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Short communication

Increased functional response to cocaine challenge following recovery from chronic corticosterone in the rat

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Abstract

Several lines of evidence suggest an interaction between glucocorticoids and the rat brain dopaminergic system. Here we demonstrate that a 14-day period of recovery from chronic corticosterone (10 mg/day for 21 consecutive days) potentiates the functional response to acute cocaine challenge in the rat by producing selective metabolic changes in limbic and motor areas, that are not measurable in vehicle-pretreated rats. These data indicate that chronic corticosterone has a long-term facilitatory role in the central effects of cocaine.
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1. Introduction

The assumption of an interaction between glucocorticoids and the rat brain dopaminergic system is supported by several experimental reports. Adrenalectomy has been shown to increase striatal tyrosine hydroxylase activity and to decrease dopamine concentrations; these effects are reversed by acute corticosterone treatment (Rastogi and Singhal, 1978; Leret et al., 1987). Conversely, chronic corticosterone treatment produces increased striatal dopamine concentrations (Wolkowitz et al., 1986).

Corticosterone has a relevant role in mediating the behavioral response to dopamine agonist drugs and, in particular, to psychomotor stimulants. The locomotor response to cocaine is reduced after adrenalectomy, an effect that is reversed by the reinstatement of corticosterone circadian fluctuations (Marinelli et al., 1994). Inhibition of the corticosterone stress response by metyrapone reduces cocaine-induced stimulation of locomotor activity and induces a relapse of cocaine self-administration (Piazza et al., 1994).

The long-term consequences of pharmacological manipulations of the hypothalamus–pituitary–adrenal axis on the effects of psychomotor stimulants have still not been completely investigated, although it is known that chronic corticosterone produces behavioral and neurochemical effects that suggest involvement of the central nervous system (Ling et al., 1981; Hall, 1982). Further, chronic corticosterone exposure reduces the number of hippocampal glucocorticoid receptors (Sapolsky et al., 1985).

We recently showed that a 14-day period of recovery from chronic high-dose corticosterone treatment potentiates the behavioral response to acute cocaine challenge in the rat (Patacchioli et al., 1997). In the present study we investigated whether this behavioral potentiation is accompanied by functional changes in the rat brain. Rates of glucose metabolism were, therefore, measured following the administration of cocaine to corticosterone- or vehicle-pretreated rats.

2. Materials and methods

Male 3 month-old Wistar rats (Charles River, Italy) were housed in pair cages with standard temperature and humidity and a 12 h light/dark cycle (light on 08.00 a.m.–08.00 p.m.). They had free access to food and water. Experiments were conform the institutional guidelines for the Care and Use of animals used in scientific procedures.

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The rats were divided into 2 groups, and treated with either corticosterone (10 mg/day, administered subcutaneously in 250 μl of sesame oil) or vehicle. Injections were made once daily for 21 consecutive days, between 12.00 a.m. and 1.00 p.m. The rats were then allowed a 14-day wash-out period, before the 2-[^{14}C]deoxyglucose procedure for measuring local rates of cerebral glucose utilization.

Briefly, on the morning of the experiment, polyethylene catheters were inserted into the left femoral artery and vein under halothane anaesthesia (Crane and Porrino, 1989). After a minimum of 3 h to recover from anaesthesia, animals belonging to both corticosterone- and vehicle-pretreated groups were randomized and treated with either cocaine (Salars, Italy) (7.5 mg/kg, intraperitoneal) or saline. The 2-[^{14}C]deoxyglucose procedure was begun 10 min after the administration of cocaine or vehicle, by the intravenous injection of a pulse of 2-[^{14}C]deoxyglucose (100 μCi/kg, specific activity 50–55 mCi/mmol, Amersham International, UK). The remainder of the procedure was carried out according to the original description (Sokoloff et al., 1977). Timed arterial blood samples were collected, immediately centrifuged and tested for plasma glucose concentrations (Beckman II Glucose Analyzer, USA) and ^{14}C concentrations (Beckman, USA). Approximately 45 min after the administration of the tracer, the animals were killed by the intravenous injection of sodium pentobarbital, the brains were rapidly removed, frozen at −40°C in isopentane, and stored at −70°C until section-

Table 1
Effects of cocaine challenge (7.5 mg/kg, i.p.) on local cerebral glucose utilization (μmol/100 g per min) in the rat after recovery from chronic high dose corticosterone treatment

