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Cocaine and cocaine expectancy increase growth hormone, ghrelin, GLP-1, IGF-1, adiponectin, and corticosterone while decreasing leptin, insulin, GIP, and prolactin

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ABSTRACT

The dopamine system—essential for mood and movement—can be activated in two ways: by excitatory inputs that cause burst firing and stamp-in learning or by slow excitatory or inhibitory inputs—like leptin, insulin, ghrelin, or corticosterone—that decrease or increase single-spike (pacemaker) firing rate and that modulate motivation. In the present study we monitored blood samples taken prior to and during intravenous cocaine or saline self-administration in rats. During cocaine-taking, growth hormone and acetylated ghrelin increased 10-fold; glucagon-like peptide-1 (GLP-1) doubled; non-acetylated ghrelin, insulin-like growth factor-1 (IGF-1), and corticosterone increased by 50% and adiponectin increased by 17%. In the same blood samples, leptin, insulin, gastric inhibitory polypeptide (GIP), and prolactin decreased by 40–70%. On the first day of testing under extinction conditions—where the animals earned unexpected saline instead of cocaine—5-fold increases were seen for growth hormone and acetylated ghrelin and equal changes—in amplitude and latency—were seen in each of the other cases except for IGF-1 (which increased at a slower rate). Single-spike firing affects the tonic activation level of the dopamine system, involving very different controls than those that drive burst firing; thus, the present data suggest interesting new targets for medications that might be used in the early stages of drug abstinence.

1. Introduction

During cocaine-taking and cocaine-seeking, we have measured blood-borne substances that might alter the rate of *pacemaker* or *tonic* firing (Grace and Bunney, 1984a)—of the dopamine system. As reported below, cocaine and cocaine-expectancy affected each of our 11 target substances. Our immediate interest was in decreases in leptin (You et al., 2016), a factor known to antagonize the rewarding effects of food (Hommel et al., 2006) and electrical brain stimulation (Fulton et al., 2000). We found that cocaine self-administration itself significantly depressed blood leptin levels on the 14th day of training sessions. There were also two expectancy effects of cocaine; one seen prior to and one seen during daily self-administration testing. First, there was a conditioned effect on baseline leptin levels prior to the time of testing. While leptin levels returned to normal (over 6 ng/ml) after each session, they decreased to under 4 ng/ml in the two hours prior to each expected testing time. This prior-to-testing decrease was lost after several days of repeated extinction testing (You et al., 2016). Second, there was an additional (cocaine-like) 40% reduction of leptin levels when cocaine was withheld and saline was offered in its place on test day 15. This conditioned depression disappeared when extinction testing was continued over two further weeks (You et al., 2016).

Here we report the effects of cocaine and cocaine-expectancy on additional blood-borne substances. Like the effect on leptin, self-administered cocaine decreased insulin, GIP, and prolactin by more than 40%; in the same sessions, it increased growth hormone, acetylated ghrelin, GIP, IGF-1, corticosterone, non-acetylated ghrelin, and adiponectin. On Day 15, when non-rewarding saline was substituted for rewarding saline, similar changes in each substance were seen. Because these blood-borne substances act to affect pacemaker (tonic) (Grace and Bunney, 1984a), rather than burst (phasic) (Grace and Bunney, 1984b) firing of the dopamine system, these findings suggest a new avenue for treating the early period of abstinence in cocaine abusers.

2. Methods

Long-Evans rats were first trained, in 4-h sessions for 14 days, on an FR-1 schedule of reinforcement, to self-administer intravenous cocaine

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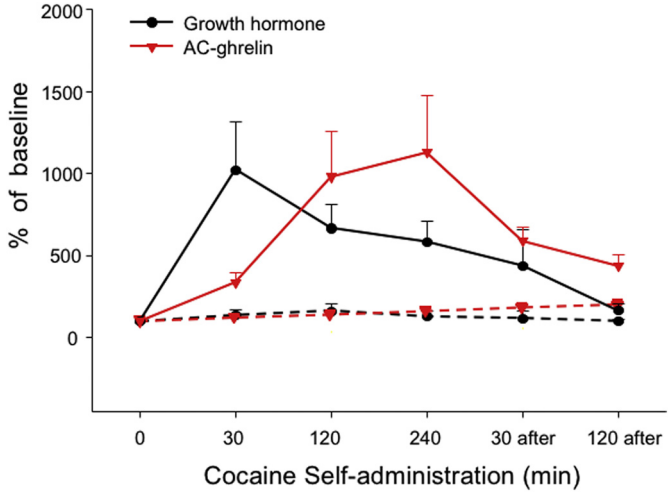

Fig. 1. Effects of cocaine (solid lines) or saline (dotted lines) self-administration on growth hormone and acetylated ghrelin (AC ghrelin) levels. Cocaine self-administration elevated growth hormone ten-fold in 30 min and elevated AC ghrelin ten-fold within 120 min; saline self-administration (dotted lines) had minimal effects on either substance.

