the United States. *Clin J Pain*. 2008; 24:528–535. [PubMed: 18574362]
- Kiyatkin EA. Brain temperature homeostasis: physiological fluctuations and pathological shifts. *Front Biosci*. 2010; 15:73–92.
- Kiyatkin EA. The hidden side of drug action: brain temperature changes induced by neuroactive drugs. *Psychopharmacology (Berl)*. 2013; 225:765–780. [PubMed: 23274506]
- Kiyatkin EA, Wise RA. Brain and body hyperthermia associated with heroin self-administration in rats. *J Neurosci*. 2002; 22:1072–1080. [PubMed: 11826136]
- Kiyatkin EA, Brown PL. Brain and body temperature homeostasis during sodium pentobarbital anesthesia with and without body warming in rats. *Physiol Behav*. 2005; 84:563–570. [PubMed: 15811391]
- Kiyatkin EA, Lenoir M. Intravenous saline injection as an interoceptive signal in rats. *Psychopharmacology*. 2012; 217:387–396.
- Kiyatkin EA, Lenoir M. Rapid fluctuations in extracellular brain glucose levels induced by natural arousing stimuli and intravenous cocaine: fueling the brain during neural activation. *J Neurophysiol*. 2012; 108:1669–1684. [PubMed: 22723672]

- Kiyatkin EA, Wakabayashi KT, Lenoir M. Physiological fluctuations in brain temperature as a factor affecting electrochemical evaluations of extracellular glutamate and glucose in behavioral experiments. *ACS Chem Neurosci*. 2013; 4:652–665. [PubMed: 23448428]
- Kontos HA. Regulation of the cerebral circulation. *Annu Rev Physiol*. 1981; 43:397–407. [PubMed: 6782941]
- Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016; 3:760–773. [PubMed: 27475769]
- Lourenco CF, Ledo A, Gerhardt GA, Laranjinha J, Barbosa RM. Neurometabolic and electrophysiological changes during cortical spreading depolarization: multimodal approach based on a lactate-glucose dual microbiosensor arrays. *Sci Rep*. 2017; 7:6764. [PubMed: 28754993]
- McNay EC, Gold PE. Age-related differences in hippocampal extracellular fluid glucose concentration during behavioral testing and following systemic glucose administration. *J Gerontol A Biol Sci Med Sci*. 2001; 56:B66–71. [PubMed: 11213269]
- Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol*. 1980; 14:69–97. [PubMed: 6999537]
- National Drug Threat Assessment. National Drug Intelligent Center (U.S.). 2017. https://www.dea.gov/docs/DIR-040-17_2017-NDTA.pdf
- Ordóñez Gallego A, Gonzalez Baron M, Espinosa Arranz E. Oxycodone: a pharmacological and clinical review. *Clin Transl Oncol*. 2007; 9:298–307. [PubMed: 17525040]
- Paxinos, G., Watson, C. The rat brain in stereotaxic coordinates. 4th. San Diego: Academic Press; 1998.
- Rosenblum A, Parrino M, Schnoll SH, Fong C, Maxwell C, Cleland CM, Magura S, Haddox JD. Prescription opioid abuse among enrollees into methadone maintenance treatment. *Drug Alcohol Depend*. 2007; 90:64–71. [PubMed: 17386981]
- Schmidt CF, Kety SS. Recent studies of cerebral blood flow and cerebral metabolism in man. *Trans Assoc Am Physicians*. 1947; 60:52–58. [PubMed: 18917240]
- Silver IA, Erecinska M. Extracellular glucose concentration in mammalian brain: continuous monitoring of changes during increased neuronal activity and upon limitation in oxygen supply in normo-, hypo-, and hyperglycemic animals. *J Neurosci*. 1994; 14:5068–5076. [PubMed: 8046468]
- Solis E Jr, Cameron-Burr KT, Kiyatkin EA. Rapid physiological fluctuations in nucleus accumbens oxygen levels induced by arousing stimuli: relationships with changes in brain glucose and metabolic neural activation. *Front Integr Neurosci*. 2017a; 11:9. [PubMed: 28484378]
- Solis E Jr, Cameron-Burr KT, Shaham Y, Kiyatkin EA. Intravenous heroin induces rapid brain hypoxia and hyperglycemia that precede brain metabolic response. *eNeuro*. 2017b:4.
- Solis E Jr, Bola RA, Fasulo BJ, Kiyatkin EA. Brain hyperglycemia induced by heroin: Association with metabolic neural activation. *ACS Chem Neurosci*. 2017c; 8:265–271. [PubMed: 27736094]
- Solis E Jr, Cameron-Burr KT, Shaham Y, Kiyatkin EA. Fentanyl-induced brain hypoxia triggers brain hyperglycemia and biphasic changes in brain temperature. *Neuropsychopharmacology*. 2018; 43:810–819. [PubMed: 28849778]
- Wade CL, Vendruscolo LF, Schlosburg JE, Hernandez DO, Koob GF. Compulsive-like responding for opioid analgesics in rats with extended access. *Neuropsychopharmacology*. 2015; 40:421–428. [PubMed: 25060491]
- Wakabayashi KT, Kiyatkin EA. Critical role of peripheral drug actions in experience-dependent changes in nucleus accumbens glutamate release induced by intravenous cocaine. *J Neurochem*. 2014; 128:672–685. [PubMed: 24111505]
- Wakabayashi KT, Kiyatkin EA. Behavior-associated and post-consumption glucose entry into the nucleus accumbens extracellular space during glucose free-drinking in trained rats. *Front Behav Neurosci*. 2015; 9:173. [PubMed: 26190984]
- White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction*. 1999; 94:961–972. [PubMed: 10707430]
- Wise, RA. The brain and reward. In: Liebman, JM., Cooper, SJ., editors. *The Neuropharmacological Basis of Reward*. Oxford: Oxford University Press; 1989. p. 377-424.
- Yeadon M, Kitchen I. Opioids and respiration. *Prog Neurobiol*. 1989; 33:1–16. [PubMed: 2548229]

