Effects of BMY-21502 on Anoxia in Mice

Manabu Amano[1,2] Arata Goto[2], Norimitsu Takahashi[2], Takaaki Hasegawa[1] and Toshitaka Nabeshima[1]

[1]*Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan*

[2]*Pharmacology Laboratory, Preclinical Research Laboratories, Bristol-Myers Squibb K.K., 1 Futagoyama, Sakazaki, Hohta-cho, Nukata-gun, Aichi 444-01, Japan*

Received October 26, 1992 Accepted November 27, 1992

ABSTRACT—The protective effects of BMY-21502 (1-[[1-[2-(trifluoromethyl)-4-pyrimidinyl]-4-piperidinyl]methyl]-2-pyrrolidinone) against cerebral anoxia were investigated using various models in mice, in comparison with those of other cerebroactive drugs. Oral administration of BMY-21502 (10-100 mg/kg) significantly prolonged the survival time in KCN (2.4 mg/kg, i.v.)-induced anoxia. Oxiracetam and idebenone exerted similar but weak protection at doses above 100 mg/kg, p.o. and only at a dose of 100 mg/kg, p.o., respectively. Significant protection by BMY-21502 against moderate hypobaric hypoxia was observed at doses of 30 and 100 mg/kg, p.o. Idebenone (100 and 300 mg/kg, p.o.) significantly prolonged the survival time of mice in this model, but oxiracetam (30-300 mg/kg, p.o.) did not. Oral administration of all of these drugs (BMY-21502, 3-300 mg/kg; Oxiracetam, 100-1000 mg/kg; Idebenone, 100-1000 mg/kg) failed to increase the number of gasps and the duration of gasping in the decapitated head of mice as a complete ischemic model. The anti-anoxic effect of BMY-21502 in the KCN-anoxia model was blocked by pretreatment with scopolamine. These findings suggest that BMY-21502 has an anti-anoxic action superior to those of the other cerebroactive drugs used, and activation of the CNS cholinergic system is involved as one of the causative mechanisms for the anti-anoxic effect of BMY-21502.

Keywords: Anti-anoxic effect, BMY-21502, Oxiracetam, Idebenone

It is well-known that a decrease in the oxygen supply to the brain (hypoxia) depresses neuronal activities and cerebral function in experimental animals and humans (1, 2). Agents with anti-anoxic activities would be useful for treating anoxic and ischemic states of the brain, such as those found in cerebrovascular diseases, head injury and other organic brain syndromes (2). A number of cerebral ischemic models of mice have been developed for screening anti-anoxic drugs, including the following: ligation of bilateral carotid arteries (3), inhalation of hypobaric hypoxic air (1, 4) or normobaric hypoxic air (1, 4-9) and intravenous injection of KCN (1, 4, 9). These models are widely used in preclinical evaluations of drugs for the treatment of cerebrovascular disorders, for example, cerebral vasodilators (10, 11), cerebroactive drugs (10, 12), central nervous system depressants (13-15), anti-convulsants (16, 17) and acetylcholine (ACh) esterase inhibitors (18, 19). Furthermore, it has been reported that the AChergic system is vulnerable to cerebral anoxia (20, 21). Physostigmine, a choline esterase inhibitor, has a significant anti-anoxic effect (9, 18, 19). Imipramine, which has anti-cholinergic activity, and atropine, which is an anti-ACh drug, reduce the survival time of mice in a cerebral anoxia model (9). From these findings, it is suggested that cholinergic neuronal pathways may play an important role in producing anti-anoxic activity.

The novel pyrrolidinone derivative BMY-21502 (1-[[1-[2-(trifluoromethyl)-4-pyrimidinyl]-4-piperidinyl]methyl]-2-pyrrolidinone) (Fig. 1), synthesized by Bristol-Myers

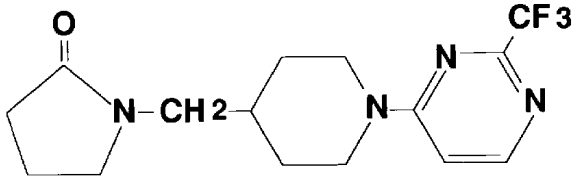

Fig. 1. Chemical structure of BMY-21502 (1-[[1-[2-(trifluoromethyl)-4-pyrimidinyl]-4-piperidinyl]methyl]-2-pyrrolidinone).