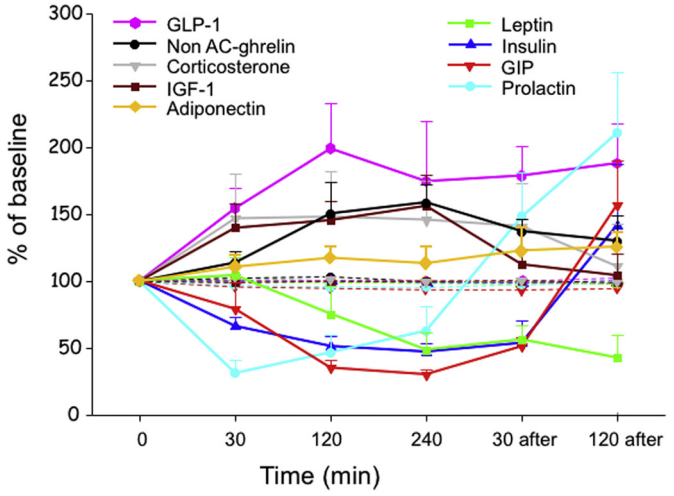

Fig. 2. Effects of cocaine (solid lines) or saline (dotted lines) self-administration on glucagon-like peptide (GLP-1), non-acetylated ghrelin, corticosterone, insulin-like growth factor (IGF-1), adiponectin, leptin, insulin, gastric inhibitory polypeptide (GIP), and prolactin.

(1 mg/injection). Following this training, the animals were tested for two further weeks in extinction conditions, where non-rewarding saline was substituted for rewarding cocaine. Small (1/4 ml) blood samples were taken before or within the self-administration or extinction sessions. The experimental methods are given in detail in You et al. (2016), where we have reported additional details on leptin. All procedures were approved by the Animal Care and Use Committee of the NIDA IRP and were consistent with the Principles of Laboratory Animal Care published by the National Institutes of Health (NIH publication 86–23, 1996).

3. Results

Self-administered cocaine increased 7 of the 11 measured analytes. Some increases were very dramatic; cocaine caused 10-fold elevations in growth hormone (30-min latency) and acetylated ghrelin (the active ghrelin metabolite: 2 h latency: Fig. 1). Cocaine doubled GLP-1 levels; increased corticosterone, IGF-1, and non-acetylated ghrelin (precursor of the active form) levels by 50%; and increased adiponectin level by over 15% (Fig. 2). Self-administered cocaine depressed leptin, insulin, GIP, and prolactin by 40–70% (Fig. 2). None of these analytes was affected significantly in cocaine-naive rats by saline self-administration (Figs. 1, 2).

Following 14 days of cocaine self-administration training, the animals were switched to extinction testing. Here the procedure was the same except that non-rewarding saline was substituted for rewarding cocaine. Self-administration of saline (on the 15th day) caused 10 of the 11 analytes to be increased or decreased to the same extent and with the same latency as did cocaine self-administration on the previous day (Fig. 3). Saline self-administration also showed conditioned increases in IGF, but they developed more slowly under saline than they had after cocaine. Each of the conditioned increases was lost and each of the conditioned decreases was partially lost during the subsequent days of extinction testing (Fig. 4).

4. Discussion

In the present study, the primary finding was not that cocaine influenced blood-borne hormones and peptides; this was well established, particularly for feeding-related substances such as leptin, ghrelin, insulin, and GLP-1 (Bouhlal et al., 2017; Figlewicz et al., 2003; Graham et al., 2013; Jerlhag, 2008; Kern et al., 2014; Moldow and Fischman, 1987). The primary finding is that saline self-administration—following experience with cocaine self-administration—can cause similar effects. Saline self-administration in cocaine-trained rats caused 5-fold

