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Metabolic and neuroanatomical correlates of barrel-rolling and oculoclonic convulsions induced by intraventricular endothelin-1: a novel peptidergic signaling mechanism in visuovestibular and oculomotor regulation?

Paul M. Gross[1,2], Richard J. Beninger[3], Steven W. Shaver[1,3], Dan S. Wainman[1], Francisco J. Espinosa[1], Donald F. Weaver[4,5]

[1] Department of Surgery (Neurosurgery), Neurosurgical Research Unit, LaSalle Building, 146 Stuart Street, Queen's University and Kingston General Hospital, Kingston, Ontario, Canada K7L 3N6
[2] Department of Physiology, Queen's University, Kingston, Ontario, Canada K7L 3N6
[3] Department of Psychology, Queen's University, Kingston, Ontario, Canada K7L 3N6
[4] Department of Medicine (Neurology), Queen's University and Kingston General Hospital, Kingston, Ontario, Canada K7L 3N6
[5] Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

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Abstract. The neuroactive peptide endothelin-1 has receptors distributed abundantly among subdivisions and nuclei of the visuovestibular and oculomotor systems. In previous work, we and others described the convulsive manifestations resulting from central injection of this neuropeptide, including nystagmus, oculoclonus, exophthalmos, tonic hindlimb extension, and a generalized repetitive motor disturbance called barrel-rolling. We applied the quantitative, autoradiographic [^{14}C]deoxyglucose method to examine the hypothesis that visuovestibular and oculomotor structures would become metabolically stimulated when endothelin was introduced into the brain via the ventricular system in conscious rats. Since previous work had demonstrated that hypermetabolic responses to endothelin in other neural systems were inhibited by an antagonist of neuronal calcium L-type channels, nimodipine, we further tested whether the increased function of vestibulooculomotor nuclei whose metabolic activity was sensitive to endothelin could be altered following nimodipine pretreatment via the ventricle. A single unilateral injection of endothelin (9 pmol in 3 µl saline) into a lateral ventricle provoked significantly increased rates of glucose metabolism in 22 of 39 individual anatomical structures of the visuovestibular and oculomotor systems. Among those affected were the superficial stratum of the caudal superior colliculus (+25%), the optic tract bilaterally (+35 to 43%), the oculomotor cranial nerve nuclei (III, IV, VI; range of +21 to 47%), and the medial terminal nucleus of the accessory optic tract which harbors dense fields of endothelin binding sites (bilateral increase of +70 to 96%). Several other nuclei involved in the proprioceptive and visuovestibular disturbance caused by endothelin displayed increased metabolic activity, including the cuneate, gracile, sensory trigeminal, and prepositus hypoglossal nuclei, the vestibular subnuclear system, and the cerebellar flocculus. Identification of hypermetabolic responsivity to endothelin in these structures provides further information on the anatomical substrates mediating the behavioral phenomenology of endothelin-induced motor convulsions which involve the paroxysmal participation of the extraocular muscles and motor control systems producing barrel-rolling convulsions. Nimodipine pretreatment inhibited both the convulsive activity and the cerebral hypermetabolic responses to intraventricular endothelin. The results indicate that the neural systems sensitive to intraventricular endothelin become functionally active via a calcium-mediated process that may involve the neuropeptide as an intrinsic signaling molecule.

Key words: Deoxyglucose – Cerebral glucose metabolism – Barrel-rolling – Neural pathways and receptors – Rat

Correspondence to: P.M. Gross, Department of Surgery

Introduction

The neuropeptide endothelin-1 (Yanagisawa et al. 1988; Koseki et al. 1989; MacCumber et al. 1990; Takahashi et

al. 1991) displays immunoreactivity and binding sites varying in distribution and density over much of the neuraxis, including numerous structures within the visual, vestibular, and oculomotor systems (Kohzuki et al. 1991). When a low picomolar concentration of endothelin is injected into a lateral cerebral ventricle of a conscious rat, it produces prolonged convulsions distinguished by facial clonus, tonic hindlimb extension, hormonal secretions, and an outflow of sympathetic nervous activity with concomitant arterial hypertension (Moser and Pelton 1989; Ouchi et al. 1989; Lecci et al. 1990; Matsumura et al. 1991; Gross et al. 1992a). As determined by quantitative [^{14}C]deoxyglucose autoradiography, intraventricular endothelin is a potent stimulant of cerebral energy metabolism, affecting brain functions diversely either by direct contact of structures bordering the ventricular system or via the effects of neural efferent projections from structures influenced by endothelin in the cerebrospinal fluid (Gross et al. 1992a), or by both. This hypermetabolic effect is not the result of ischemia caused by the vasoconstrictor activity of endothelin because the level of blood flow reduction is modest at a time when the tissue metabolic rate is simultaneously high (Gross et al. 1992b).

In our previous examination of the convulsions elicited by intraventricular endothelin (Gross et al. 1992a), we identified distinctive effects on eye control, including exophthalmos, nystagmus, and oculoclonic activity. These effects were observable during the generalized motor convulsions expressed by repetitive "barrel" rotations about the long axis of the body (Moser and Pelton 1989). Barrel-rolling has been found previously to occur following central injection of certain neuropeptides and glutamate analogs (Morency et al. 1987; Balaban et al. 1989; Marrannes and Wauquier 1988). The metabolic patterns resulting in the brain during these convulsions have been described only partially (e.g., Wurpel et al. 1988), and there has been no previous analysis focused specifically on those integrated structures involved in control of the visual, oculomotor, vestibular, and proprioceptive systems.

Because binding sites for endothelin are abundantly localized in central visual, vestibular, cerebellar, and eye-control nuclei (Kohzuki et al. 1991), and these highly integrated systems have not been analyzed comprehensively to date during their simultaneous stimulation by a neuroactive peptide, we sought to describe the metabolic and neuroanatomical correlates of the barrel-rolling and oculoclonic convulsions resulting from intraventricular endothelin. As our previous work revealed that neuronal calcium L-channels appeared to be involved in the hypermetabolic responses of numerous structures to intraventricular endothelin (Gross et al. 1992a), we further tested whether central pretreatment with nimodipine, a calcium L-channel inhibitor, would affect the rates of glucose metabolism in vestibulooculomotor nuclei to central endothelin.

Materials and methods

Animals and surgery

The rats used in this study were housed in individual wire cages in an air-conditioned room with pellets and water always available except for food withdrawal on the day before study. All surgical and experimental procedures were approved by the university's Animal Care Committee before the project was started.

Twenty adult male Sprague-Dawley rats (range of body weight 326–395 g) were anesthetized with 65 mg/kg pentobarbital sodium and placed in a stereotaxic frame with the skull leveled. Using bregma as reference, we trephined a hole in the parietal bone to expose the dural surface at coordinates L 1.7 mm and P −1.0 mm. A 22-gauge, stainless steel guide cannula was lowered 3.7 mm ventral from the dural surface into the lateral cerebral ventricle at the level of the hippocampal fimbria and caudate nucleus (Paxinos and Watson 1986, Plate 22). Using three jeweler's screws placed in the skull as anchors, we constructed a cranioplastic cap, holding the cannula, through which was inserted a 28-gauge obturator with a nylon screw fitting to maintain patency (Plastic Products , Roanoke, Va.). The rats were then returned to their individual cages for at least 48 h of recovery.