Squibb K.K., was expected to have anti-amnesic effect from the results of animal experiments and clinical utility for treating disorders characterized by learning and memory impairment. BMY-21502 is not bound to cholinergic receptor sites in the brain, nor does it alter high affinity choline uptake (22). It protects against memory disruption induced by the amnesic agent scopolamine and electroconvulsive shock, and it enhances acquisition and retention of information in both normal and nucleus-basalis-destroyed animals (22–24). In in vitro experiments, however, it does increase the firing rate of presumed cholinergic cells in the basal forebrain (22). From these results, BMY-21502 may augument the activity of cholinergic neurons in the brain secondarily, and we thought that it might have a possible protective effect against cerebrovascular disturbance. In the present study, we examined the cerebral protective effect of BMY-21502 in various anoxia models in comparison with those of oxiracetam, whose chemical structure is similar to that of BMY-21502, and idebenone, which is currently being used in the therapy of patients with cerebral vascular diseases.

MATERIALS AND METHODS

Animals

Male ddY mice (6-week-old) were purchased from Japan SLC, Inc. (Hamamatsu). The animals were housed in a room controlled at 23±0.5℃ and 60±0.5% relative humidity on a 12-hr light-dark cycle (9:00–21:00). The mice were housed in a group of 5 or 6 per cage and were given food and water ad libitum. They were used in experiments following adaptation to laboratory conditions for at least 7 days.

Drugs

The chemical structure of BMY-21502 (Bristol-Myers Squibb K.K., Tokyo) is shown in Fig. 1. Oxiracetam (synthesized and supplied by Daiichi Pharmaceutical Co., Ltd., Tokyo) and idebenone (Takeda Co., Osaka) were used as reference drugs. BMY-21502 and oxiracetam were suspended in 0.5% sodium carboxymethyl cellulose solution, and idebenone was suspended in 5% gum arabic solution. Each mouse was orally given (0.1 ml/10 g) 0.5% sodium carboxymethyl cellulose, 5% gum arabic or a test drug solution 20 min before each test. Scopolamine hydrobromide (Katayama Chemicals, Osaka) was dissolved in saline and administered intraperitoneally (0.1 ml/10 g) 30 min before KCN injection.

KCN-induced anoxia

This anoxia was produced by i.v. injection of KCN (2.4 mg/kg) at the speed of 0.1 ml/10 sec. Survival time was defined as the time interval between the completion of KCN injection and the cessation of respiratory movements.

Hypobaric hypoxia (Experiment 1)

Mice were put into a chamber (4-l desiccator), and the inside pressure of this chamber was lowered to 190 mmHg in approximately 20 sec with a vacuum pump. Two mice were tested at the same time. Survival time was defined as the time interval between the start of hypoxia and the cessation of respiratory movements.

Hypobaric hypoxia (Experiment 2)

Mice were put into a chamber (4-l desiccator), and the inside pressure of this chamber was lowered to 190 mmHg in approximately 30 sec with a vacuum pump. The mice were tested one at a time. Survival time was defined as the time interval between the start of hypoxia and the cessation of respiratory movements.

Complete ischemia by decapitation

Cerebral ischemia was produced by decapitation according to the method described by Holowach-Thurston et al. (25). The time between decapitation and the last gasp, gasping duration, and the number of gasps were recorded.

Statistical analysis

The results are expressed as the mean±S.E. Following the *F*-test, statistical analyses were performed by Student's *t*-test or the Cochran-Cox test, and differences were considered significant when $P<0.05$ (two-tailed).

RESULTS

Effect on KCN-induced anoxia in mice

The protective effects of BMY-21502 and reference drugs against KCN-induced anoxia are shown in Table 1. When surviving animals were found, we eliminated the data from these animals when determining the survival time. The average survival time of the vehicle-treated mice was around 23 sec. BMY-21502 (10–100 mg/kg) significantly increased the survival time in a dose-dependent manner. After administration of oxiracetam, there was also a significant prolongation of the survival time at the doses of 100 and 300 mg/kg. Although idebenone at 100 mg/kg significantly increased the survival time of anoxic mice, 300 mg/kg only tended to increase the survival time, the difference not being statistically significant. All of these drugs failed to increase the number of survivors.

