ELSEVIER

European Journal of Pharmacology 302 (1996) 49–51

ejp

Short communication

Intravenous morphine increases glucose utilization in the shell of the rat nucleus accumbens

Francesco Orzi [b], Francesca Passarelli [a], Maurizio La Riccia [a], Renato Di Grezia [b], Francesco E. Pontieri [a,*]

[a] *Dipartimento di Scienze Neurologiche, Università 'La Sapienza', Roma, Italy*
[b] *INM 'Neuromed', Pozzilli (IS), Italy*

Received 13 November 1995; revised 5 February 1996; accepted 9 February 1996

Abstract

The [^{14}C]2-deoxyglucose method was applied to measure the effects of the acute intravenous administration of morphine sulphate (0.2–0.4 mg/kg) on cerebral glucose utilization in rats. Morphine produced dose-dependent increases of glucose metabolism in the shell of the nucleus accumbens, without affecting functional activity in any other brain area. These results provide further evidence for the preferential effects of intravenously abused substances in the shell of the nucleus accumbens.

Keywords: Morphine; Deoxyglucose; Nucleus accumbens; Shell; Drug abuse

1. Introduction

Drugs of abuse are thought to exert their reinforcing effects through activation of neural pathways which subserve natural rewards. In this view, the nucleus accumbens and its neural projections that use dopamine as a neurotransmitter are currently recognized as a critical target for drugs and substances of abuse (Di Chiara and North, 1992; Di Chiara, 1995). The anatomical and biochemical identity of the nucleus accumbens has been, however, thoroughly revised with the distinction of two different portions: a 'shell', viewed as a transition area belonging to the 'extended amygdaloid complex', and a 'core' as part of the striato-pallidal system (Alheid and Heimer, 1988; Heimer et al., 1991). Consequently, the issue has been whether there is also functional heterogeneity within the nucleus accumbens as to the effects of abused substances. We previously showed that acute intravenous administration of cocaine and amphetamine, at dosages corresponding to those that sustain self-administration in the rat, modify energy metabolism preferentially in the 'shell' of the nucleus accumbens (Pontieri et al., 1994). Moreover, preferential activation of dopamine transmission in the 'shell' of the nucleus accumbens with respect to the 'core' has been recently demonstrated following intravenous administration of cocaine, amphetamine and also morphine to rats (Pontieri et al., 1995). This preferential effect in the 'shell' of the nucleus accumbens appears, therefore, related to the general abuse liability of these drugs, rather than to the specific neurochemical mechanism of action of each substance.

The present study was undertaken to verify whether, under experimental conditions similar to those previously utilized (Pontieri et al., 1995), morphine has any selective effect on functional activity within the nucleus accumbens in the rat. Rates of glucose metabolism were therefore measured by means of the autoradiographic [^{14}C]2-deoxyglucose technique in rats treated with intravenous morphine or vehicle. Furthermore, simultaneous mapping of functional activity in the entire central nervous system allowed us to compare the general effects of intravenous morphine to those of other abused substances.

2. Materials and methods

2.1. Animals

The experiments were performed on male Sprague-Dawley rats (Harlan, Italy), weighing 280–320 g. The

* Corresponding author. Dipartimento di Scienze Neurologiche, I Clinica Neurologica, Università degli Studi 'La Sapienza', Viale dell'Università 30, 00185-Roma, Italy. Tel.: 39-6-49914708; fax: 39-6-4440790.

PII S0014-2999(96)00128-8

animals were housed in group cages under standard conditions of temperature and humidity, on a 12 h light/dark cycle (light on 07:00–19:00). The rats had free access to food and water.

2.2. Local cerebral glucose utilization

On the morning of the experiment, the femoral vessels were catheterized under halothane anaesthesia, according to the procedure described by Crane and Porrino (1989). The animals were allowed at least 3 h to recover from anaesthesia, then were divided into three groups and treated with either morphine sulphate (0.2–0.4 mg/kg) (Sigma, USA) or vehicle. The drug was dissolved in fresh saline soon before use, and was injected intravenously in a volume of 1 ml/kg. The [^{14}C]2-deoxyglucose procedure was begun 15 min after the administration of drug or vehicle, by injecting an intravenous pulse of [^{14}C]2-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 method (Sokoloff et al., 1977). Approximately 45 min after the administration of the tracer, the animals were killed by the intravenous administration of sodium pentobarbital, the brains were rapidly removed, frozen in isopentane at −40°C and stored at −80°C until sectioning. 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]methylmetacrylate standards (Amersham International, UK). The autoradiograms were analyzed by quantitative densitometry with 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 by densitometric analysis of the autoradiograms of the calibrated standards. Rates of glucose metabolism were then calculated from local ^{14}C concentrations and time courses of arterial plasma glucose and [^{14}C]2-deoxyglucose concentrations by means of the operational equation of the method (Sokoloff et al., 1977).