Selection of doses for endothelin and nimodipine and experimental design

Endothelin-1 in a single 9-pmol dose was specifically used as it was shown previously to be within a narrow range of concentrations capable of eliciting barrel-rolling behavior and mediating a moderate systemic pressor effect (Moser and Pelton 1989; Ouchi et al. 1989; Lecci et al. 1990; Gross et al. 1992a).

The concentration of the calcium L-channel inhibitor nimodipine (30 µg or 72 nmol in 1 µl polyethylene glycol) was selected from previously reported experiments in which it proved to be an effective inhibitor of the endothelin-induced hypermetabolic responses in the brain (Gross et al. 1992a).

Five rats per group were given: (1) saline (3 µl at 1 µl/min); (2) endothelin (9 pmol in 3 µl saline); (3) nimodipine plus saline; or (4) nimodipine plus endothelin.

Measurement of focal rates of cerebral glucose metabolism in conscious rats

Rats were fasted the night before the metabolic studies. We inserted femoral venous and arterial catheters, while the rats were under gaseous anesthetic (1:1 nitrous oxide and oxygen, 1.5% halothane), and gave 500 units of heparin i.v. The rats were lightly restrained by placement of a loose-fitting plaster cast around the hindquarters (see Sokoloff et al. 1977), then were allowed to recover under a heat lamp for a period of 2–3 h during which we monitored several physiological variables to assure normal status before experimentation.

Following intraventricular injection, we waited 20 min before beginning the experiment to allow blood pressure to stabilize. We assessed rates of glucose metabolism using the quantitative autoradiographic technique employing [^{14}C]deoxyglucose as the tracer (2-deoxy-*D*-[1-^{14}C]glucose, specific activity 50–60 mCi/mmol; American Radiolabeled Chemicals, St. Louis, Mo.) following the prescribed procedure (Sokoloff et al. 1977). Briefly, [^{14}C]deoxyglucose was injected i.v. as a bolus (125 µCi/kg in 0.5 ml saline) after which 16 timed arterial blood samples were drawn at predetermined intervals to derive plasma concentrations of ^{14}C and glucose. After 45-min experiments, the rats were killed by i.v. overdose with pentobarbital sodium and the brains rapidly extracted and frozen in isopentane at −35°C. Before sectioning, the brains were equilibrat-

ed at −18°C in a cryostat and cut coronally in 20-μm-thick sections. Every 200 μm from the caudal medulla oblongata to the frontoorbital cortex, triplicate sections for autoradiography were collected and dried on coverslips which were then glued to cardboard sequentially and placed with [^{14}C]methylmethacrylate standards in cassettes for 14 days with OM-1 Kodak film (Rochester, N.Y.). An additional section at each level was obtained on a glass slide for staining with thionin and histological identification of individual nuclei and subregions according to the atlas of Paxinos and Watson (1986).

We determined rates of glucose metabolism in 39 individual structures and subregions of the visuovestibular and oculomotor systems from three to six autoradiographic images magnified and enhanced by a microcomputer-based imaging system (Imaging Research, St. Catharines, Ont., Canada). Brain optical densities were fitted by a computer program to the standard curve to derive rates of glucose metabolism according to the method's operational equation (Sokoloff et al. 1977).

Bilateral structures were analyzed bilaterally to compare ipsilateral responses with those contralateral to the side of injection. Structures were chosen for analysis in relation to their endothelin binding distributions (Kohzuki et al. 1991), or their neural connections within the visual, oculomotor, and vestibular systems (Precht 1981; Büttner and Büttner-Ennever 1988; Parnavelas et al. 1989). Sections kept for histological analysis were inspected and catalogued under light microscopy according to an atlas of rat brain nuclei (Paxinos and Watson 1986), then coregistered in image memory for analysis in conjunction with the corresponding autoradiographs (Imaging Research).

Metabolic data for individual structures between groups were assessed by analysis of variance and the Duncan multiple-range test, and those between hemispheres in the same group by dependent *t*-test. A 0.05 level of significance was accepted for the statistical evaluations.

Results

Behavioral observations and injectate distribution following intraventricular administration of endothelin

As reported previously (Gross et al. 1992a), the intraventricular injection of 9 pmol endothelin produced barrel-rolling attempts and other convulsive signs within 5–8 min of administration in all rats; as the animals of this report were lightly restrained (to facilitate blood sampling for quantitation in the deoxyglucose method; Materials and methods, above), the full expression of the convulsive activity caused by endothelin did not occur as in unrestrained rats. Nevertheless, we felt it was important to record our observations of the rats' responses following the intraventricular injections.

Although the barrel-roll attempts were repetitive (6–15 rotations/min), it was possible to observe during interictal periods that clonus of the eye and facial muscles occurred concurrently with nystagmus and exophthalmos. Saline, and the combination of nimodipine and saline, had no effect on behavior, whereas nimodipine pretreatment followed by endothelin resulted in fewer convulsive effects, including elimination of the barrel-rolling attempts. Facial and oculomotor convulsions persisted in these animals, however, appearing to be less intense than those in the rats injected with endothelin alone.

In our previous report (Gross et al. 1992a), we evaluated the distribution of the injectates and the toxicological effect of intraventricular endothelin. These analyses revealed no histological evidence for cellular toxicity or ischemia in periventricular tissue following intraventricular administration of endothelin. As determined at the time of cryostat sectioning of the brain, the Evans blue dye-labeled injectates were distributed throughout the ipsilateral lateral ventricle, third ventricle, and cerebral aqueduct to the level of the central gray and dorsal raphe in the midbrain. Only in two rats (one injected with saline, one with nimodipine and endothelin) did we find dye in the fourth cerebral ventricle.

Endothelin increased arterial blood pressure (+22%) and heart rate (+15%) in the conscious animals, as found by others in studies using lateral ventricular injections (rats, Ouchi et al. 1989; rabbits, Matsumura et al. 1991).

Patterns of cerebral metabolic activity

Among 39 structures included in the present assessment of local rates of glucose metabolism, there were no ipsilateral effects of saline (3 μl) or nimodipine and saline (total of 4 μl) injected into the lateral ventricle (Table 1).

Endothelin by itself evoked increases in the rates of glucose metabolism in 22 of the structures listed in Table 1; the range of significant increases was 21–83% ($P < 0.05$). Stimulation was present at several rostrocaudal levels of the neural systems under study, including caudal medullary nuclei involved in proprioceptive activity (e.g., cuneate nucleus and fasciculus; Fig. 1, top row), the cerebellar flocculus (Fig. 1, bottom row), the superficial stratum of the caudal superior colliculus (Fig. 2), the medial longitudinal fasciculus, prepositus hypoglossal nucleus, inferior olivary nucleus, and the pontine tegmental nuclei (Table 1). Endothelin increased the metabolic rate of the superior, medial, lateral and spinal vestibular subnuclei (average increase of 34%, Table 1). A significant bilateral increase in metabolic activity was detected in the white matter optic tract (+35 to 59%), but not in other visual control structures, such as the nucleus of the optic tract, the red nucleus, or the frontoorbital cortex (Table 1).