Effect on hypobaric hypoxia in mice (Experiment 1)

The data are summarized in Table 2. The average sur-

Table 1. Effects of drugs on KCN-induced anoxia in mice

Treatment	Dose (mg/kg, p.o.)	Survival time (sec)	% Change	No. of survivors /used
Control (CMC)		22.34±1.55		0/10
BMY-21502	3	24.94±1.79	11.6	0/10
	10	27.24±1.71*	21.9	1/10
	30	31.85±3.15*	42.6	0/10
	100	34.47±1.98***	54.3	1/10
Control (CMC)		23.29±1.40		0/ 9
Oxiracetam	30	24.66±1.18	5.9	0/ 9
	100	28.66±1.26*	23.1	0/10
	300	33.97±1.48***	45.9	0/10
Control (gum Arabic)		24.13±0.83		0/19
Idebenone	30	24.53±1.49	1.5	0/10
	100	29.82±1.45**	23.6	0/10
	300	27.83±1.42	15.3	1/13

Each value represents the mean±S.E. *$P<0.05$, **$P<0.01$, ***$P<0.001$, compared with the control value. Mice were given KCN (2.4 mg/kg, i.v.) 20 min after test drug administration. % Change = {(Drug treated value − Control value)/ Control value} × 100

Table 2. Effects of drugs on hypobaric hypoxia in mice (Experiment 1)

Treatment	Dose (mg/kg, p.o.)	Survival time (sec)	% Change	No. of animals used
Control (CMC)		125.60±15.86		10
BMY-21502	3	139.26±11.36	10.9	10
	10	143.79±16.11	14.5	11
	30	155.23± 8.81	23.6	11
	100	130.58±17.13	4.0	10
Control (CMC)		115.46± 8.30		20
Oxiracetam	30	106.59± 7.26	−7.7	21
	100	120.09± 9.39	4.0	22
	300	115.80±10.05	0.3	21
Control (gum Arabic)		114.37± 7.29		19
Idebenone	30	109.72± 6.82	−4.1	20
	100	99.85± 6.26	−12.7	18
	300	113.47± 7.46	−0.8	20

Each value represents the mean±S.E. Drugs were administered 20 min before the hypoxic condition (190 mmHg at 20 sec). % Change = {(Drug treated value − Control value)/Control value} × 100

vival times of the vehicle-treated groups were 114−126 sec. BMY-21502 (3−100 mg/kg), oxiracetam (30−300 mg/kg) and idebenone (30−300 mg/kg) failed to increase the survival time significantly. However, BMY-21502 (3−30 mg/kg) showed a tendency to increase the survival time in a dose-dependent manner. These results suggested that these experimental conditions were too severe, so accordingly, additional experiments were carried out using milder conditions.

Effect on hypobaric hypoxia in mice (Experiment 2)

The results obtained are presented in Table 3. Under this condition, the average survival time of the vahicle-treated mice was about 130 sec. BMY-21502 and idebenone increased the survival time of hypoxic mice in a dose-dependent manner. The minimum effective doses

Table 3. Effects of drugs on hypobaric hypoxia in mice (Experiment 2)

Treatment	Dose (mg/kg, p.o.)	Survival time (sec)	% Change	No. of animals used
Control (CMC)		128.74± 8.00		10
BMY-21502	3	143.91±16.94	11.8	11
	10	150.26± 9.66	16.7	11
	30	205.52±29.33*	59.6	11
	100	212.86±32.92*	65.3	11
Control (CMC)		131.66±14.20		13
Oxiracetam	30	156.27±23.83	18.7	13
	100	178.93±20.31	35.9	13
	300	172.34±19.72	30.9	13
Control (gum Arabic)		119.09± 9.49		10
Idebenone	30	162.79±26.49	36.7	10
	100	183.50±17.02**	54.1	11
	300	239.57±32.43**	101.2	11

Each value represents the mean±S.E. *$P<0.05$, **$P<0.01$, compared with the control value. Drugs were administered 20 min before the hypoxic condition (190 mmHg at 30 sec). % Change = {(Drug treated value − Control value)/Control value} × 100

