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Protection by nicorandil against the dysfunction of the central vagal baroreflex system following transient global cerebral ischaemia in dogs

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1 A possible cerebroprotective effect of nicorandil was investigated in a canine model of 5 min global cerebral ischaemia, and compared with protective effects of nitroglycerin and nicardipine.

2 Cerebral ischaemia was produced by occlusion of the left subclavian and the brachiocephalic arteries with preceding ligation of the intercostal arteries. The decrease in baroreflex sensitivity (BRS), measured by phenylephrine-induced reflex bradycardia, was used to assess the cerebroprotective effect.

3 Nicorandil (10 or 30 $\mu g\,kg^{-1}\,min^{-1}$, i.v.), nitroglycerin (3 $\mu g\,kg^{-1}\,min^{-1}$, i.v.) or nicardipine (0.3 $\mu g\,kg^{-1}\,min^{-1}$, i.v.) were infused for 60 min just before ischaemia. Nitroglycerin and nicardipine decreased mean arterial blood pressure to an extent similar to that induced by the lower dose of nicorandil. Blood flow in the dorsal medulla oblongata was increased by nicorandil and nicardipine, but not by nitroglycerin.

4 Nicorandil at both doses and nitroglycerin prevented the post-ischaemic decrease in BRS. In these cases, bilateral vagotomy during the reperfusion period decreased BRS, indicating that the vagal component of BRS was protected from ischaemia. On the other hand, nicardipine failed to exert a cerebroprotective effect.

5 The present study suggests that nicorandil may possess a direct cerebroprotective effect and that its property as a nitrate might, at least in part, be important for the observed cerebral protection.

Keywords: Cerebral ischaemia; baroreceptor reflex; nicorandil; nitroglycerin; nicardipine

Introduction

Nicorandil, N-(2-hydroxyethyl) nicotinamide nitrate (ester), is an antianginal vasodilator with a dual mechanism of action as a nitrate and a K^+ channel opener (Taira, 1989). Thus, nicorandil has been shown to increase guanosine 3':5'-cyclic monophosphate (cyclic GMP) in blood vessels (Holtzmann, 1983; Kukovetz *et al.*, 1991) and to increase K^+ conductance in vascular smooth muscle (Furukawa *et al.*, 1981) and myocardium (Nakayama *et al.*, 1991). Additionally, nicorandil possesses a direct cardioprotective effect that may be independent of its haemodynamic effects and attributable to the opening of myocardial K^+ channels (Ohta *et al.*, 1991; Auchampach *et al.*, 1992), inhibition of oxygen free radical production by neutrophils and scavenging of hydroxyl radicals (Pieper & Gross, 1992), and/or reduction in free fatty acid uptake during ischaemia (Pieper & Gross, 1987). However, such a cytoprotective effect of nicorandil has yet to be established in organs other than the heart.

In this context, the present study was conducted to investigate a possible cerebroprotective effect of nicorandil in a canine model of transient global cerebral ischaemia in which we have already confirmed the cerebroprotective effects of some drugs including flunarizine (Kurihara *et al.*, 1989b; 1990b), ifenprodil (Kurihara *et al.*, 1990b), beraprost (Kurihara *et al.*, 1990a) and halothane (Kurihara *et al.*, 1992). The results were compared with those obtained with nitroglycerin and nicardipine.

Methods

Preparation of animals

Mongrel dogs of either sex weighing 6 to 16 kg were anaesthetized with sodium pentobarbitone (32 mg kg^{-1}, i.v. followed by an infusion of 3.2 mg $kg^{-1}\,h^{-1}$, i.v.). Under artificial ventilation with room air (a tidal volume of 20 ml kg^{-1} at a rate of 20 breaths min^{-1}) animals were immobilized with suxamethonium chloride (2 mg kg^{-1}, i.v. followed by an infusion of 1 mg $kg^{-1}\,h^{-1}$, i.v.). Appropriate volumes of O_2 and CO_2 were provided to maintain arterial P_{O_2} and P_{CO_2} at about 100 mmHg and 35 mmHg, respectively. Rectal temperature was maintained at about 38°C. Arterial blood pressure was measured from the left femoral artery by means of a pressure transducer (Nihon Kohden, TP-200T, Japan) and heart rate was measured by a heart rate counter (Nihon Kohden, AT-600G) triggered by lead II ECG.

Thoracotomy was performed at the fifth intercostal space and approximately 14 intercostal arteries descending along the thoracic aorta were permanently ligated. Pneumatic vascular occluders were placed around the left subclavian artery and the brachiocephalic artery as close as possible to the aortic arch.

