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Short Communication

Effects of Naftidrofuryl on Local Cerebral Glucose Utilization in the Rat

*F. Orzi, †F. Schuier, and *C. Fieschi

Department of Neurology, University of Rome, Rome, Italy, and †Department of Neurology, Univeristy of Dusseldorf, Dusseldorf, Federal Republic of Germany

Summary: The effects of naftidrofuryl on local cerebral glucose utilization have been examined in 21 lightly restrained, conscious rats by means of the quantitative autoradiographic 2-deoxyglucose technique. Naftidrofuryl (15, 30, and 45 mg/kg, i.p.) did not significantly alter the rate of glucose utilization in any of the 29 gray matter or 4 white matter areas that were examined.

Because of the close relationship between energy metabolism and physiological function in the central nervous system, the 2-deoxyglucose (2-DG) method is particularly suitable for mapping of functional neuroanatomical pathways (Sokoloff et al., 1977). We have used this method in animals pretreated with naftidrofuryl. Naftidrofuryl is a new drug thought to have vasodilating effects. It has gangliosympatholytic, sympathoplegic, and local anesthetic actions. The vasodilator effect, shown at the level of the muscle and of the brain, is accompanied by actions on blood viscosity and a moderate "activation" of EEG (Fontaine et al., 1968, 1969; Pourrias and Raynaud, 1972; Takagi et al., 1972; Yanagita et al., 1972). Clinical studies have reported that the drug produces generic improvement in dementia, in mental deterioration in the elderly, and in "cerebral arteriosclerosis" when a parameter such as memory or "intellectual function" is tested (Judge and Urquhart, 1972; Robinson, 1972; Bouvier et al., 1974; Gerin, 1974; Cox, 1975). Better neurological progress than in the control group has been described in a double-blind study in patients with acute stroke treated with naftidrofuryl (Admani, 1978).

Address correspondence and reprint requests to Dr. Orzi at Building 36, Room 1A-27, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, Maryland 20205.

Abbreviations used: 2-DG, 2-Deoxyglucose; LCGU, Local cerebral glucose utilization.

Recently it has been reported that oral administration of naftidrofuryl modifies cerebral metabolism, especially as regards glucose catabolism (Meynaud et al., 1973; Meynaud et al., 1975; Cretet, et al., 1978).

MATERIALS AND METHOD

Animals

The experiments were carried out on normal adult male Sprague-Dawley rats weighing 350–420 g.

Materials

2-Deoxy-D-[1-^{14}C]glucose (spec. act., 50–55 mCi/mmol) and calibrated [^{14}C]toluene, used for the internal standardization of the samples, were purchased from New England Nuclear Corp. (Boston, Mass.). Naftidrofuryl (Praxilene®) was obtained from Lipha, Lyon, France.

Experimental Procedure

Local cerebral glucose utilization (LCGU) was measured by the method of Sokoloff et al. (1977). Rats were anesthetized with halothane (1.5%) and N_2O (70%), and polyethylene catheters (PE-50) were inserted in a femoral artery and vein. The animals were then placed in a loose-fitting plaster

cast and allowed to recover from the effects of anesthesia for at least 2 h. The drug was injected intraperitoneally in three different doses (15, 30, and 45 mg/kg) 30 or 45 min before the intravenous injection of a pulse of [^{14}C]DG (125 μCi/kg body weight). During the following 45 min, 13 timed blood samples were drawn; the blood was immediately centrifuged and the plasma placed on ice until further analysis. At the end of the 45 min the animals were killed by decapitation, and the brains were removed and frozen in isopentane chilled to −40°C. The brains were then coated with an embedding medium and stored in a plastic bag at −70°C until they were cut in serial sections of 20 μm thickness and prepared for the autoradiography as previously described (Sokoloff et al., 1977). The [^{14}C]DG plasma concentration was determined by liquid scintillation counting and the glucose concentration by means of a Beckman glucose analyzer (Beckman Instrument Co., Fullerton, Calif). The areas of interest in the autoradiography were read densitometrically with a photovolt densitometer, and the mean of several readings in each area was used to determine the tissue concentration by means of an individual calibration curve for each film. LCGU was calculated according to the operational equation developed by Sokoloff et al., 1977. Moreover, the means of the values of 6 areas of cortex (''mean cortex''), 23 gray structures (''mean gray''), and of 4 white (''mean white'') were computed.

Statistical Analysis

LCGU was measured in 33 structures (29 gray and 4 white) in 9 controls and 12 treated animals. Each structure was analyzed for statistically significant difference from control by the Student *t*-test.

RESULTS

The physiological variables measured were not significantly different in the experimental animals and controls. The LCGU of the control group was generally lower than the values published in the original report (Sokoloff et al., 1977), with a reduction up to 30% in the auditory cortex. A different level of noise during the experiments might explain the difference; however, these values are not inconsistent with the results currently being obtained in the laboratory.

None of the drug-treated groups showed any significant differences in LCGU from the levels in the controls (Table 1).