Table 4. Effects of drugs on decapitation-induced gasping in mice

Treatment	Dose (mg/kg, p.o.)	No. of animals used	No. of gasps	% Change	Duration of gasping (sec)	% Change
Control (CMC)		10	6.1±0.9		15.74±0.77	
BMY-21502	3	10	5.6±1.3	−8.2	15.34±0.96	−2.5
	10	10	7.0±0.6	14.8	14.78±0.66	−8.6
	30	11	5.9±0.9	−3.3	15.74±0.44	0.0
	100	10	6.5±0.9	6.6	16.07±0.45	2.1
	300	10	6.4±1.3	4.9	16.34±1.32	3.8
Control (CMC)		11	6.7±0.6		15.79±0.43	
Oxiracetam	100	10	6.4±1.2	−4.5	15.88±0.43	0.6
	300	11	5.9±0.8	−11.9	16.89±0.33	7.0
	1000	11	7.0±0.9	4.5	16.16±0.41	2.3
Control (gum Arabic)		10	6.6±0.8		15.90±0.39	
Idebenone	100	10	6.7±0.8	1.5	14.42±0.82	−9.3
	300	11	7.0±1.0	6.1	16.92±0.47	6.4
	1000	10	7.0±0.8	6.1	14.87±0.70	−6.5

Each value represents the mean±S.E. Mice were decapitated 20 min after test drug administration. % Change = {(Drug treated value − Control value)/Control value} × 100

were estimated to be 30 mg/kg for BMY-21502 and 100 mg/kg for idebenone. In this hypoxic model, oxiracetam (30−300 mg/kg) showed a tendency to increase the survival time, but the difference did not reach statistical significance.

Effect on complete ischemia in mice

The effects of BMY-21502, oxiracetam and idebenone on gasping duration and the number of gasps induced by complete ischemia were investigated. The data are summarized in Table 4. The average number of gasps and gasping duration in the vehicle-treated animal was 6−7 and 16 sec, respectively. BMY-21502 (3−300 mg/kg), oxiracetam (100−1000 mg/kg) and idebenone (100−1000 mg/kg) failed to prolong the gasping duration or to increase the number of gasps. They had no protective effects against

Table 5. Effects of scopolamine on KCN-induced anoxia and on the anti-anoxic action of BMY-21502 in mice

Treatment	Dose (mg/kg, route)	No. of animals used	Survival time (sec)	% Change
Control (Saline)	i.p.	13	23.26±1.40	
Scopolamine	0.5, i.p.	13	26.20±2.09	12.6
	1.0, i.p.	12	23.59±1.22	1.4
	1.5, i.p.	12	21.18±1.12	−8.9
	2.0, i.p.	7	18.50±1.18*	−20.5
Saline	i.p.			
+ BMY-21502	100, p.o.	10	31.09±2.08**	33.7
Scopolamine	0.5, i.p.			
+ BMY-21502	100, p.o.	10	28.89±1.42**	24.2
Scopolamine	1.5, i.p.			
+ BMY-21502	100, p.o.	10	24.02±1.50#	3.3

Each value represents the mean±S.E. *$P<0.05$, **$P<0.01$, compared with the control value. #$P<0.05$, compared with the saline+BMY-21502 value. Mice were given scopolamine and/or BMY-21502 30 min and 20 min respectively, before KCN administration. % Change = {(Drug treated value − Control value)/Control value} × 100

complete ischemia.

Effect of scopolamine on the anti-anoxic action of BMY-21502

Scopolamine shortened the survival time of KCN-induced anoxic mice. The minimum effective dose of scopolamine was 2 mg/kg. The anti-anoxic effect of BMY-21502 (100 mg/kg) in the KCN-anoxia model was clearly blocked by the pretreatment of scopolamine at the dose of 1.5 mg/kg, but not at the dose of 0.5 mg/kg (Table 5).

DISCUSSION

It has become clear that there is a marked difference between ischemic brain damage in which the supply of oxygen and glucose is abolished and hypoxia in which only the supply of oxygen is impaired (21). However, many drugs that are used in the therapy of patients with cerebral vascular diseases and other organic brain syndromes have beneficial effects in several hypoxic animal models (1−15). Thus, these experimental models are recognized as good screening methods for assessment of an agent's anti-ischemic activity. Therefore, in the present studies, KCN-induced anoxia, hypobaric hypoxia, and cerebral ischemia induced by decapitation were used to evaluate the anti-anoxic activity of BMY-21502 in comparison with those of idebenone and oxiracetam.