Relatively higher levels of stimulation (38–96% higher than saline effects) were present among components of the oculomotor complex – specifically, the oculomotor nucleus (Fig. 3, top row), medial accessory oculomotor nucleus, interstitial nucleus of Cajal, Darkschewitsch nucleus, and the medial terminal nucleus of the accessory optic tract (Fig. 3, bottom row). The trochlear and abducens nerve nuclei were stimulated (Table 1), but there was no effect measured in the Edinger-Westphal nucleus analyzed specifically in sections where its bilateral components merge to form a continuous midline structure (Plate 45 of Paxinos and Watson 1986).

Nimodipine injected with saline into the lateral ventricle did not elicit significant effects on regional glucose metabolism (Table 1). Following intraventricular pretreatment with nimodipine, endothelin significantly stimulated only 5 of the 22 structures that were affected by endothelin alone (Table 1). These structures all had similar or lower relative increases in glucose metabolism

Table 1. Effects of intraventricular endothelin-1 on rates of glucose metabolism in 39 individual structures and subregions of the visuovestibular and oculomotor systems

	Saline		Endothelin[a]		Increase in ipsilateral structure (%)	Nimodipine		Nimodipine + endothelin		Increase in ipsilateral structure (%)
	Contralateral	Ipsilateral	Contralateral	Ipsilateral		Contralateral	Ipsilateral	Contralateral	Ipsilateral	
Visual system										
Superior colliculus strata										
Caudal griseum superficialis	0.74 ±0.05	0.73 ±0.04	0.74 ±0.07	0.91 ±0.15*	25	0.76 ±0.03	0.73 ±0.04	0.81 ±0.12	0.75 ±0.02	
Caudal opticum	0.63 ±0.04	0.62 ±0.02	0.71 ±0.10	0.69 ±0.06		0.72 ±0.02	0.68 ±0.03	0.83 ±0.12	0.72 ±0.04	
Caudal griseum profundum	0.74 ±0.07	0.74 ±0.06	0.64 ±0.07	0.61 ±0.04		0.68 ±0.02	0.63 ±0.01	0.75 ±0.08	0.68 ±0.03	
Rostral griseum superficialis	0.71 ±0.04	0.69 ±0.03	0.61 ±0.04	0.58 ±0.02		0.82 ±0.02	0.76 ±0.02	0.76 ±0.04	0.74 ±0.04	
Rostral opticum	0.63 ±0.04	0.62 ±0.05	0.66 ±0.06	0.63 ±0.05		0.77 ±0.01	0.73 ±0.01	0.72 ±0.04	0.70 ±0.04	
Rostral griseum profundum	0.67 ±0.03	0.64 ±0.02	0.64 ±0.03	0.59 ±0.04		0.71 ±0.02	0.69 ±0.02	0.59 ±0.02	0.59 ±0.02	
Lateral geniculate nucleus	0.73 ±0.05	0.74 ±0.05	0.68 ±0.04	0.66 ±0.02		0.78 ±0.02	0.77 ±0.04	0.79 ±0.03	0.76 ±0.03	
Visual cortex	0.88 ±0.09	0.85 ±0.07	0.85 ±0.09	0.80 ±0.06		0.89 ±0.03	0.83 ±0.10	0.87 ±0.03	0.81 ±0.07	
N. optic tract	0.70 ±0.06	0.69 ±0.03	0.71 ±0.04	0.71 ±0.05		0.66 ±0.03	0.65 ±0.02	0.70 ±0.07	0.70 ±0.05	
Optic tract	0.17 ±0.01	0.17 ±0.01	0.27 ±0.03*	0.23 ±0.03*	35	0.21 ±0.01	0.20 ±0.01	0.22 ±0.03	0.19 ±0.03	
Orbital cortex	0.76 ±0.05	0.72 ±0.04	0.86 ±0.05	0.84 ±0.06		0.72 ±0.06	0.67 ±0.05	0.82 ±0.05	0.77 ±0.04	
Red nucleus	0.62 ±0.04	0.59 ±0.03	0.57 ±0.02	0.64 ±0.03		0.51 ±0.02	0.53 ±0.02	0.58 ±0.06	0.55 ±0.03	
Proprioceptive system and integrative nuclei										
Cuneate nucleus	0.53 ±0.02	0.52 ±0.02	0.76 ±0.02*	0.74 ±0.05*	35	0.52 ±0.04	0.54 ±0.03	0.56 ±0.02	0.46 ±0.04	
Cuneate fasciculus	0.43 ±0.01	0.45 ±0.02	0.65 ±0.10*	0.65 ±0.06*	44	0.47 ±0.03	0.45 ±0.04	0.55 ±0.04	0.44 ±0.04	
Gracilis nucleus	0.49 ±0.04	0.50 ±0.03	0.61 ±0.05*	0.61 ±0.07*	22	0.57 ±0.03	0.58 ±0.05	0.77 ±0.11*	0.69 ±0.02*	19
Spinal trigeminal nucleus	0.52 ±0.03	0.52 ±0.02	0.63 ±0.05	0.62 ±0.03		0.49 ±0.03	0.54 ±0.03	0.42 ±0.05	0.45 ±0.07	
Trigeminal nucleus (sensory)	0.66 ±0.03	0.65 ±0.03	0.95 ±0.08*	0.89 ±0.09*	37	0.63 ±0.03	0.62 ±0.04	0.66 ±0.03	0.67 ±0.06	
Prepositus hypoglossal nucleus	0.60 ±0.03	0.59 ±0.02	0.93 ±0.04*	0.91 ±0.03*	54	0.53 ±0.03	0.52 ±0.03	0.70 ±0.08*	0.72 ±0.06*	38
Medial longitudinal fasciculus	0.42 ±0.03		0.63 ±0.05*		50	0.42 ±0.02		0.47 ±0.04		
Facial nucleus	1.10 ±0.09	1.08 ±0.08	1.04 ±0.07	1.05 ±0.05		1.07 ±0.06	1.06 ±0.04	1.06 ±0.10	1.09 ±0.07	
Superior olivary nucleus	0.93 ±0.04	0.86 ±0.03	0.90 ±0.09	0.94 ±0.08		1.11 ±0.08	0.96 ±0.12	1.12 ±0.04	1.06 ±0.04	