Highlights

- At low doses, iv oxycodone increases NAc levels of oxygen and glucose
- These effects likely result from cerebral vasodilation due to neural activation
- At low doses, iv oxycodone induces modest brain and body hyperthermia
- This effect results primarily from peripheral vasoconstriction
- At higher doses, oxycodone decreases NAc oxygen levels due to respiratory depression

Figure 1. Mean ($\pm$ SEM) changes in NAc glucose (A) and oxygen (B) induced by oxycodone at different doses in awake, freely-moving rats

The moment of drug injection ($=0$ min) is shown by vertical dotted lines with arrows. n is the number of tests averaged. Data are shown with 1-min time resolution. Filled symbols show values significantly different from baseline ($p<0.05$). The bottom row (C) shows correlative relationships between changes in oxygen and glucose induced by oxycodone at different doses. These data are shown as the relative change in percent vs. pre-injection baseline ($=100\%$). Each graph shows regression lines and coefficients of correlation. Red symbols show basal values (100%) and cyan symbols show values spanning from the first measured glucose change to the peak of the glucose response.

Figure 2. High-resolution changes in NAc glucose (A) and oxygen (B) induced by oxycodone at different doses in awake, freely-moving rats

Data are plotted as mean $\pm$ SEM and shown with 10-s time resolution for 15 min post-injection. The moment of drug injection (=0 min) is shown by vertical dotted lines with arrows. Filled symbols show values significantly different from baseline. The bottom graphs show correlative relationships between changes in oxygen and glucose induced by oxycodone at 0.6 (C) and 1.2 mg/kg (D) doses. All data are shown as relative change in percent vs. pre-injection baseline (=100%). Each graph shows regression lines and coefficients of correlation calculated separately for glucose decreases (cyan values) and glucose increases (magenta values). r_0 is the total correlation.

Figure 3.

Mean ($\pm$ SEM) changes in NAc, muscle and skin temperature (A), NAc-muscle and skin-muscle differentials (B), and locomotion (C) induced by oxycodone at different doses in awake, freely-moving rats. The moment of drug injection (=0 min) is shown by vertical dotted lines; n is the number of tests averaged. Data are shown with 1-min time resolution. Filled symbols show values significantly different from baseline. Temperature data are shown as relative change with respect to pre-injection baseline (0°C). Horizontal dotted lines for locomotion represent pre-injection baseline of locomotion assessed for 10 minutes preceding drug injections.

Figure 4. Correlative relationships between changes in NAc temperature and NAc-muscle (blue symbols) and skin-muscle (red symbols) temperature differentials induced by oxycodone at different doses in wake, freely-moving rats

Data are shown with 1-min time resolution. Each graph shows regression lines and coefficients of correlation.

Figure 5. Correlative relationships between changes in NAc glucose (left panel, red) and oxygen (right panel, blue) and several temperature parameters (NAc temperature, NAc-muscle and skin-muscle temperature differentials)

Data are shown for oxycodone at the 0.3 mg/kg dose with 1-min time resolution. Each graph shows regression lines and coefficients of correlation. See text for further explanations.