First we examined the effect of BMY-21502 against KCN-induced anoxia. BMY-21502 significantly increased the survival time in a dose-dependent manner at doses above 10 mg/kg. Our data also indicated that oxiracetam and idebenone were effective in prolonging the survival time at doses of 100 and 300 mg/kg and only at 100 mg/kg, respectively, in this model. Taking into account the molecular weights of these drugs (BMY-21502: M.W. 328, Oxiracetam: M.W. 157, Idebenone: M.W. 338), the protective effect of BMY-21502 is about 20 and 10 times more potent than those of oxiracetam and idebenone, respectively, in the KCN-anoxia model. Scopolamine, an anti-cholinergic drug, shortened the survival time of KCN-induced anoxic mice at the dose of 2 mg/kg. The anti-anoxic effect of BMY-21502 (100 mg/kg) in the KCN-anoxia model was clearly blocked by the pretreatment of scopolamine at the dose of 1.5 mg/kg, which had no effect on the survival time. This finding may suggest that activation of the CNS cholinergic system is involved as one of the causative mechanisms for anti-anoxic effect of BMY-21502. It is generally accepted that the acute toxicity of KCN is largely due to the inhibition of mitochondrial cytochrome oxidase, producing cytotoxic anoxia (26−29). Although the mechanisms of the anti-anoxic effects of BMY-21502 remain unclear, the fact that BMY-21502 showed a more potent anti-anoxic effect than idebenone, which improves the cerebral energy metabolism without affecting the cerebral blood flow (30, 31), is very interesting.

In the moderate hypobaric hypoxia model, in which the pressure was decreased to 190 mmHg in approximately 30 sec, BMY-21502 prolonged the survival time at doses above 30 mg/kg. Idebenone was also effective in prolonging the survival time at doses above 100 mg/kg, but oxiracetam failed to increase the survival time even at a dose of 300 mg/kg. These observations suggest again that the

cerebral protective effect of BMY-21502 is the strongest among the drugs tested, and about 3 times more potent than that of idebenone. However, under severe hypobaric hypoxia conditions, in which the pressure was decreased to 190 mmHg in approximately 20 sec, none of these drugs showed any protective effect. The average survival time of the control groups was approximately 120 sec under these conditions, and it was 130 sec under moderate hypobaric hypoxia conditions. The difference of the averaged survival time under these conditions may be due to differences of the speed to decrease oxygen by the vacuum pump and the number of tested animals in a chamber. Although the differences of average survival time in the control groups were no more than 10 sec under these conditions, the potencies of the drugs were remarkably different as described above. The sensitivity of animals to hypobaric hypoxia may be dependent on when the amimals were supplied to us.

We also examined the anti-anoxic activity of BMY-21502 in a complete ischemia model induced by decapitation. In this study, none of the drugs caused significant change in either the gasping duration or the number of gasps. This may be due to most severe ischemia conditions induced by decapitation.

A number of investigators have reported apparent protective effects of barbiturate and other CNS depressants, e.g., anti-anxiety drugs, against cerebral anoxia (15, 32). The mechanisms of the cerebral protective effect of these drugs have been explained by cerebral metabolic depression and/or suppression of the energy demand. BMY-21502 was also found to decrease the locomotor activity and to potentiate the thiopental-induced anesthesia at doses above 200 mg/kg, p.o. and at 800 mg/kg, p.o., respectively in mice (M. Amano et al., unpublished data). These doses are much higher than anti-anoxic doses.

The AChergic system is said to be vulnerable to cerebral anoxia as described in the Introduction (20, 21). Anti-cholinergic drugs decrease the survival time in hypoxic models (9), but the anti-choline esterase drug physostigmine increases cerebral blood flow and has an anti-anoxic effect. Cholinergic mechanisms control the cortical blood flow accompanied by cortical electroencephalogram desynchronization (18, 33, 34). These findings support the notion that the protective effects against cerebral anoxia are closely related to actions in the cholinergic system of the brain. In fact, we found that the anti-cholinergic drug scopolamine augumented the anoxic effect of KCN at a high dose, and the anti-anoxic effect of BMY-21502 in the KCN-anoxia model was clearly blocked by scopolamine treatment. BMY-21502 protects memory from disruption by scopolamine in mice and enhances acquisition in rats with the nucleus basalis lesions induced by ibotenic acid (22, 23). BMY-21502 is not bound to cholinergic receptor sites in the brain nor alter high affinity choline uptake. However, it does increase the firing rate of presumed cholinergic cells in the basal forebrain (22). Although the mechanisms of the anti-anoxic action of BMY-21502 remains unclear, these results suggest that increased CNS cholinergic function induced by BMY-21502 may play an important role in its anti-anoxic effects. In addition, BMY-21502 has been reported to increase PC-12 cell survival in culture under serum-free conditions (22), and this effect may be, at least in part, also related to its anti-anoxic effects. In any event, further elucidation of the mechanisms of action for BMY-21502 will be necessary.