Inferior olivary nucleus	0.65 ±0.06	0.63 ±0.04	0.77 ±0.10	0.91 ±0.11*	44	0.54 ±0.05	0.55 ±0.03	0.65 ±0.06	0.64 ±0.07	
Pontine reticular tegmental nucleus	0.46 ±0.03	0.46 ±0.03	0.58 ±0.02*	0.58 ±0.02*	26	0.46 ±0.02	0.48 ±0.02	0.52 ±0.03	0.50 ±0.04	
Pedunculopontine tegmental nucleus	0.53 ±0.05	0.52 ±0.05	0.65 ±0.03*	0.73 ±0.05*	40	0.55 ±0.05	0.54 ±0.05	0.69 ±0.09	0.60 ±0.03	
Thalamic pretectal nucleus	0.73 ±0.04	0.73 ±0.04	0.79 ±0.04	0.86 ±0.06		0.87 ±0.08	0.84 ±0.03	0.83 ±0.03	0.85 ±0.03	
Peripeduncular nucleus	0.46 ±0.02	0.45 ±0.03	0.70 ±0.03*	0.78 ±0.09*	73	0.54 ±0.05	0.47 ±0.02	0.61 ±0.06	0.55 ±0.04	
Cerebellar flocculus	0.46 ±0.03	0.47 ±0.04	0.77 ±0.06*	0.86 ±0.09*	83	0.47 ±0.04	0.49 ±0.05	0.61 ±0.06*	0.67 ±0.05*	37
Vestibular nuclei										
Superior	1.00 ±0.03	0.98 ±0.04	1.16 ±0.04*	1.29 ±0.06*	32	1.00 ±0.04	0.95 ±0.04	1.14 ±0.06	1.15 ±0.08	
Lateral	0.88 ±0.05	0.89 ±0.04	1.00 ±0.04	1.21 ±0.06*	36	0.94 ±0.03	0.95 ±0.04	1.11 ±0.10	1.13 ±0.09	
Medial	1.04 ±0.05	1.05 ±0.05	1.20 ±0.05*	1.38 ±0.07*	31	0.96 ±0.05	0.97 ±0.03	1.13 ±0.14	1.14 ±0.09	
Spinal	0.88 ±0.04	0.86 ±0.03	1.07 ±0.04*	1.17 ±0.05*	36	0.99 ±0.03	0.99 ±0.03	1.04 ±0.06	1.07 ±0.06	
Oculomotor complex										
Abducens nucleus	0.57 ±0.06	0.55 ±0.05	0.76 ±0.06*	0.74 ±0.07*	35	0.52 ±0.02	0.51 ±0.02	0.61 ±0.03	0.61 ±0.03	
Trochlear nucleus	0.59 ±0.02	0.58 ±0.03	0.66 ±0.04	0.70 ±0.05*	21	0.60 ±0.02	0.59 ±0.02	0.74 ±0.11*	0.74 ±0.11*	25
Oculomotor nucleus	0.72 ±0.05	0.70 ±0.06	1.06 ±0.10**	0.77 ±0.03		0.67 ±0.03	0.64 ±0.03	0.82 ±0.08*	0.82 ±0.06*	28
Medial accessory oculomotor nucleus	0.80 ±0.02	0.76 ±0.02	1.10 ±0.09**	0.84 ±0.02		0.88 ±0.02	0.89 ±0.02	0.89 ±0.11	0.81 ±0.10	
Interstitial nucleus of Cajal	0.65 ±0.04	0.64 ±0.03	0.94 ±0.06**	0.77 ±0.05*	20	0.63 ±0.02	0.63 ±0.01	0.74 ±0.04	0.74 ±0.04	
Darkschewitsch nucleus	0.78 ±0.02	0.77 ±0.02	1.13 ±0.05**	0.97 ±0.04*	26	0.74 ±0.02	0.73 ±0.02	0.85 ±0.08	0.84 ±0.06	
Edinger-Westphal nucleus	0.72±0.03		0.78±0.07			0.63±0.03		0.75±0.05		
Medial terminal nucleus accessory optic tract	0.48 ±0.04	0.46 ±0.04	0.94 ±0.15**	0.78 ±0.06*	70	0.62 ±0.04	0.62 ±0.04	0.69 ±0.12	0.62 ±0.07	

Values are means±SEM in units of micromoles per gram per minute for five rats per group
* $P<0.05$ compared with corresponding side in saline or nimodipine-injected rats (independent t-test)
** Contralateral response significantly exceeds ipsilateral response ($P<0.05$). Range of increases was 38–96% compared with contralateral responses in saline-injected animals
[a] Injection of 9 pmol endothelin-1 into the lateral cerebral ventricle (3 µl volume)