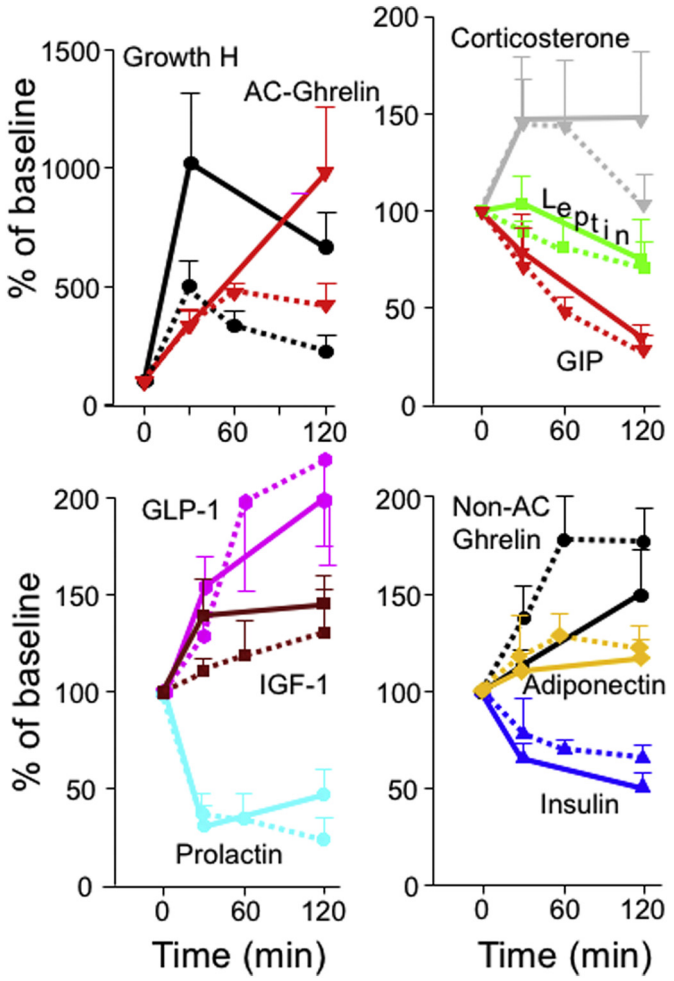

Fig. 3. Effects of cocaine self-administration (Day 14; solid lines) and saline self-administration (extinction: Day 15; dotted lines) on hormones and peptides.

