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Beneficial Effects of Idebenone on Memory Impairment in Rats

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ABSTRACT

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Idebenone showed beneficial effects on memory impairments in the passive avoidance, radial maze, and T-maze tests in rats with cerebral ischemia, cerebral infarction, basal forebrain lesions, and treatment with an anticholinergic drug. The drug ameliorated neurological deficits following the onset of cerebrovascular lesions in stroke-prone rats. In the neurochemical study, idebenone normalized reduced levels of 5-hydroxy indole acetic acid (5-HIAA) and acetylcholine (ACh) in various regions of the brain and inhibited the decrease in adenosine triphosphate (ATP) and the increase in lactate that occurs after cerebral ischemia. Furthermore, the drug activates mitochondrial respiratory function and inhibits lipid peroxidation in brain tissue. From these results, it is suggested that idebenone primarily ameliorates the energy failures in damaged brain tissues, partially normalizes the altered neural transmission in the tissues, and improves memory disturbance in rats.

Key words: memory behavioral tests, anticholinergic drugs, acetylcholine dementia, stroke

INTRODUCTION

Cerebral hemodynamic changes caused by cerebrovascular lesions produce tissue ischemia that interferes with cerebral energy metabolism by inhibiting mitochondrial respiration. This energy failure disturbs brain functions such as memory, and may lead to serious medical and social problems. Therefore, it has been long desired to develop new drugs that will restore brain function by ameliorating cerebral energy failures.

In this report we speculate on the possible application of idebenone, which improves cerebral metabolism, to treat patients with senile dementia, especially of the vascular type.

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MATERIALS AND METHODS

Chemistry

Idebenone, 6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, is a newly synthesized benzoquinone derivative.

Animals

Various cerebral lesions were produced in male Wistar rats weighing 250–300 g as follows. Cerebral ischemia was induced by the method of Pulsinelli and Brierley [1979]; cerebral embolization (multi-infarction) was produced by injecting carbon microspheres (35 μm in diameter, 2,000 pieces) into the left internal carotid artery [Kogure et al., 1973]. Bilateral electrolytic lesions of the basal forebrain (BF) were affected by passing an anodal DC current (1 mA, 20 sec) through the uninsulated tip (0.8 mm) of an stereotaxically inserted electrode [Miyamoto et al.,1985]. The lesion coordinates were A 6.4, L 2.8, and H −1.8 [Pellegrino and Cushman, 1967]. In addition, stroke-prone spontaneously hypertensive rats (SHRSP) were used for evaluation of the effect of idebenone on neurologic deficits.

Passive-Avoidance Response

Rats with cerebral ischemia, cerebral embolization, or basal forebrain lesions were subjected to avoidance tasks using a step-through passive avoidance apparatus. Cerebral ischemia was induced by bilateral occlusion of the vertebral and carotid arteries for 200 sec, immediately after the acquisition trial of the passive avoidance response. The retention test was performed 24 hr after the acquisition trial [Yamazaki et al., 1984]. Rats with cerebral embolization were subjected to the acquisition trial seven days after the operation, and the retention test 24 hr after the acquisition trial [Kiyota et al., 1985]. Rats with basal forebrain lesions were subjected to the acquisition trial ten days after the lesioning, and the first retention test was carried out 24 hr after the acquisition trial; this was followed by three further retention tests at 48-hr intervals.

Radial-Maze Task

Rats with cerebral embolization were placed in the center of a radial eight-arm maze positioned 33 cm above the floor. In each test, a food pellet (45 mg) was placed in a cup located at the end of five of eight arms. Each rat was given one trial per day for 36 days, and the trials were divided into 12 "blocks." Two indices were used: "correct response," the number of times a rat chose an arm with a pellet of its initial five choices; and "total errors," the number of errors made until the rat found all five food pellets.

Delayed-Alternation Task

Rats were initially forced to go into one arm of a T-maze; this was followed by a free-choice run into either arm of the maze after the delay of 60 sec. A "correct response" was defined as a turn into the opposite arm to that in the prior forced run; "correct responses" were rewarded with food pellets [Yamazaki et al., 1985].

Neurological Deficits in SHRSP With Cerebrovascular Lesions (CVL)

Stroke-prone spontaneously hypertensive rats (ten weeks old) were given 1% NaCl solution as drinking water to advance the onset of CVL [Nagaoka et al., 1976; 1980]. After the occurrence of a stroke, the salt solution was exchanged for tapwater. The neurological deficits (i.e., a decrease in spontaneous locomotor activity, an increase in irritability, and paralysis of the hind limbs, etc.) in individual rats were scored on a five-point scale from normal to severe disturbance each day for 21 days [Nagaoka et al., 1984].