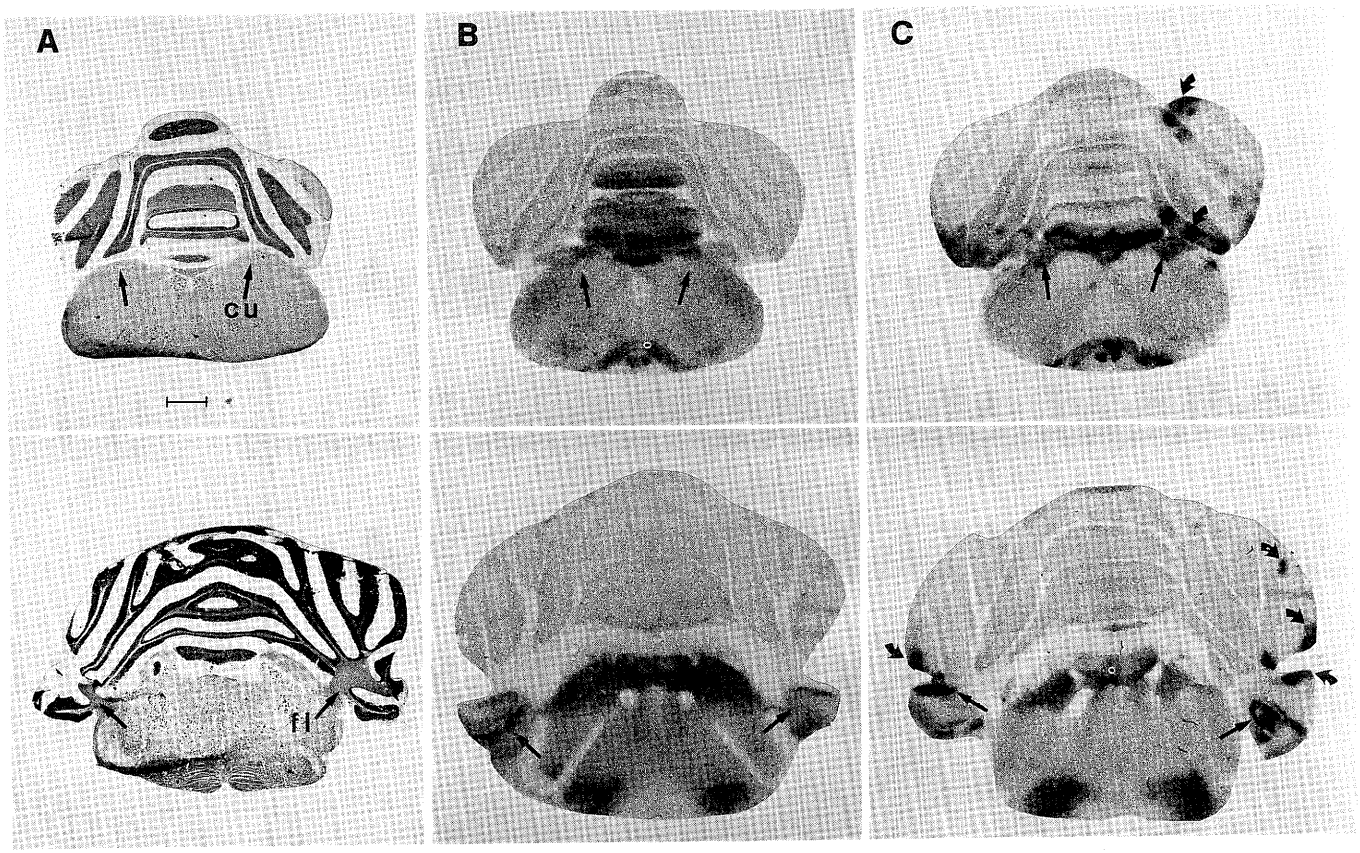

Fig. 1. Thionin-stained histological sections (**A**) displayed adjacent to [^{14}C]deoxyglucose autoradiographs from rats given an injection of saline (**B**) or endothelin-1 (**C**) into the right lateral ventricle. *Top row*, level of the cuneate nucleus (*cu*; approximate to Plate 75 of Paxinos and Watson 1986); *bottom row*, level of the cerebellar flocculus (approximate to Plate 58 of Paxinos and Watson 1986). *Straight arrows* point to the structure identified in **A**; *curved arrows* indicate regions with high rates of glucose metabolism which are proportional to the increased optical densities in the autoradiographs in *C*. The metabolic stimulation of the cerebellar cortex showed a high degree of focal responsiveness in the sagittal plane (see Gross et al. 1992a, for original metabolic data). *Scale bar* of (**A**) 1 mm

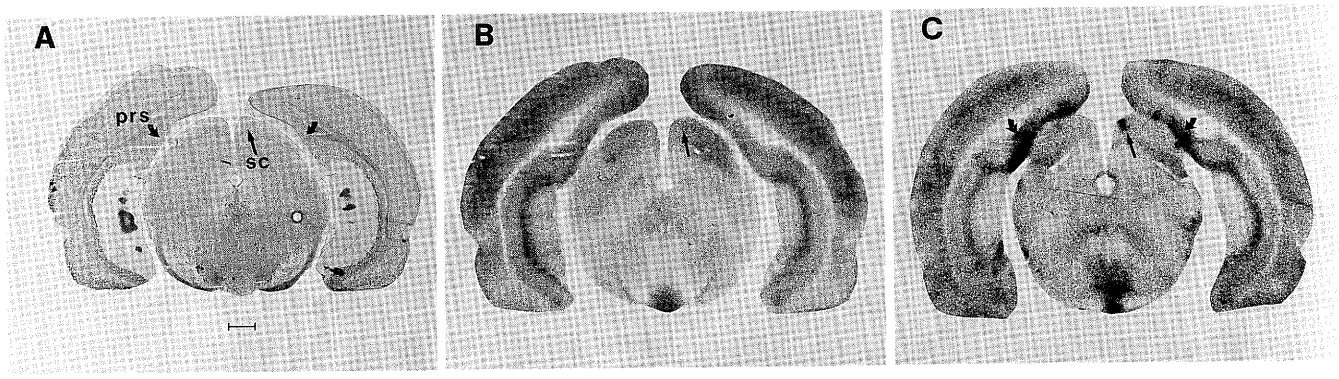

Fig. 2. Thionin-stained histological section (**A**) displayed adjacent to [^{14}C]deoxyglucose autoradiographs from rats given an injection of saline (**B**) or endothelin-1 (**C**) into the right lateral ventricle. Level of the presubiculum (*prs*) and superior colliculus (*sc*) (approximate to Plate 49 of Paxinos and Watson 1986). *Straight arrows* point to the focal region of the superior colliculus identified in **A**; only in this specific stratum did endothelin produce such a regionally specific metabolic effect (**C**, (Table 1). *Curved arrows* indicate regions with high rates of glucose metabolism which are proportional to the increased optical densities in the autoradiograph in **C**. See Gross et al. (1992a) for original metabolic data for the presubiculum. *Scale bar* under (**A**) 1 mm

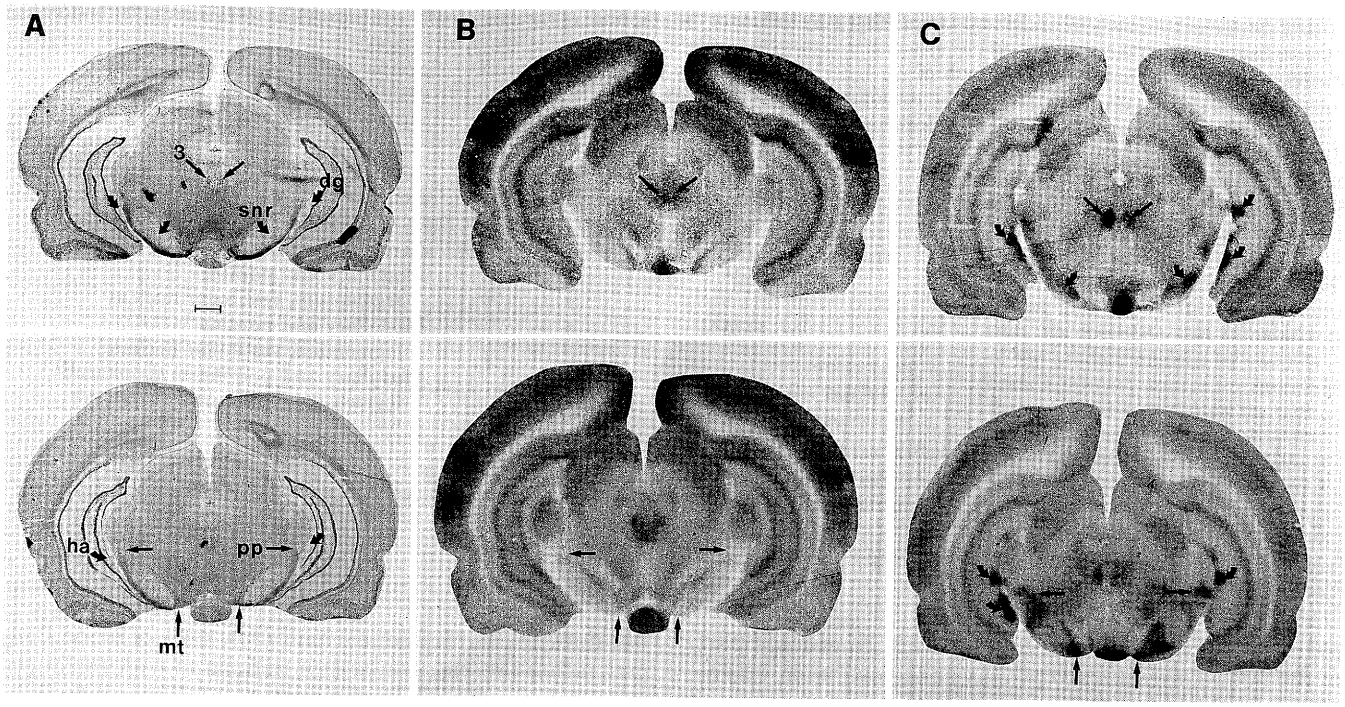

Fig. 3. Thionin-stained histological sections (**A**) displayed adjacent to [^{14}C]deoxyglucose autoradiographs from rats given an injection of saline (**B**) or endothelin-1 (**C**) into the right lateral ventricle. *Top row*, level of the oculomotor nerve nucleus (*3*), substantia nigra pars reticulata (*snr*), and the dentate gyrus (*dg*; approximate to Plate 42 of Paxinos and Watson 1986); *bottom row*, level of the medial terminal nucleus of the accessory optic tract (*mt*), peripeduncular nucleus (*pp*), substantia nigra pars reticulata, and the alveus-pyramidale layers of the hippocampus (*ha*; approximate to Plate 39 of Paxinos and Watson 1986). *Straight arrows* point to the structure identified in **A**; *curved arrows* indicate high rates of glucose metabolism which are proportional to the increased optical densities in the autoradiographs in **C**. Pars reticulata of the substantia nigra displayed a high degree of focal responsiveness in the coronal and sagittal planes. See Gross et al. (1992a) for the original metabolic data for the substantia nigra pars reticulata, dentate gyrus, and hippocampus. *Scale bar* under top section of (**A**) 1 mm

compared with the ipsilateral effect in rats treated with nimodipine and saline (Table 1).