SStructure	Control ($n = 4$)	Recovery ($n = 6$)	Control + cocaine ($n = 6$)	Recovery + cocaine ($n = 6$)
Medial prefrontal cortex	69 ± 2	65 ± 3	71 ± 5	70 ± 2
Lateral prefrontal cortex	85 ± 4	81 ± 1	86 ± 5	82 ± 2
Nucleus accumbens, shell	78 ± 4	69 ± 4	78 ± 5	84 ± 3 [b]
Nucleus accumbens, core	83 ± 4	76 ± 3	79 ± 3	84 ± 3
Anterior cingulate cortex	96 ± 5	86 ± 4	92 ± 5	96 ± 4
Sensory-motor cortex	87 ± 3	82 ± 1	88 ± 5	83 ± 2
Caudate nucleus, dorsolateral	102 ± 5	96 ± 2	100 ± 5	99 ± 3
Caudate nucleus, dorsomedial	98 ± 6	92 ± 2	99 ± 6	98 ± 3
Caudate nucleus, ventral	91 ± 5	81 ± 2	86 ± 4	85 ± 2
Lateral septal nucleus	58 ± 4	53 ± 4	54 ± 3	58 ± 2
Medial septal nucleus	79 ± 5	75 ± 3	80 ± 5	84 ± 2
Globus pallidus	54 ± 1	50 ± 2	55 ± 5	54 ± 2
Amygdala, basolateral	86 ± 7	81 ± 5	83 ± 3	81 ± 5
Amygdala, central	48 ± 3	43 ± 2	47 ± 3	46 ± 1
Thalamus, ventromedial	110 ± 6	116 ± 4	130 ± 7 [a]	130 ± 5 [b]
Thalamus, ventrolateral	88 ± 3	93 ± 3	100 ± 4 [a]	101 ± 3 [b]
Thalamus, ventroposterolateral	87 ± 5	88 ± 3	96 ± 4	94 ± 2
Entopeduncular nucleus	46 ± 3	47 ± 2	53 ± 3	55 ± 3 [b]
Thalamus, dorsomedial	118 ± 4	116 ± 5	142 ± 11 [a]	134 ± 7 [b]
Thalamus, laterodorsal	113 ± 6	110 ± 6	128 ± 8	125 ± 5 [b]
Habenula, medial	63 ± 1	63 ± 3	65 ± 4	70 ± 1
Habenula, lateral (medial)	93 ± 7	93 ± 6	84 ± 4	92 ± 3
Habenula, lateral (lateral)	111 ± 5	111 ± 6	100 ± 4	108 ± 4
Subthalamic nucleus	87 ± 5	84 ± 2	93 ± 4	96 ± 2
Hippocampus, ca1	60 ± 4	60 ± 3	69 ± 4	69 ± 2 [b]
Hippocampus, ca2	71 ± 4	66 ± 5	77 ± 6	78 ± 3 [b]
Hippocampus, ca3	63 ± 3	59 ± 3	70 ± 5	72 ± 2 [b]
Hippocampus, ca4	52 ± 2	51 ± 2	59 ± 4	60 ± 2 [b]
Dentate gyrus	73 ± 3	73 ± 4	80 ± 5	82 ± 3
Lateral geniculate body	84 ± 5	85 ± 4	86 ± 5	90 ± 2
Auditory cortex	120 ± 9	107 ± 4	130 ± 8	133 ± 4 [b]
Medial geniculate body	110 ± 9	100 ± 3	113 ± 5	113 ± 3
Substantia nigra compacta	64 ± 3	64 ± 3	65 ± 4	71 ± 1
Substantia nigra reticulata	52 ± 3	50 ± 2	60 ± 4	61 ± 2 [b]
Visual cortex	89 ± 4	84 ± 3	91 ± 5	92 ± 1
Superior colliculus, external	82 ± 4	82 ± 5	80 ± 5	83 ± 3
Superior colliculus, deep	91 ± 5	85 ± 5	94 ± 6	100 ± 3 [b]
Inferior colliculus	114 ± 10	111 ± 10	138 ± 6	136 ± 4 [b]
Cerebellar cortex	58 ± 2	51 ± 2 [a]	60 ± 2	62 ± 2 [b]

Values represent means ± S.E.M. for the number of animals in parentheses.
[a] $P < 0.05$ different from group 'control'.
[b] $P < 0.05$ different from group 'recovery', Fisher's t-test statistic.

ing. Cryostatic coronal sections (20 μm) were thaw-mounted on glass coverslips and autoradiographed on Kodak Min-R X-ray films (Kodak, Italy), along with a set of calibrated [^{14}C]methylmethacrylate standards (Amersham International, UK). The autoradiograms were analyzed by quantitative densitometry, using a computerized image-processing system (MCID, Imaging Research, Canada). Local tissue ^{14}C concentrations were determined from the optical densities and a calibration curve was obtained from densitometric analysis of the calibrated standards. The rates of glucose metabolism were then calculated from the local ^{14}C concentrations and the time courses of the arterial plasma glucose and 2-[^{14}C]deoxyglucose concentrations were obtained from the operational equation of the method.