REFERENCES

1 Sakurai, T., Hatanaka, S., Tanaka, S., Yamasaki, T., Kojima, H. and Akashi, A.: Protective effect of DM-9384, a novel pyrrolidone derivative, against experimental cerebral anoxia. Japan. J. Pharmacol. **54**, 33–43 (1990)

2 Yamamoto, M. and Shimizu, M.: Effects of indeloxazine hydrochloride (YM-08054) on anoxia. Arch. Int. Pharmacodyn. Ther. **286**, 272–281 (1987)

3 Takeo, S., Tanonaka, K., Hirano, T., Miyake, K. and Okamoto, J.: Cerebroprotective action of naftidrofuryl oxalate I: Prolongation of survival time and protection of cerebral energy metabolism in bilateral carotid artery-ligated mice. Folia Pharmacol. Japon. **91**, 267–273 (1988) (Abs. in English)

4 Karasawa, A., Kumada, Y., Yamada, K., Shuto, K. and Nakamizo, N.: Protective effect of flunarizine against cerebral hypoxia-anoxia in mice and rats. J. Pharmacobiodyn. **5**, 295–300 (1982)

5 Nagaoka, A., Miyamoto, M., Hamajo, K. and Kiyota, Y.: Protective action of vinpocetine against cerebral ischemia and anoxia. Basic Pharmacol. Ther. **12**, 2867–2871 (1984) (Abs. in English)

6 Von Krieglstein, J. and Hauer, H.: On the usefulness of a model of acute hypoxia for testing cerebro-protective drugs. Drug Res. **36**, 1568–1571 (1986)

7 King, G.A.: Protection against hypoxia-induced lethality in mice: a comparison of the effects of hypothermia and drugs. Arch. Int. Pharmacodyn. Ther. **286**, 282–298 (1987)

8 King, G.A.: Protective effects of vinpocetine and structurally related drugs on the lethal consequences of hypoxia in mice. Arch. Int. Pharmacodyn. Ther. **286**, 299–307 (1987)

9 Tobe, A., Egawa, M. and Hashimoto, N.: Anti-anoxic effect of 4-(*o*-benzylphenoxy)-*N*-methylbutylamine hydrochloride (MCI-2016). Folia Pharmacol. Japon. **81**, 421–429 (1983) (Abs. in English)

10 Rossignol, P. and Margaret, E.I.: Drugs against hypoxia. Trends Pharmacol. Sci. **1**, 287–289 (1980)

11 Hoffmeister, F., Benz, U., Heise, A., Krause, H.P. and Neuser, V.: Behavioral effects of nimodipine in animals. Arzneimittelforschung **32**, 347–360 (1982)

12 Sara, S.J. and Lefevre, D.: Hypoxia-induced amnesia in one-trial learning and pharmacological protection by piracetam. Psychopharmacologia (Berlin) **25**, 32–40 (1972)