Discussion

The main finding of the present studies was that intraventricular administration of endothelin induced a hypermetabolic state among numerous nuclei and subregions of the visuovestibular and oculomotor systems in which endothelin is potentially an intrinsic neurotransmitter. Following central administration of endothelin, 22 of 39 anatomically verified structures displayed significant increases in their rates of glucose utilization, which are reliable quantitative indices of functional neural activity in individual nuclei. The structures displaying hypermetabolic responses to endothelin represent both primary and accessory processing of visuovestibular and oculomotor functions in animals under the sensorimotor and proprioceptive activation by endothelin, an endogenous neuropeptide with dose-dependent convulsive properties. Furthermore, the endothelin-induced hypermetabolism in these pathways was abolished or attenuated by pretreatment of the rats with intraventricular administration of nimodipine, a calcium L-channel antagonist.

These results furnish several kinds of new information and introduce a new hypothesis that endothelin is a mediator of neurotransmission in visuovestibular and oculomotor functions. We shall address the following issues to emphasize the relationship of the metabolic patterns to: (1) the distribution of endothelin binding sites; (2) the neural circuitry of the visuovestibular and oculomotor systems (the evaluation of which permits speculation about the putative neural substrates of barrel-rolling behavior, nystagmus, and oculoclonus provoked by the central injection of endothelin); and (3) the role of calcium L-type channels in mediating the hypermetabolic response of the vestibulooculomotor systems to endothelin.

Relationship of metabolic stimulation to sites of endothelin binding

The detailed autoradiographic study of binding sites for endothelin in the brain by Kohzuki and coworkers (1991) has provided a basis from which functional responses to this neuropeptide can be examined quantitatively with resolution to individual units that contain endothelin receptors. Among the highly differentiated patterns of endothelin receptor distribution in the brain, binding is

Table 2. Selective summary of nuclei and factors that may influence the response of the extraocular eye muscles to intraventricular endothelin

Nuclei	Strength of metabolic response to icv endothelin	Proximity to ventricular system (μm)	Density of endothelin receptors[c]	Source of major afferent inputs[d]
Darkschewitsch	+ +	300[a]	+ +	Tegmentum
Medial terminal nucleus accessory optic tract	+ + +	2875[a]	+ + +	Oculomotor complex
Vestibular	+ +	Border IV	+ +	Cerebellum, tegmentum
Oculomotor	+ +	750[a]	+ + +	Medullary and pontine tegmentum, vestibular nucleus
Trochlear	+	1125[a]	+ +	Medullary and pontine tegmentum, vestibular nucleus
Abducens	+ +	300[b]	+	Medullary and pontine tegmentum, vestibular nucleus

icv, intracerebroventricular; IV, fourth cerebral ventricle
[a] Estimated distance from cerebral aqueduct (Paxinos and Watson 1986)
[b] Estimated distance from fourth cerebral ventricle (Paxinos and Watson 1986)
[c] Estimated from Kohzuki et al. 1991
[d] Summarized from Evinger 1988 and Goldberg et al. 1991

particularly dense in structures that are considered part of the neural circuits governing visual, vestibular, oculomotor, and proprioceptive functions. All of these integrated systems are under stimulation during the barrel-rolling, oculoclonus, nystagmus, exophthalmos, and other convulsions manifested by intraventricular administration of endothelin.

We reasoned that endothelin stimulates energy metabolism in visuovestibular and oculomotor nuclei and their integrated neural streams via one or all of three mechanisms that may furnish a clue about the intrinsic chemistry of neurotransmission in these functional circuits. Firstly, if endothelin circulating in the ventricular cerebrospinal fluid were to permeate ependymal layers and distribute interstitially over distances greater than 300 μm (Table 2) during the course of the deoxyglucose experiment (20 min following injection, but before the deoxyglucose experiment, plus another 45 min to complete the tracer study), then it could make direct contact with receptors in the structures under study over this 65-min period of time. This is unlikely, however, since we used Evans blue dye to color and track the distribution of the injectate which was not detected interstitially, but rather was confined to the injected lateral ventricle, third ventricle, the cerebral aqueduct, and infrequently in the fourth ventricle (Results). Other than the vestibular nuclei, none of the structures controlling visuovestibular and oculomotor functions borders the ventricular space (Mitro and Palkovits 1981; Paxinos and Watson 1986; Kohzuki et al. 1991; Table 2). This finding is also relevant to the consideration of whether the potent vasoconstrictor activity of endothelin (Yanagisawa et al. 1988; Simonson and Dunn 1992) contributed to the effects observed, especially if the tissue became ischemic. However, in previous autoradiographic studies which involved analysis of the rates of perfusion precisely within the same periventricular brain areas demonstrating high metabolic activity, blood flow was reduced only moderately (Gross et al. 1992b). Therefore, when endothelin produces its strong stimulatory effect on cerebral metabolism, the tissue does not display concurrently low rates of blood flow, but rather the vasoconstrictor actions of endothelin appear to be countered by the concurrent dilator influences of tissue metabolites.

Endothelin acts on neuronal voltage-sensitive calcium channels and, as a candidate extracellular signaling molecule in the nervous system, its ligand-receptor complex likely engages a G protein family coupled to the inositol phospholipid pathway (MacCumber et al. 1990; Chuang et al. 1991; Miller et al. 1993). Consequences of such signaling may be the cellular release of other neurotransmitter substances, such as excitatory amino acids (Kataoka et al. 1989; Chuang et al. 1991), nitric oxide (Reiser 1992), or other neuropeptides (Balaban et al. 1989). Based on the strong evidence that endothelin has these diverse G protein-coupled effects in several organs (Simonson and Dunn 1992; Miller et al. 1993), we speculate that endothelin is an extracellular signaling molecule intrinsic to those neural circuits in which its binding density is high, such as the visuovestibular and oculomotor systems (Kohzuki et al. 1991).

A third potential mechanism of endothelin is that it evokes the projection of efferent activity to other nuclei within the neural circuitry of the source structures (e.g., periventricular caudate nucleus), some of these including components of the visuovestibular and oculomotor systems (Precht 1981; Parnavelas et al. 1989; Goldberg et al. 1991). These responses shall be interpreted further in the following subsection: *Endothelin stimulation of the neural circuitry in the visuovestibular and oculomotor systems.*

Four areas mentioned in the paper by Kohzuki et al. (1991) are particularly relevant to a comparison of densities for endothelin binding sites with rates of glucose utilization as determined in the present study; these include the location of endothelin receptors in primary and accessory visual structures, the proprioceptive system, vestibular nuclei, and cerebellar/precerebellar nuclei (Table 1).