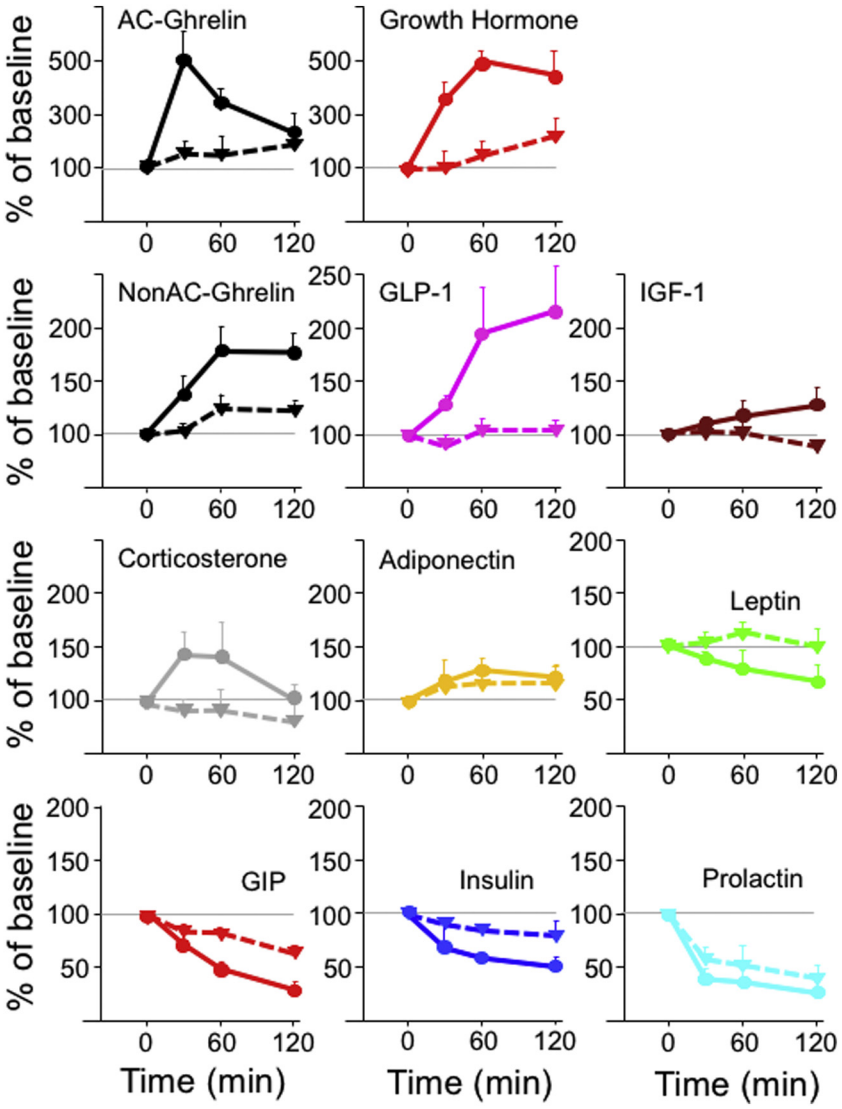

Fig. 4. Effects of the first (Day 15, solid lines) and the fourteenth (Day 28, dotted lines) days of extinction testing. Note the differences in scale and that extinction testing caused decreases in the seven data points that were elevated and increases in the four that were depressed by first-day extinction conditions.

elevations of growth hormone and ghrelin—half as effective and with equal latency as the effects of cocaine itself—and caused smaller increases in GLP-1, non-acetylated ghrelin, corticosterone, and adiponectin—these changes were equal in amplitude and had the same latency as changes caused by cocaine itself. In the same animals, it caused 40% or greater decreases in leptin, insulin, GIP, and prolactin. The saline-conditioned changes were decreased or eliminated by repeated saline (extinction testing) and no significant changes in any of these analytes was caused by saline self-administration in cocaine-naive animals. These four analytes have motivational functions; they mediate hunger and satiety for foods. They each activate or depress the dopamine system; GLP-1 has a trans-synaptic effect on inputs to the dopamine system (Alhadeff et al., 2012), and receptors for leptin, insulin, and ghrelin are expressed by ventral tegmental dopaminergic neurons themselves (Figlewicz et al., 2003; Kern et al., 2014). Each of these substances can influence the phasic firing of dopaminergic neurons.

The dopamine system has two functions in goal-directed behavior (Wise, 2013). First, it is involved in *motivation*: the rate of tonic or "pacemaker" firing (Grace and Bunney, 1984a) of the dopamine system controls, through the basal ganglia and prefrontal cortex, the animal's interest in reward-predictive stimuli (Caggiula, 1970; Delgado and Anand, 1963; Hutchinson and Renfrew, 1966; MacDonnell and Flynn, 1966; Olds and Milner, 1954). Second, it is involved in *reinforcement*: burst firing (Grace and Bunney, 1984b) is necessary for the stamping-in of stimulus-stimulus and stimulus-response associations (Schultz, 1997; White, 1997) that guide goal-directed behavior as the animal passes through the environment (Bindra, 1969; Bolles, 1972). Blood-borne hormones and peptides are not known to affect reinforcement-associated burst firing (Grace and Bunney, 1984b), but do affect motivation-associated single-spike firing. Single-spike or pacemaker firing is triggered by a depolarizing intracellular current (Grace and Bunney, 1984a), and its effects are modulated by tonic changes in these and other motivational factors.

The direct actions of slow accumulations of blood-borne hormones or peptides modulate slow accumulating changes—increases or decreases—in the rates of pacemaker dopaminergic firing rather than by precipitating burst firing that enables long-term synaptic potentiation. Here motivation refers to the modulation of the effectiveness of reinforcement-predictive stimuli in influencing goal-directed behavior (Hinde, 1960). Research on this topic will take many directions. We need to know the effects of physiological doses of these agents given singly and in combination. Leptin and GLP-1 have similar inhibitory effects on food intake, but they are modulated in opposite directions by cocaine intoxication. We also must learn the relative functional

importance of different doses. Finally, the 11 substances assayed here were not selected by hypothesis; they were the substances for which we had assays at the time. Given that each was altered by cocaine, it seems likely that there are others, not yet tested (norepinephrine, for example), that might be similarly affected. These issues will probably call for work with the intravenous self-administration model, although conditioned place preference studies do isolate one set of situational predictive stimuli (Jerlhag, 2008; Graham et al., 2013; You et al., 2016). Time of testing is another important variable (You et al., 2016). The search for medications have focused largely on the reinforcement function of dopamine. Exploration of these and other substances that modify the pacemaker firing of the dopamine system—the core motivational function of dopamine—offers a different influence than do the stimuli that elicit burst-firing and reinforcement; this suggests alternative medications for addiction.

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