13 Arnfred, I. and Secher, Q.: Anoxia and barbiturate. Arch. Int. Pharmacodyn. Ther. **139**, 67–74 (1962)

14 Mrsulja, B.B., Mrsulja, B.J., Spatz, M., Ito, U., Walker, J.T. and Klatzo, I.: Experimental cerebral ischemia in mongolian gerbils. Acta Neuropathol. **36**, 1–8 (1976)
15 Yasuda, H., Shuto, S., Tsumagari, T. and Nakajima, A.: Protective effect of a novel imidazole derivative against cerebral anoxia. Arch. Int. Pharmacodyn. Ther. **233**, 136–144 (1978)
16 Caillard, C., Menu, A., Plotkine, M. and Rossignol, P.: Do anticonvulsant drugs exert protective effect against hypoxia? Life Sci. **16**, 1607–1612 (1975)
17 Fukuda, A., Akagi, K., Masuda, Y. and Zushi, K.: Protective effect of anticonvulsant drugs against cerebral hypoxia in mice. J. Clin. Exp. Med. **144**, 917–918 (1988) (Abs. in English)
18 Scremin, A.M.E. and Scremin, O.U.: Physostigmine-induced cerebral protection against hypoxia. Stroke **10**, 142–143 (1979)
19 Artru, A.A. and Michenfelder, J.D.: A reexamination of physostigmine-induced cerebral protection in the hypoxic mouse. Stroke **11**, 197–199 (1980)
20 Gibson, G.E. and Blass, J.P.: Impaired synthesis of acetylcholine in brain accompanying mild hypoxia and hypoglycemia. J. Neurochem. **27**, 37–42 (1976)
21 Gibson, G.E., Misahisa, S. and Blass, J.P.: Protection by tris (hydroxymethyl)aminomethan against behavioral and neurochemical effects of hypoxia. Biochem. Pharmacol. **28**, 747–750 (1979)
22 Shrotriya, R.C., Stallone, F., Robinson, D., Brady, M. and Temple, D.: Clinical pharmacology of BMY-21502—a potential cognition enhancer. 17th Congress of Collegium Internationale Neuro-Psychopharmacologicum, Abst. **2**, 230 (1990)
23 Mattson, R.J., Loukas, E.P., Yevich, J.P. and Eison, M.E.: Synthesis and amnesia-reversal activity of a series of novel pyrrolidinone derivatives: identification of BMY-21502 as a potential treatment for cognitive disorders. Soc. Neurosci. Abst. **14**, 87.11 (1988)
24 Fitten, L.J., Perryman, K.M., Hanna, J.A. and Menon, M.K.: Effect of BMY-21502 on acquisition of shape descrimination and memory retention in monkey. Pharmacol. Biochem. Behav. **35**, 553–556 (1990)
25 Holowach-Thurston, J., Hauhart, P.E. and Jones, E.M.: Anoxia in mice: Reduced glucose in brain with normal or elevated glucose in plasma and increased survival after glucose treatment. Pediatr. Res. **8**, 238–243 (1974)
26 Schubert, J. and Brill, W.A.: Antagonism of experimental cyanide toxicity in relation to the in vivo activity of cytochrome oxidase. J. Pharmacol. Exp. Ther. **162**, 352–359 (1968)
27 Ballantyne, B., Boardman, S.P., Bright, J., Coffee, D.J., Webber, T.D. and Williams, P.: Tissue cyanide concentrations and cytochrome oxidase activity in experimental cyanide poisoning. Br. J. Pharmacol. **44**, 382–383 (1972)
28 Ashton, D., Van Reempts, J. and Wauquier, A.: Behavioural, electroencephalographic and histological study of the protective effect of etomidate against histotoxic dysoxia produced by cyanide. Arch. Int. Pharmacodyn. Ther. **254**, 196–213 (1981)
29 Isom, G.E., Burrows, G.E. and Way, J.L.: Effect of oxygen on the antagonism of cyanide intoxication-cytochrome oxidase, in vivo. Toxicol. Appl. Pharmacol. **65**, 250–256 (1982)
30 Nagaoka, A.: Idebenone. *In* New Cardiovascular Drugs, Edited by Scriabine, A., pp. 217–236, Raven Press, New York (1987)
31 Sugiyama, Y. and Fujita, T.: Stimulation of the respiratory and phosphorylating activities in rat brain mitochondria by idebenone (CV-2619), a new agent improving cerebral metabolism. FEBS Lett. **184**, 48–51 (1985)
32 Wauquier, A., Ashton, D., Clincke, G. and Niemegeers, C.J.E.: Anti-hypoxic effects of etomidate, thiopental and methohexital. Arch. Int. Pharmacodyn. Ther. **249**, 330–334 (1981)
33 Scremin, O.U., Rovere, A.A. and Raynald, A.C.: Cholinergic control of blood flow in the cerebral cortex of the rat. Stroke **4**, 232–239 (1973)
34 Scremin, O.U., Rubinstein, E.H. and Sonnenschein, R.R.: Effects of atropine and eserine on cerebral blood flow and oxygen consumption in the rabbit. Fed. Proc. **37**, 874 (1978)