The autoradiographs of endothelin receptor distribution (Kohzuki et al. 1991) reveal moderate to high densi-

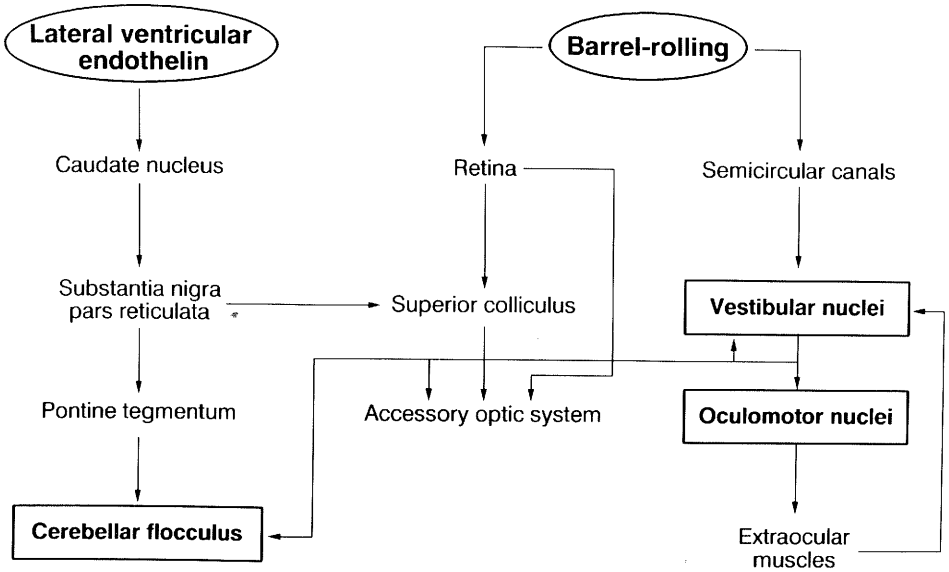

Fig. 4. Schematic diagram to illustrate key structures involved in the behavioral and hypermetabolic responses to intraventricular endothelin in conscious rats. By activation of the periventricular margin of the caudate nucleus, endothelin is presumed to induce both the projected neural efferent activity through the indicated circuits and the motor disturbances expressed by barrel-rolling and visuovestibular stimulation. We speculate that stimulation of the caudate nucleus by endothelin is a primary source for initiating the projected stimulation through neural pathways to structures that subsequently become metabolically activated (*bold boxes*; Table 1) and are involved in barrel-rolling behavior and other convulsions observed, such as oculoclonus and nystagmus. (Major references for these projections are Hoffmann 1986; Blanks 1988; Büttner and Büttner-Ennever 1988; Evinger 1988; Buisseret-Delmas et al. 1990; Goldberg et al. 1991)

ties in several nuclei involved in visual and oculomotor processing, including especially the medial terminal nucleus of the accessory optic tract in which we found an unusually strong metabolic response both ipsilaterally (+70%) and contralaterally (+98%) to the side of injection (Tables 1, 2, Fig. 3, bottom). This small nucleus has the highest density of endothelin binding sites among the visual control structures specified by Kohzuki and colleagues (1991). Notable among other responses was stimulation of the white matter optic tract, which appears to have low densities of endothelin receptors (Kohzuki et al. 1991); since endothelin binding is low in optic white matter, the elevation of metabolic activity in the optic tract by intraventricular endothelin most likely results from projected efferent signals passing through this trunk from other visual-control nuclei with activated function (discussed further below). A subregion of the ipsilateral superficial stratum of the superior colliculus (although only in its caudal extent; Fig. 2) and the contralateral nucleus of the oculomotor nerve itself (+51%, Fig. 3, top row) were also specifically stimulated. Both the superior colliculus and oculomotor nerve nucleus exhibit high densities of endothelin receptors (Kohzuki et al. 1991). It is possible, furthermore, that a retinal input to the superior colliculus influenced the focal hypermetabolic response in this structure (Fig. 2C).

Bilateral metabolic stimulation in two accessory oculomotor centers – the interstitial nuclei of Cajal and Darkschewitsch nuclei – was evident (Table 1). It is interesting that endothelin provoked greater stimulation in some *contralateral* structures of the oculomotor complex, such as the medial terminal and Darkschewitsch nuclei, in which there are abundant numbers of endothelin receptors and which receive afferent fibers via decussated pathways originating in the vestibular and abducens nerve nuclei (Kimm et al. 1979; Precht 1981; Pierrot-Deseilligny 1990; Goldberg et al. 1991). These findings indicate that the endothelin stimulus following unilateral injection of the peptide into the lateral ventricle may have been projected primarily from the excitatory vestibular neurons which decussate via the medial longitudinal fasciculi to innervate the oculomotor complex (Pierrot-Deseilligny 1990).

Components of the somatosensory, vestibular, and cerebellar or precerebellar systems, which we present in Table 1 as *"proprioceptive"* and *"integrative nuclei"*, were stimulated mostly in a uniform way on the side of the brain ipsilateral to injection (Table 1), although some structures displayed moderate contralateral effects (Figs. 1, 3; Table 1). The structures analyzed represent different levels of function across the rostrocaudal plane, from the reticular and pedunculopontine tegmental nuclei of the rostral pons (associated with somatosensory, motor and eye-position activities) to the cuneate nuclei and fasciculi in the caudal medulla oblongata (associated with proprioception; Büttner-Ennever and Holstege 1986; Büttner and Büttner-Ennever 1988). All of these structures harbor appreciable populations of binding sites for endothelin (Kohzuki et al. 1991). The superior, medial, lateral, and spinal subnuclei of the vestibular nuclear apparatus, in which endothelin binding is extraordinary (Fig. 7C-G of Kohzuki et al. 1991), had increased rates of glucose metabolism (+31–36%) following endothelin injection (Table 1). These findings indicate that the metabolism of vestibular neurons is increased substantially during the motor disturbances evoked by intraventricular endothelin, although it is impossible to tell from our results whether the effect was direct via the cerebrospinal fluid or projected from other nuclei, which may also include retrograde projections from the extraocular motoneurons to the vestibular nuclei (Buisseret-Delmas et al. 1990; Fig. 4).

We can conclude that the neural elements of the visuovestibular and oculomotor systems containing moderate to high densities of endothelin receptors (Kohzuki et al. 1991) were metabolically activated, in some cases bilaterally, by a unilateral intraventricular injection of 9 pmol endothelin. The low concentration and long duration of action of endothelin in the injected dose suggest a potential physiological role for this peptide in affecting metabolic activity tonically in these pathways. In several structures, the strength of the metabolic activation appears to be related directly to the density of endothelin binding sites (Table 2). This interpretation, however, must be considered cautiously in the context that neural afferent inputs also contribute importantly to the focal level of cerebral glucose metabolism (Sokoloff 1983; Kadekaro et al. 1985).