Neurochemical Analysis

Norepinephrine (NE), dopamine (DA), serotonin (5-HT), and their metabolites (MHPG, DOPAC, HVA, and 5-HIAA) were determined in the brains of rats subjected to cerebral ischemia for 200 sec by high-performance liquid chromatography using an electrochemical detector [Narumi et al., 1985]; acetylcholine (ACh) and choline were determined by pyrolysis gas chromatography [Kakihana et al., 1984]. Lactate, pyruvate, and ATP in the brains of SHRSP rats subjected to bilateral carotid artery occlusion were determined by a standard enzymatic method [Lowry et al., 1964, Folbergrova et al., 1972; Nagaoka et al., 1984]. The glucose utilization rate was determined using 2-deoxy-[^{14}C]glucose in rats with basal forebrain lesions [Nagai et al., 1985] and SHRSP with CVL [17]. The distribution of idebenone in the brain was investigated by autoradiography using ^{14}C-idebenone. The distribution of unchanged ^{14}C-idebenone in various brain regions was determined by separating from the metabolites using thin-layer chromatography [Nagai et al., 1986].

RESULTS AND DISCUSSION

Effects of Idebenone on Memory Impairment Models

The anti-amnesic effects of idebenone on the performance of five different kinds of memory tasks were assessed. The tasks consisted of three kinds of passive avoidance response, a radial maze task, and a delayed alternation task. Amnesia models induced by experimental cerebral ischemia and cerebral embolism were used, as these are typical animal models of memory deficits caused by stroke. The transient cerebral ischemia for 200 sec or more caused significant memory impairment in rats [Narumi et al., 1985]. Thus, ischemia of 200-sec duration was adopted in this experiment. Administration of idebenone at 10 and 30 mg/kg i.p. or p.o., 24 hr after the ischemic insult and 30 min before the retention test, significantly restored the median latency (Fig. 1). Thus, idebenone seems to improve the retention process of memory.

Cerebral embolization is considered to be a prototypical model of vascular-type dementia caused by multiple cerebral infarction. Long-term administration of idebenone at 30 mg/kg i.p. to rats with cerebral embolization significantly and dose-dependently prolonged the mean latency (Fig. 2). Improvements were also observed after administration of the choline esterase inhibitor physostigmine (0.5 mg/kg i.p.), immediately after the acquisition test and 30 min before the retention test.

In patients with Alzheimer's dementia the nucleus basalis of Meynert projects cholinergic neurons to cortical areas degenerates [Divac 1975; Whitehouse et al., 1982]; this suggests an important role for the cholinergic system in the learning and memory [LoConte et al., 1982; Flicker et al., 1983]. Rats with lesions in the basal forebrain (BF), which corresponds to the nucleus basalis of Meynert in humans, also show a marked impairment of memory [Miyamoto et al., 1985]. In the animals with BF lesions, long-term administration of idebenone (3–10 mg/kg i.p.) improved the performance of a memory task (Fig. 3).

In addition to the passive-avoidance test, the effect of idebenone on spacial memory using an eight-arm radial-maze task was assessed in rats with cerebral infarction. The numbers of correct responses made by rats in the sham-operated, the untreated embolization, and the idebenone-treated embolization groups are shown in the upper part of Figure 4, and the total number of errors are shown in the lower part of Figure 4. The number of correct responses made by the sham-operated controls increased with time. The rats in the embolization group made significantly fewer correct responses than the controls from the 8th to the 12th blocks. However, the rats in the idebenone-treated (30 mg/kg p.o.) embolization group showed a response pattern similar to that of the controls, and made significantly more correct responses in the 9th, 11th, and 12th blocks than the rats in the untreated embolization group. The improvement in performance of the maze task effected by idebenone is more clearly shown by