Local rates of glucose utilization were measured in 30 discrete brain areas. Statistical analysis was carried out by means of a two-way analysis of variance followed by Fisher's *t*-test for multiple comparisons.

3. Results

Local rates of cerebral glucose utilization in the different groups of animals are summarized in Table 1. Briefly, rates of energy metabolism in rats pretreated with corticosterone (group 'recovery') tended to be lower than those measured in controls (group 'control'). Significance was, however, reached only in the cerebellar cortex.

The administration of cocaine produced increased metabolic activity in thalamic nuclei, whether pretreatment was vehicle or corticosterone ('control + cocaine' vs. 'control' and 'recovery + cocaine' vs. 'recovery', respectively, see Table 1). A significant effect of corticosterone pretreatment on the metabolic response to cocaine was, however, measured in selected brain areas. Increased energy metabolism with respect to that in the corresponding control group was measured in limbic (shell of the nucleus accumbens, hippocampus) as well as motor areas (entopeduncular nucleus, substantia nigra reticulata, deep layer of the superior colliculus) following the administration of cocaine only in corticosterone-pretreated rats solely ('recovery + cocaine' vs. 'recovery').

4. Discussion

The results of the present study demonstrated that chronic treatment with corticosterone produces long-lasting facilitatory effects on the functional response to acute cocaine administration in the rat. These data thus demonstrate that the potentiation of the behavioral effects of cocaine previously reported by our group (Patacchioli et al., 1997) is accompanied by selective metabolic alterations in the rat brain. It is noteworthy to recall that the cocaine-induced increase in plasma corticosterone was significantly potentiated after recovery from chronic high-dose corticosterone treatment (Patacchioli et al., 1997). It is then conceivable that the functional derangement of the hypothalamus–pituitary–adrenal axis previously demonstrated following this protocol of corticosterone administration (Patacchioli et al., 1997) has a role in the increased functional response to cocaine administration.

Based on the topography of the effects now measured, it appears that the long-lasting facilitatory effects of corticosterone pretreatment on the metabolic response to cocaine are measurable in limbic as well as motor areas. Within the limbic system, metabolic activation in the shell of the nucleus accumbens had been reported following the intravenous administration of reinforcing doses of cocaine, amphetamine, morphine or nicotine (Pontieri et al., 1994, 1996; Orzi et al., 1996). It has been demonstrated that the increased metabolism in the nucleus accumbens following acute cocaine administration in drug-naive rats depends on the route of administration, as it does not occur following the intraperitoneal injection (Porrino, 1993). The critical role of the mesolimbic dopamine terminals in the shell of the nucleus accumbens for the reinforcing effects of psychostimulants as well as opiates or nicotine had been suggested earlier (Pontieri et al., 1995, 1996). The results of the present study are cogent to this issue in that they show that circulating corticosterone contributes to the metabolic activation in the shell of the nucleus accumbens, at least following the administration of cocaine. Our results thus provide further insight into the neuropharmacology of the interaction between glucocorticoids and drugs acting on the central dopamine reward system. Moreover, the increased metabolic activity in the hippocampal complex following cocaine challenge in corticosterone pretreated rats suggests that the disinhibition of the hypothalamus–pituitary–adrenal axis affects the functional response to cocaine administration in the same areas where altered central glucocorticoid binding occurs following chronic corticosterone treatment (Sapolsky et al., 1985). These data thus support the hypothesis that central corticosterone receptors might play a modulating role in the central effects of cocaine.

Cocaine-induced motor activity is potentiated after recovery from high-dose corticosterone treatment (Patacchioli et al., 1997). In the present study, increased metabolic activity was measured in thalamic nuclei following cocaine challenge in both corticosterone- and vehicle-pretreated rats, possibly as the consequence of the motor activation produced by the drug (Patacchioli et al., 1997). Our data demonstrated that the facilitatory role of the functional derangement of the hypothalamus–pituitary–adrenal axis for the effects of an acute cocaine challenge are also measurable in motor areas such as the substantia nigra pars reticulata and entopeduncular nucleus, area that represent the output stations of the basal ganglia, and in the deep layer of the superior colliculus that receives a direct input from the basal ganglia. These results might represent the anatomo–functional basis for the markedly increased mo-

tor response to cocaine observed after wash-out from chronic corticosterone treatment (Patacchioli et al., 1997).

In conclusion, the present results extend our knowledge about the interaction between glucocorticoids and psychomotor stimulants by showing selective long-lasting alterations in the metabolic response to cocaine challenge in rats pretreated with high dose of corticosterone.

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