Endothelin stimulation of the neural circuitry for the visuovestibular and oculomotor systems

A critical consideration of the present metabolic results is the evaluation of the role of neural afferent traffic on the level of glucose metabolism in individual structures of the visuovestibular and oculomotor nuclei that were activated by ventricular endothelin. Although it can be reasonably speculated that the rate of glucose metabolism varies directly with the density and frequency of afferent neural traffic (Kadekaro et al. 1985), it is important to consider the possible primary substrates of stimulation and the specific targets of their efferent trajectories. For these reasons, we have developed a schematic presentation (Table 2, Fig. 4) based on neuroanatomical simplifications of the circuitry of the visuovestibular and oculomotor system. Using this strategy for interpreting the [^{14}C]deoxyglucose results and the neural connections of these systems, we offer an elementary functional explanation that may provide insight to the anatomical correlates of the convulsive activities induced by intraventricular endothelin.

The neural architecture and radiations of the visuovestibular and oculomotor systems are complex but reasonably well understood (Büttner and Büttner-Ennever 1988; Büttner-Ennever and Büttner 1988; Evinger 1988). To appreciate this complexity, yet characterize succinctly a synthetic view of our metabolic results, we have approached the analysis by considering the hippocampal formation, lateral septal nucleus, and caudate nucleus (which border the injected lateral ventricle near the location of endothelin injection) as the substrates most probably inducing neural activity that eventually engages increased energy metabolism of cells in the visuovestibular and oculomotor systems; the rates of glucose metabolism in these and other periventricular structures are strongly activated by intraventricular endothelin (Gross et al. 1992a).

Hippocampal efferents pass either through the precommissural fornix en route to the rostral telencephalon or via postcommissural fibers into the hypothalamus and thalamus where structures innervated by the "subiculothalamic tract" (Swanson et al. 1987), such as the superior colliculus and pontine tegmental nuclei, could be stimulated; these trajectories, however, do not seem to be substantial and may be only supplementary pathways of stimulation by endothelin. As there are no major projections from the lateral septal nuclei toward structures of the visual, vestibular, or oculomotor systems (Swanson et al. 1987), we dismiss the importance of septal efferents on the responses observed and deduce that the striatonigral efferents (Alexander and Crutcher 1990; Côte and Crutcher 1991; Goldberg et al. 1991), originating in the periventricular margin of the caudate nucleus (see Fig. 1D of Gross et al. 1992a), are the strongest source of neural inputs determining many of the metabolic responses evoked by intraventricular endothelin presented in this report (Fig. 4).

The periventricular caudate nucleus and its subsequent efferent radiations to a specific subregion of the substantia nigra pars reticulata (Fig. 3C), which projects to the superficial and optic strata of the superior colliculus (Fig. 2C), displayed intense metabolic activation from intraventricular endothelin (Gross et al. 1992a). These structures have been proven to act concertedly in regulation of rotational behavior (Pycock 1980) and of eye control during saccades, nystagmus, defensive responses, and seizure activity (Hikosaka and Wurtz 1983; Gale 1986; Hikosaka and Sakamoto 1986; Hoffmann 1986; Dean et al. 1989). The findings further emphasize the likely importance of the substantia nigra pars reticulata in transmitting the diffuse hypermetabolic activity associated with endothelin-induced convulsions (Gale 1986). These results are compatible with other studies defining the role of the substantia nigra pars reticulata; for example, other deoxyglucose studies have shown a similar degree of nigral involvement in the metabolic profile of various generalized seizures (Gale 1986). Gale (1986) has suggested that GABAergic mechanisms at the level of the substantia nigra pars reticulata are central to the neurochemistry of proconvulsant activity and has postulated that nigral outputs are important for sustaining and amplifying seizure activity.

Reciprocal connections within the circuitry of the visuovestibular and oculomotor systems are abundant and likely have a role in evoking or amplifying metabolic activation following stimulation by endothelin. For example, as we display in Fig. 4, there are intricate links between the striatum, substantia nigra pars reticulata, optic tectum, pontine tegmentum, vestibular nuclei, and cerebellar subregions to form a functional circuit that could affect the extraocular motoneurons (Blanks 1988; Buisseret-Delmas et al. 1990; Büttner-Ennever and Büttner 1988; Ghez 1991; Highstein and McCrae 1988; McCrae 1988). These structures and their projections have been implicated previously in the motor behavioral responses, such as circling or barrel-rolling, to central chemical stimulation (Pycock 1980; Childs and Gale 1984; Morency et al. 1987; Marrannes and Wauquier 1988; Wurpel et al. 1988; Balaban et al. 1989).

As many of these nuclei in the path of the striatonigral projections also bear binding sites for endothelin, the possibility thus exists that endothelin is an innate transmitter substance for this system, and the pathways impli-

cated by the receptor distributions (Kohzuki et al. 1991) and metabolic mapping reported here may be regulated intrinsically by endothelinergic nerves. Colocalization and integration of endothelin with other transmitter substances in these neural circuits, such as the catecholamines, GABA, acetylcholine, serotonin, enkephalins and other neuropeptides, glutamate, and aspartate (Pycock 1980; Childs and Gale 1984; Gale 1986; Balaban et al. 1989; Parnavelas et al. 1989; Côte and Crutcher 1991; Kevetter and Hoffman 1991), indicate the need for evaluating potential interactions between several chemical mediators of visuovestibular and oculomotor functions.

Metabolic stimulation mediated by calcium L-channels

The calcium L-channel antagonist nimodipine had no metabolic effect of its own, yet completely blocked the hypermetabolism induced by endothelin in 17 of the 22 stimulated structures and reduced the magnitude of activation in 3 other nuclei (Table 1). These findings indicate that nimodipine-sensitive, voltage-regulated calcium L-channels (Sher et al. 1991) are part of the mechanism of endothelin's metabolic effect on visuovestibular and oculomotor structures. This interpretation takes into account that the periventricular sites of initial metabolic stimulation by endothelin, such as the caudate nucleus or hippocampus, are the likely locations where nimodipine exerted its primary effect and blocked the transmission of stimulation to other efferent structures. This consideration also allows for the possibility of blockade at some point within the input path of activated structures if nimodipine were to diffuse from the ventricular spaces to deeper brain regions.

It is interesting that the neurochemical influences by endothelin bear similarity to the effects of glutamate excitation through the mechanism of metabotropic receptors and activation of G proteins (Ross et al. 1990; Young and Fagg 1990; Conn and Desai 1991). In some clinical strategies, effective blockade of this stimulation related to glutamate receptors results from employing glutamate-receptor and calcium-channel antagonists together (Choi 1990). This pharmacological approach may prove useful in further research relating endothelin to vestibular and oculomotor functions in health and disease.

In conclusion, the results of the present analysis show that endothelin has stimulatory properties on the metabolic rate of cell groups within the visual, vestibular, and oculomotor systems of conscious rats. The hypermetabolism caused by endothelin is mediated in part by nimodipine-sensitive calcium channels, probably within a neural network involving the striatum and substantia nigra pars reticulata as sources propagating the initial endothelin stimulus through the circuits of the interrelated visual, vestibular, and oculomotor structures. Since many of the nuclei activated by endothelin contain appreciable numbers of binding sites, and are not adjacent to the ventricular fluid, we speculate that the metabolic data of this study are evidence for endothelin acting as an intrinsic transmitter for the neural relays of visuovestibular and oculomotor functions.

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