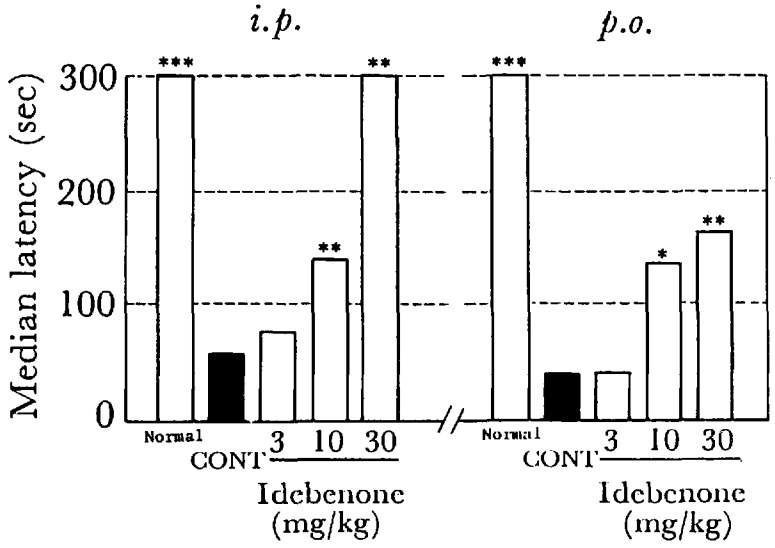

Fig. 1. Effect of idebenone administered intraperitoneally (i.p.) or orally (p.o.) on the retention of passive avoidance response in rats. Cerebral ischemia of 200-sec duration was induced immediately after the acquisition trial. The test trial was performed 24 hr after induction of ischemia. The drug was given 30 min before the test trial. The number of rats used was 9–28. Normal = control animals not subjected to cerebral ischemia; CONT = animals subjected to cerebral ischemia and given saline. $*P<0.05$; $**P<0.01$; $***P<0.002$ (U-test) vs. CONT.

comparison of the number of total errors. The number of errors gradually decreased in the sham-operated control group, but not in the untreated embolization group. In the group treated with idebenone, the number of errors was markedly lower than in the untreated embolization group from the 8th to the 12th block.

Additionally, the effect of idebenone on short-term memory was evaluated by the delayed alternation task using a T-maze. When the time interval between the forced run and free-choice run was set at 60 sec, scopolamine (0.2 mg/kg i.p.) administered 20 min before the test produced memory impairment. Idebenone (3, 10, or 30 mg/kg i.p.) administered simultaneously with scopolamine ameliorated the impairment in the performance of the task, with the highest efficacy being observed at 10 mg/kg (Fig. 5).

Effects of Idebenone on Neurological Deficits in SHRSP with CVL

Changes in spontaneity (i.e., a decrease in spontaneous locomotor activity) and emotional disturbances (i.e., hyperirritability, excitement, and no response to external stimulus) are usually observed in SHRSP with CVL. The effects of idebenone (30 and 100 mg/kg/day p.o.) on the neurologic deficits and decrease in food intake were assessed for 21 days after occurrence of a stroke. As shown in Figure 6, the higher dose of idebenone ameliorated the poststroke symptoms.

Neurochemical Studies

The effects of idebenone on neurochemical changes in neurotransmitters and energy metabolism, and on the distribution of idebenone in the brain were investigated to elucidate the neurochemical mechanisms underlying the beneficial effects of idebenone on memory and neurological deficits.