DISCUSSION

The clinical studies previously mentioned need to be confirmed; however, the neurological conditions to which they refer are not likely to be improved by the vasodilator action of the naftidrofuryl, and its useful effect has been widely attributed to its reported capacity to enhance cellular energy metabolism. This capacity was claimed essentially on the basis of the observation that the brain concentrations of glucose, ATP, and phosphocreatine are augmented and the lactate concentration decreased in animals treated with the drug, but there is no direct evidence that the drug enhances glucose utilization in the brain.

Our study shows that naftidrofuryl has no significant effects on glucose utilization in the brain, either as a whole or regionally in normal, awake rats. This observation is confined to the species under study and also to acute administration of 15, 30, and 45 mg/kg of the drug. We noticed at the intermediate dosage a slight, but not statistically significant, increase in LCGU in cerebral structures that was not confirmed at higher doses. It is fair to state, therefore, that with an acute administration of up to 10−20 times that suggested for clinical use (i.e., 1−2 mg/kg), naftidrofuryl is ineffective in altering local cerebral energy metabolism in normal laboratory rats. This study provides a model by which the metabolic effects of drugs can be studied quantitatively and at a local level in the brain. We just mention, as an example, the studies previously done in animals treated with amphetamine (Wechsler et al., 1979), β-endorphin (Sakurada et al., 1978), and adrenoreceptor blockers (Savaki et al., 1978), in which a modification of the LCGU has been clearly shown and measured, circumventing the uncertainties and criticism applicable to a vast amount of controversial information obtained with qualitative or observational techniques.

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TABLE 1. *Effect of naftidrofuryl on local cerebral glucose utilization in the conscious rat*

Brain region	Controls (9)	Pretreated 15 mg/kg (4)	Pretreated 30 mg/kg (4)	Pretreated 45 mg/kg (4)
Visual cortex	93 ± 11	81 ± 7	100 ± 8	94 ± 21
Auditory cortex	123 ± 30	110 ± 8	128 ± 21	120 ± 20
Parietal cortex	93 ± 11	84 ± 4	104 ± 8	86 ± 6
Sensorimotor cortex	94 ± 12	86 ± 9	106 ± 7	90 ± 8
Olfactory cortex	89 ± 12	82 ± 8	92 ± 21	86 ± 11
Frontal cortex	90 ± 8	86 ± 2	94 ± 8	83 ± 6
Thalamus D.M.	94 ± 7	86 ± 2	89 ± 2	91 ± 14
Thalamus V.L.	80 ± 7	73 ± 4	76 ± 11	77 ± 11
Medial geniculate	103 ± 17	92 ± 8	99 ± 6	96 ± 22
Lateral geniculate	85 ± 12	75 ± 7	83 ± 4	83 ± 8
Hypothalamus	52 ± 7	50 ± 7	52 ± 9	49 ± 7
Hypothalamus, mamm. b.	90 ± 6	80 ± 4	90 ± 7	87 ± 16
Hippocampus	69 ± 7	67 ± 9	67 ± 2	67 ± 11
Hippocampus, dent. gyr.	61 ± 4	58 ± 6	57 ± 5	64 ± 11
Amygdala	42 ± 6	44 ± 7	42 ± 4	38 ± 5
Septal nucleus	53 ± 5	69 ± 6	58 ± 7	55 ± 4
Caudatus	95 ± 10	84 ± 9	87 ± 8	91 ± 12
Accumbens	73 ± 11	69 ± 7	72 ± 9	70 ± 9
Globus pallidus	54 ± 9	53 ± 7	51 ± 3	46 ± 8
Substantia nigra	58 ± 8	60 ± 8	62 ± 3	57 ± 8
Vestibular nucleus	102 ± 6	90 ± 4	101 ± 9	91 ± 12
Cochlear nucleus	93 ± 6	86 ± 17	95 ± 15	85 ± 20
Superior olives	114 ± 16	100 ± 15	120 ± 19	96 ± 10
Lateral lemniscus	93 ± 13	79 ± 10	86 ± 17	75 ± 15
Inferior colliculus	161 ± 13	129 ± 14	164 ± 9	129 ± 18
Superior colliculus	77 ± 10	64 ± 8	77 ± 5	69 ± 10
Pontine gray	52 ± 5	47 ± 2	53 ± 6	48 ± 6
Cerebellar hemisphere	49 ± 7	42 ± 4	48 ± 8	45 ± 4
Cerebellar nuclei	86 ± 10	73 ± 4	86 ± 3	70 ± 9
Corpus callosum	31 ± 5	32 ± 2	32 ± 2	33 ± 7
Corpus callosum, genu	25 ± 3	26 ± 5	25 ± 3	21 ± 2
Internal capsule	26 ± 2	28 ± 4	34 ± 7	24 ± 3
Cerebellum, white	32 ± 6	32 ± 4	34 ± 5	29 ± 6

Means ± SD of the values of local cerebral glucose utilization (μmol/100 g/min) from measurements made in the number of rats indicated in parentheses.

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