2.3. Statistical analysis

Rates of glucose metabolism were measured in 39 discrete brain areas. Statistical analysis was carried out for each structure independently by means of a one-way analysis of variance followed by Dunnett's t-test for multiple comparisons.

3. Results

Administration of morphine produced dose-dependent increases in energy metabolism in the 'shell' of the nucleus accumbens, whereas no significant difference between morphine-treated rats and controls was found in the 'core' or in any other brain area examined (Table 1).

Table 1
Effects of the intravenous administration of morphine sulphate on the local rates of cerebral glucose utilization (μmol/100 g/min) in freely moving rats

Structure	Morphine sulphate (mg/kg)		
	0.0	0.2	0.4
Medial prefrontal cortex	74± 5	78± 5	73± 5
Nucleus accumbens (shell)	82± 4	99± 5 [a]	103± 4 [b]
Nucleus accumbens (core)	84± 4	90± 4	93± 5
Caudate-putamen (dorsolateral)	116± 7	118± 9	109± 7
Caudate-putamen (dorsomedial)	116± 8	116± 8	108± 6
Caudate-putamen (ventral)	99± 5	100± 8	95± 6
Lateral septal nucleus	64± 4	69± 6	60± 6
Medial septal nucleus	85± 6	88± 7	81± 7
Anterior cingulate cortex	110± 7	120± 9	117± 8
Globus pallidus (ventral)	65± 4	66± 5	61± 4
Globus pallidus (ventral)	60± 4	63± 6	55± 4
Sensory motor cortex	110± 8	113±12	106± 7
Lateral hypothalamus	68± 3	72± 3	65± 4
Habenula (medial)	79± 5	85± 8	84± 8
Habenula (mediolateral)	103± 7	107± 5	107± 9
Habenula (lateral)	121± 9	122± 7	119± 8
Amygdala (central)	52± 2	55± 3	50± 3
Amygdala (basolateral)	95± 6	107± 6	96± 7
Hippocampus (CA1)	68± 4	75± 5	72± 7
Hippocampus (CA2)	81± 6	87± 5	84± 7
Hippocampus (CA3)	74± 5	80± 5	74± 6
Hippocampus (CA4)	61± 4	67± 5	62± 6
Dentate gyrus	80± 5	86± 5	82± 6
Thalamus (ventromedial)	127± 7	135±11	122±10
Thalamus (ventrolateral)	106± 6	106±12	94± 8
Thalamus (mediodorsal)	125± 9	133± 9	118±11
Subthalamic nucleus	96± 6	104± 8	93± 7
Substantia nigra compacta	77± 4	84± 6	73± 6
Substantia nigra reticulata	64± 3	71± 5	61± 5
Auditory cortex	146±10	151±12	152±16
Medial geniculate body	132± 7	133±13	135±17
Inferior colliculus	150±10	157±13	147±19
Visual cortex	116± 8	125±13	108± 9
Lateral geniculate body	99± 6	102± 9	96±10
Superior colliculus (external)	91± 6	103± 9	95±11
Superior colliculus (deep)	104± 7	111± 8	109±11
Pontine gray	74± 5	77± 5	66± 5
Cerebellar cortex	60± 5	60± 4	53± 4
Corpus callosum	28± 2	25± 2	27± 2

Values represent means ± S.E.M., $n = 6$ in each group. [a] $P < 0.05$, [b] $P < 0.01$ different from vehicle-treated; Dunnett's t-test statistics.

4. Discussion

The results of the present study provide evidence that acute intravenous administration of morphine, at dosages corresponding to those that maintain self-administration in the rat (Weeks and Collins, 1976), selectively modifies functional activity in the 'shell' of the nucleus accumbens. The effects of intravenous morphine on the two subportions of the nucleus accumbens measured in this study are

similar to those produced by psychomotor stimulants such as cocaine and amphetamine (Pontieri et al., 1994). It appears, therefore, that altered functional activity in the 'shell', that represents the more typically 'limbic' portion of the nucleus accumbens, is a consequence of the intravenous administration of abused substances, independently from their neurochemical mechanism of action. It also appears that the 'shell' of the nucleus accumbens is the most sensitive site of action of abused drugs in the rat brain.