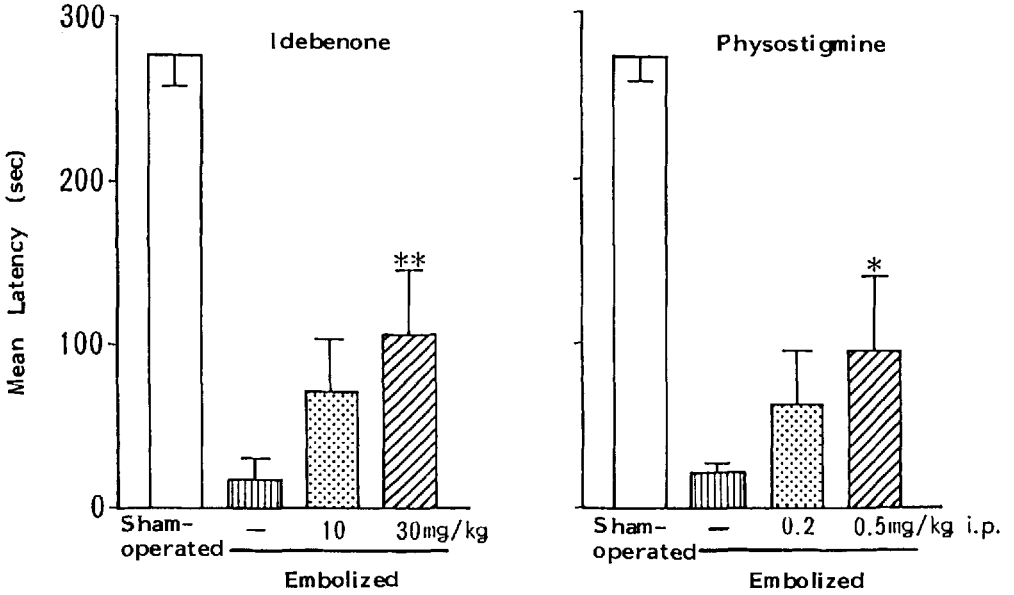

Fig. 2. Effects of idebenone and physostigmine on impairment of the passive avoidance response in rats with cerebral embolization. Idebenone (10 or 30 mg/kg i.p.) was given once a day from the day of operation to the retention test day. Physostigmine (0.2 or 0.5 mg/kg i.p.) was given immediately after the acquisition trial and again 30 min before to the retention test. The acquisition trial was done 7 days after the operation. The retention test was performed 24 hr after the acquisition trial. Each value is the mean ± S.E. (sec). $*P<0.05$; $**P<0.01$, compared with vehicle-treated control.

The physiological mechanisms responsible for learning and memory remain almost unknown. However, as considerable experimental evidence has indicated failure of the cholinergic system in senile dementia of the Alzheimer type [Divac 1975; Whitehouse et al., 1982], we first investigated the effects of idebenone on ACh and choline contents in rats subjected to cerebral ischemia for 200 sec [Narumi et al., 1985]. Idebenone (10 mg/kg i.p.) reversed the reduction in ACh levels in the cerebral cortex, hippocampus, and diencephalon.

The levels of 5-HT [Palmer et al., 1987] and other monoamines are lower in the brains of patients with senile dementia [Winblad et al., 1981]; 5-HT is the most sensitive amine to hypoxia caused by ischemia [Take et al., 1984]. After 200 sec of cerebral ischemia, 5-HT and its main metabolite, 5-HIAA, were markedly reduced in comparison with controls. It was found that idebenone (10 mg/kg i.p.) significantly normalized 5-HIAA levels in the cerebral cortex, hippocampus, diencephalon, and brain stem without changing the monoamine contents [Narumi et al., 1985].

Cerebral ischemia also inhibits respiration in the mitochondria, resulting in decrease in high-energy phosphate metabolites [Naruse et al., 1983] and an increase in the production of lactate [Paschen et al., 1987]. The accumulation of lactate induces tissue acidosis and this ultimately leads to cell damage [Kalimo et al., 1981]. It has been reported that when idebenone (100 mg/kg) was administered orally to SHRSP rats with cerebral ischemia, the reduction of ATP and the production of lactate were suppressed in the cerebral cortex [Nagaoka et al., 1984]. These results indicate that idebenone improves anaerobic metabolism and so protects the injured brain.

Effects of Idebenone on Glucose Utilization

The brain usually uses glucose as an energy substrate. As glucose storage in the brain is limited, it must be constantly supplied by the blood. Sokoloff et al. [Sokoloff et al., 1977]

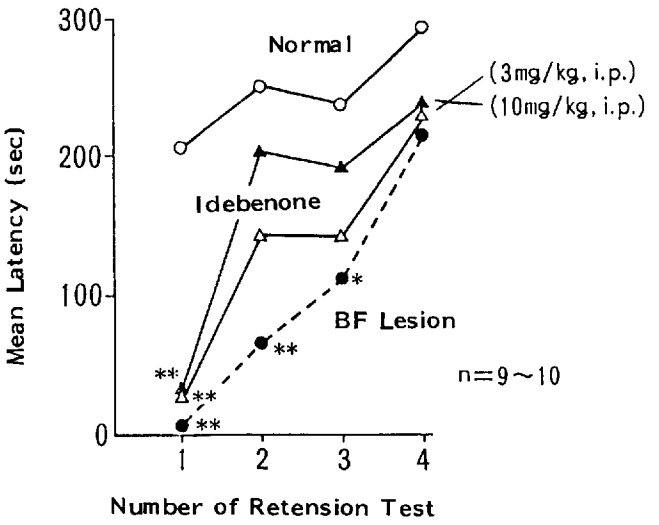

Fig. 3. Effects of idebenone on impairment of passive avoidance response in rats with basal forebrain (BF) lesions. The acquisition trial was performed 10 days after the operation. The first retention test (R1) was carried out 24 hr after the acquisition trial, followed by three further retention tests at 48-hr intervals. Idebenone was given once daily from 7 days after operation to the final retention test day. Idebenone was administered 30 min before the trial. $^{*}P<0.05$; $^{**}P<0.01$, compared with sham-operated control.

developed a technique to determine the rate of local cerebral glucose utilization (LCGU) using 2-deoxy-[^{14}C]glucose. 2-Deoxyglucose, a glucose derivative, is trapped in the tissues after phosphorylation by hexokinase, because its chemical structure prevents further metabolism. The coupling between energy consumption and local neuronal activity makes it possible to estimate the possible sites of action of idebenone in the brain. In rats with BF lesions and SHRSP with CVL, idebenone (10 or 30 mg/kg i.p.) given for three days reversed the reduction of glucose utilization in various regions of the brain. Table 1 summarizes the LCGU in SHRSP with CVL. Idebenone restored LCGU markedly in the temporal cortex, thalamus dorsomedial nucleus, subthalamic nucleus, mamillary body, hippocampus dentate gyrus, caudate-putamen, inferior colliculus, and cerebellar nucleus.

Distribution of Idebenone in the Brain

Five minutes after intravenous administration of [^{14}C]-idebenone (10 mg/kg), the distribution into the brain was 0.45–0.56% of the dose given. Autoradiography showed that ^{14}C-levels were higher in the white matter than in the gray matter, in which marked regional differences in the distribution were not observed. The analysis of unchanged idebenone and its metabolites after intraperitoneal administration of 30 mg/kg-idebenone [^{14}C] revealed that SHRSP had higher levels in the plasma and brain than normal rats. We reported previously that unchanged idebenone was relatively high in the cerebral cortex, thalamus, and cerebellum than in the other regions of the brain [Nagai et al., 1986].

SUMMARY AND CONCLUSIONS

Idebenone ameliorated impairments in the passive-avoidance response induced by cerebral ischemia, cerebral multiple infarction, or basal forebrain lesions in rats, memory disturbance (i.e., radial-maze performance) in rats with cerebral multiple infarction, and