Recent data on the effects of intravenous administration of morphine, at the same range of doses as used in the present study, on dopamine release within the nucleus accumbens demonstrate a selective action of the drug on dopaminergic terminals in the 'shell' (Pontieri et al., 1995). Therefore, a strict topographic homology exists between changes in dopamine transmission and alterations in functional activity produced by intravenous morphine, similar to the one reported for psychostimulants. Combined [^{14}C]2-deoxyglucose/microdialysis studies will be necessary to further define the correlation between changes in energy metabolism and modifications of dopamine transmission produced by abused substances.

On the other hand, morphine appears different from psychostimulants in that slight, not significant metabolic depressions were measured following the higher dose of the drug, whereas dose-dependent increases in energy metabolism were measured in limbic and motor areas following intravenous administration of either amphetamine (Porrino et al., 1984) or cocaine (Porrino et al., 1988). In this respect, the tendency of the higher dose of intravenous morphine to depress functional activity reported herein is consistent with previous reports on functional mapping of the effects of intraperitoneal administration of morphine at dosages that produce analgesia (Levy et al., 1986; London et al., 1986; Beck et al., 1989). Analgesic doses of morphine are much higher than those which produce reinforcement. The present data, however, suggest that a certain overlap of effects may occur at the highest reinforcing dosages.

The relevance of the route of administration for determining the topographic pattern of alterations of energy metabolism has been demonstrated following acute cocaine administration (Porrino, 1993), as increased rates of glucose metabolism in the nucleus accumbens were measured following intravenous but not intraperitoneal administration of the drug. In accordance with these previous results obtained with cocaine, the changes in energy metabolism produced by morphine in the 'shell' of the nucleus accumbens appear strategically linked to the intravenous route of administration. In conclusion, the results of the present study demonstrate further the key role of the 'shell' of the nucleus accumbens in mediating the effects of intravenously abused drugs.

References

Alheid, G.F. and L. Heimer, 1988, New perspective in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid and corticopetal components of substantia innominata, Neuroscience 27, 1.

Beck, T., J. Wenzel, K. Kuschinski and J. Krieglstein, 1989, Morphine-induced alterations of local cerebral glucose utilization in the basal ganglia of rats, Brain Res. 497, 205.

Crane, A.M. and L.J. Porrino, 1989, Adaptation of the quantitative 2-[^{14}C]-deoxyglucose method for use in freely moving rats, Brain Res. 499, 87.

Di Chiara, G., 1995, The role of dopamine in drug abuse viewed from the perspective of its role in motivation, Drug Alcohol Depend. 38, 95.

Di Chiara, G. and R.A. North, 1992, Neurobiology of opiate abuse, Trends Pharmacol. Sci. 13, 185.

Heimer, L., J. DeOlmos, G.F. Alheid and L. Zaborski, 1991, 'Perestroika' in the basal forebrain: opening the border between neurology and psychiatry, Prog. Brain Res. 87, 109.

Levy, R.M., H.L. Fields, M.P. Stryke and M.M. Heinricher, 1986, The effects of analgesic doses of morphine on regional cerebral glucose metabolism in pain-related structures, Brain Res. 368, 170.

London, E., R. Fanelli, M. Szikszay and D. Jasinski, 1986, Effects of opioid analgesics on local cerebral glucose utilization, NIDA Res. Monogr. 75, 379.

Pontieri, F.E., V. Colangelo, M. La Riccia, C. Pozzilli, F. Passarelli and F. Orzi, 1994, Psychostimulant drugs increase glucose utilization in the shell of the rat nucleus accumbens, NeuroReport 5, 2561.

Pontieri, F.E., G. Tanda and G. Di Chiara, 1995, Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the 'shell' as compared to the 'core' of the rat nucleus accumbens, Proc. Natl. Acad. Sci. USA 92, 12304.

Porrino, L.J., 1993, Functional consequences of acute cocaine treatment depend on route of administration, Psychopharmacology 112, 343.

Porrino, L.J., G. Lucignani, D. Dow-Edwards and L. Sokoloff, 1984, Dose-dependent effect of acute amphetamine administration on functional brain metabolism in rats, Brain Res. 307, 311.

Porrino, L.J., F.R. Domer, A.M. Crane and L. Sokoloff, 1988, Selective alterations in cerebral metabolism within the mesocorticolimbic dopaminergic system produced by acute cocaine administration in rats, Neuropsychopharmacology 1, 109.

Sokoloff, L., M. Reivich, C. Kennedy, M.H. DesRosiers, C.S. Patlack, K.D. Pettigrew, O. Sakurada and M. Shinohara, 1977, The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat, J. Neurochem. 28, 897.

Weeks, J.R. and R.J. Collins, 1976, Changes in morphine self-administration in rats induced by prostaglandin E and naloxone, Prostaglandins 12, 11.