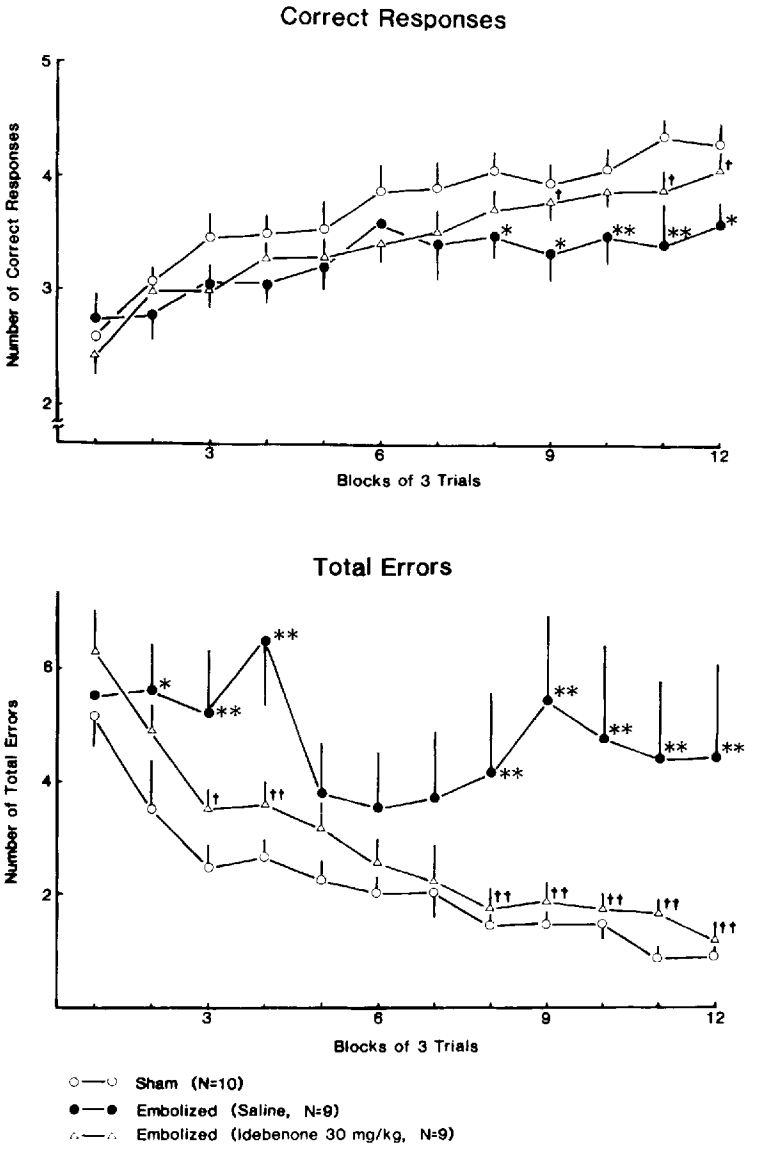

Fig. 4. Effects of idebenone on impairment of radial-maze learning in rats with cerebral embolization. In each test, a food pellet was placed in cups located at the end of five out of eight arms. Correct response: the number of times that each rat chose an arm with a pellet out of its initial five choices. Total errors: the number of errors made until the rat got all five food pellets. $^{*}P<0.05$; $^{**}P<0.01$ vs. sham-operated group. $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.01$ vs. embolized control group.

impairment of short-term memory (T-maze) induced by an anticholinergic drug. Additionally, idebenone ameliorated neurological deficits following the onset of cerebrovascular lesions in SHRSP. These results suggest that idebenone can be used as a new therapeutic drug for senile dementia, especially of the vascular type. In the neurochemical studies, idebenone was found

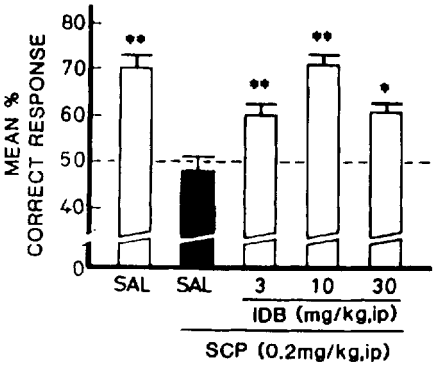

Fig. 5. Effect of idebenone (IDB) on the 60 sec-delayed alternation task in rats treated with scopolamine (SCP). IDB was given concomitantly with SCP (n = 15). *$P<0.05$; **$P<0.01$ Newman-Keuls test vs. SCP-treated group.

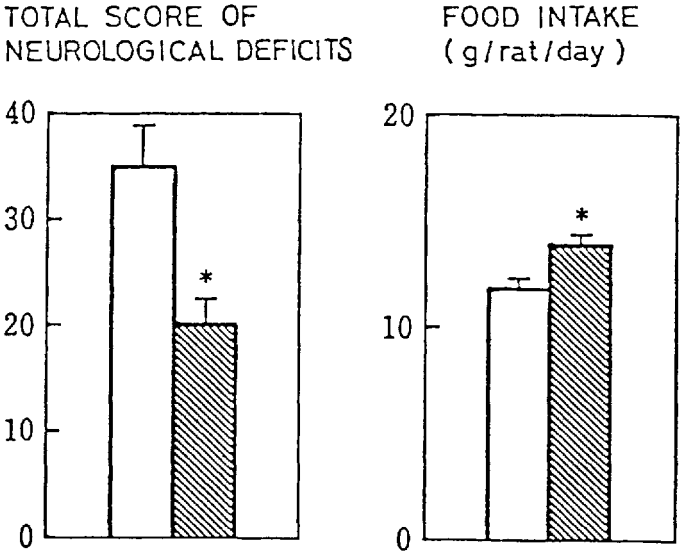

Fig. 6. Effects of idebenone (100 mg/kg/day p.o. for 3 weeks) on neurological deficits and food intake in SHRSP with CVL. Means ± SE. Plain column, control; hatched column, idebenone-treated group. *$P<0.05$ vs. control. n = 13–14.

to normalize the reduced levels of 5-HIAA and ACh in various regions of the brain, and to inhibit the decrease in ATP and production of lactate after cerebral ischemia. These results indicate that idebenone primarily ameliorates the energy failures in damaged brain tissues and so results in the partial normalization of neural transmission. It has also been reported that idebenone activates mitochondrial respiratory function by working as an electron carrier in the mitochondria [Sugiyama et al., 1985a, 1985b], and inhibits lipid peroxidation induced by radicals [Suno and Nagaoka, 1984a, 1984, 1985]. Therefore, the stimulation of respiratory activity in the mitochondria of brain tissue is considered to be responsible for the action of idebenone on cerebral metabolism.

TABLE 1. Effect of Idebenone on Local Cerebral Glucose Utilization in SHRSP With CVL†

Structure	WKY	SHRSP		
		Vehicle (μmol/100 g/min)	Idebenone	Recovery (%)
Visual cortex	70.2 (11.2)	21.8 (5.1)**	33.5 (3.4)#	54
Auditory cortex	94.8 (8.8)	26.9 (9.3)**	51.6 (7.7)#	92
Parietal cortex	71.1 (14.0)	27.6 (8.1)*	38.7 (8.7)	40
Sensory-motor cortex	65.7 (11.0)	29.6 (8.1)*	41.2 (0.9)	39
Olfactory cortex	75.3 (12.4)	29.5 (7.8)*	44.1 (9.8)	49
Frontal cortex	67.2 (8.2)	34.4 (10.2)*	41.1 (6.7)	19
Thalamus				
Lateral nucleus	68.2 (9.2)	25.8 (7.6)**	38.2 (6.4)	48
Ventral nucleus	59.1 (12.6)	19.3 (6.5)*	33.6 (6.5)#	74
Dorsomedial nucleus	75.8 (7.3)	33.6 (9.8)*	66.6 (7.3)‡	98
Habenula	83.1 (15.1)	32.5 (9.4)*	67.0 (11.8)#	106
Subthalamic nucleus	52.2 (11.6)	19.6 (6.6)*	38.2 (4.1)‡	95
Medial geniculate body	77.5 (17.2)	25.9 (9.5)*	45.5 (3.9)#	76
Lateral geniculate body	61.4 (5.4)	27.9 (3.1)**	36.3 (3.7)	30
Hypothalamus	39.3 (4.6)	20.1 (2.5)*	24.9 (0.9)	24
Mamillary body	79.2 (16.0)	35.7 (13.1)	60.1 (3.5)#	68
Hippocampus				
Ammon's horn	52.6 (6.3)	24.8 (4.9)**	33.6 (1.0)	35
Dentate gyrus	52.3 (9.0)	14.4 (5.4)**	24.5 (5.0)#	70
Amygdala	37.0 (3.9)	12.4 (4.8)**	18.9 (1.3)	52
Septal nucleus	39.2 (4.1)	11.3 (5.8)**	21.2 (4.6)‡	87
Caudate-putamen	68.0 (4.2)	27.4 (6.2)***	50.8 (3.1)‡	85
Nucleus accumbens	66.1 (5.0)	27.5 (7.8)**	41.8 (3.1)	52
Globus pallidus	28.6 (3.5)	6.0 (3.5)**	9.2 (5.3)	53
Substantia nigra	44.2 (4.6)	21.2 (2.9)**	28.4 (2.2)#	35
Raphe nucleus	62.6 (5.6)	28.5 (9.8)*	39.7 (3.4)	39
Locus caeruleus	60.6 (9.3)	27.3 (9.4)*	40.4 (2.1)	48
Vestibular nucleus	87.9 (9.5)	41.5 (11.9)*	55.6 (1.7)	34
Cochlear nucleus	94.0 (13.9)	50.4 (11.7)*	67.3 (4.6)	34
Superior olivary nucleus	102.3 (9.9)	53.6 (15.1)*	80.4 (6.0)	50
Lateral lemniscus	78.2 (8.1)	36.5 (8.8)*	55.5 (1.7)#	52
Inferior colliculus	147.7 (21.5)	76.3 (6.7)*	95.0 (3.4)‡	25
Superior colliculus	58.0 (4.8)	26.3 (9.0)*	43.3 (4.5)#	65
Pontine gray matter	38.9 (3.1)	15.4 (5.9)*	21.5 (5.7)	40
Cerebellar cortex	28.6 (1.2)	15.5 (5.8)**	20.8 (6.4)	34
Cerebellar nucleus	57.3 (11.4)	32.4 (6.9)	50.8 (1.7)‡	57
Internal capsule	28.0 (3.0)	21.4 (4.5)	27.5 (5.0)	29

†All values are the mean and S.E.M. of the results for four rats. Idebenone (30 mg/kg i.p.) or the vehicle was administered once a day for 3 days to SHRSP 3 weeks after the occurrence of stroke. WKY, control Wistar-Kyoto rats.

*$P<0.05$, **$P<0.01$., ***$P<0.001$ vs. WKY.

‡$P<0.05$, #$P<0.10$ or recovery more than 60% vs. vehicle.

The possible sites of action for the main pharmacological effects of idebenone were estimated from the determination of LCGU and the distribution of idebenone in the brain. Idebenone ameliorated the emotional disturbances such as aggressive behavior and abnormal irritability that follow the occurrence of a stroke in SHRSP. The hypothalamus and the limbic system such as the hippocampal formation, septal nucleus, amygdala, prefrontal cortex, and

TABLE 2. Possible Sites of Action for the Main Pharmacological Effects of Idebenone Judged From Its Distribution in the Brain and Its Effect on Local Cerebral Glucose Utilization (LCGU)

Pharmacological action		Idebenone	
		Distribution[d]	LCGU*
Amelioration of neurological deficits after stroke			
Abnormal emotionality[a]	Mamillary body	+	+
	Hippocampus dentate gyrus	+	+
	Septal nucleus	+ +	+
	Amygdala	+ +	±
	Thalamus dorsomedial nucleus	+ +	+ +
	Frontal cortex	+ +	±
Motor dysfunction[b]	Subthalamic nucleus	+ +	+ +
	Caudate-putamen	+	+ +
	Globus pallidus	+	±
	Cerebellar nucleus	+ +	+ +
	Sensory-motor cortex	+	±
	Nucleus accumbens	+ +	±
	Substantia nigra	+	±
	Habenula	+ +	+
Amelioration of memory impairments[c]	Temporal cortex	+ +	+
	Hippocampus dentate gyrus	+	+
	Septal nucleus	+ +	+
	Thalamus dorsomedial nucleus	+ +	+ +
	Mamillary body	+	+
	Amygdala	+ +	±

[a]Ameliorating action of idebenone on abnormal emotionality such as depression of spontaneous motor activity, aggressive behavior, and abnormal irritability following the occurrence of stroke in SHRSP.
[b]Ameliorating action of idebenone on motor dysfunction such as akinesia and paralysis of legs in SHRSP with CVL.
[c]Beneficial effects on memory impairments in animal models produced by cerebral embolization, cerebral ischemia, or basal forebrain lesions.
[d]+ +, high (over 0.40 μg/g); +, relatively high (0.28–0.40 μg/g).
*+ +, Significant recovery ($P<0.05$), +; tendency to recovery ($P<0.10$) or recovery more than 60%; ±, slight recovery (15–59%). The structures underlined are main possible action sites of idebenone in the brain.

cingurate gyrus have been implicated in the control of emotion. Among these regions, the hippocampus dentate gyrus, septal nucleus, mamillary body, and thalamus dorsomedial nucleus which project from the limbic system may be the important areas for the action of idebenone. Idebenone also ameliorated motor dysfunction such as akinesia, paralysis of the legs, and depression of spontaneous motor activity in SHRSP. These actions may be related to the restoration of LCGU in regions such as the subthalamic nucleus, caudate-putamen, habenula, and cerebellar nucleus. Most of these regions are part of the extrapyramidal system, which controls the essential postural adjustments for the activity of the limbs and maintains proper muscle tone. Recent neurochemical studies of Alzheimer's type dementia have revealed abnormalities in cholinergic [Rossor et al., 1982; Henke and Lang, 1983] and monoaminergic transmission [Palmer et al., 1987], and reductions in glutamate receptor binding [Greenamyre et al., 1987] and glucose metabolism [Farkas et al., 1982] in addition to neuropathological changes [Bowen and Davidson, 1986] in the cerebral cortex and hippocampus. Thus, the restoration of LCGU affected by idebenone in the temporal cortex and hippocampus dentate

gyrus may be responsible for its beneficial effects on memory deficits. The thalamus dorsomedial nucleus and mamillary body have been reported to play an important role in perceptual and cognitive abilities, and hemorrhagic or necrotic lesions of these regions induce disturbances in learning and memory. One such disturbance is known as Korsakoff's syndrome, which results from the toxic effects of alcohol or from vitamin B deficiency [Mair and McEntee, 1983]. The marked amelioration of the reduction of LCGU in the thalamus dorsomedial nucleus and mamillary body in SHRSP, suggests the importance of these regions in the action of idebenone in memory improvement. The possible sites of action of idebenone in the brain are summarized in Table 2.

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