The animals were finally placed in a prone position and the head was fixed in a stereotaxic frame. The head was tilted down at an angle of about 30 degrees to help in the manipulation of the brainstem. The foramen magnum was enlarged by removal of the caudal edge of the occipital bone. A plate type thermocouple electrode was placed on the surface of the right fasciculus cuneatus in the dorsal medulla oblongata proximal to the obex, and the regional blood flow was continuously measured by a tissue flow monitor (Unique Medical, UMW-101, Japan). The cortical EEG was recorded by means of stainless steel electrodes screwed bilaterally into the parietal skull, and continuously analyzed by a frequency analyzer (Nihon Kohden, OEE-7102) to confirm the steady level of anaesthesia throughout the experiment.

Measurement of baroreflex sensitivity (BRS)

Five or more bolus injections of (−)-phenylephrine hydrochloride were performed for each BRS measurement. The

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doses which increase mean arterial blood pressure by the range of about 5 to 25 mmHg were used; the dose-range was usually 0.3 to 10 $\mu g\,kg^{-1}$, i.v. The pressor response to phenylephrine was accompanied by a transient reflex bradycardia. Thus, the increase in pulse interval (ms) was correlated with the increase in mean arterial blood pressure (mmHg) by the method of least squares. The linearity of the regression line was always statistically significant, judging from the correlation coefficient. Then, the slope of the regression line (ms $mmHg^{-1}$) was used as a measure of BRS, because ischaemia did not displace the regression line, but altered the slope (Kurihara *et al.*, 1989a).

According to a previous study (Kurihara *et al.*, 1990b), an ischaemic insult of 5 min duration produces a selective dysfunction of the vagal component of BRS. Thus, the influence of bilateral section of the cervical vagosympathetic trunk (vagotomy) on BRS was investigated during the reperfusion period, following 5 min ischaemia, in order to evaluate the extent of the residual function of the vagal component of BRS. The practical timing of BRS measurement was as follows: BRS was measured before ischaemia and during the reperfusion period of 60 to 100 min. Then, the vagotomy was performed just after the second BRS measurement, and the third BRS measurement was started about 15 min later.

Production of cerebral ischaemia

Transient global cerebral ischaemia was produced by inflating the pneumatic occluders for 5 min. Since the severity of ischaemia in the dorsal medulla oblongata has been shown to be a good determinant of the post-ischaemic dysfunction of the vagal baroreflex (Kurihara *et al.*, 1990b), it was assessed by calculating the mean residual blood flow during ischaemia as described previously (Kurihara *et al.*, 1989c; 1990b).

Drugs

Nicorandil was supplied by Chugai Pharmaceutical Co., Ltd., Japan and dissolved in saline (1 or 3 $mg\,ml^{-1}$) just before use. Nitroglycerin solution (Nippon Kayaku, Japan) was diluted with saline to 0.3 $mg\,ml^{-1}$. Nicardipine hydrochloride (Sigma Chemical Company, U.S.A.) was dissolved in distilled water and diluted with saline to 30 $\mu g\,ml^{-1}$. The solutions of these three drugs or saline were infused into the right saphenous vein of 6 animals in each group with a syringe infusion pump (Harvard Apparatus, 2400–003, U.S.A.) at a rate of 10 $\mu l\,kg^{-1}\,min^{-1}$ for 60 min just prior to ischaemic insult. (−)-Phenylephrine hydrochloride (Sigma Chemical Company, U.S.A.) and suxamethonium chloride (Tokyo Kasei, Japan) were dissolved in saline and administered into the cephalic vein.

Statistics

Results are expressed as means ± s.e.mean. Values in different groups were analysed by the one-way analysis of variance followed by Bonferroni's multiple-comparison test. Differences between the values before and after ischaemia were analyzed by Dunnett's t test. Differences giving $P<0.05$ were regarded as statistically significant.

Results

Effects on blood pressure and heart rate

As shown in Table 1, all drugs tested decreased arterial blood pressure and the hypotensive effect of nicorandil was dose-dependent. The magnitude of the decrease in systolic blood pressure induced by nicorandil and nitroglycerin was greater than the decrease in diastolic blood pressure. Although the hypotensive effect of nitroglycerin developed more rapidly than that of nicorandil and reached a steady state within 10 min of infusion, the magnitude of the decrease in blood pressure at the end of infusion was similar to that produced by the lower dose of nicorandil. On the other hand, nicardipine preferentially decreased diastolic blood pressure. At the end of the infusion, the magnitude of the decrease in diastolic blood pressure produced by nicardipine was similar to that caused by the higher dose of nicorandil, while the decrease in systolic blood pressure was similar to that produced by the lower dose of nicorandil.

Heart rate was increased by the drugs, and there was no statistically significant difference in the maximum increase in heart rate. In all groups, tachycardia tended to recover during the infusion period despite the consistent decrease in blood pressure. In particular, in 4 animals which received the higher dose of nicorandil, tachycardia reversed to bradycardia by the end of infusion.

Effects on cerebral circulation

Regional arterial resistance (rAR) was calculated by dividing mean arterial blood pressure by regional cerebral blood flow in the dorsal medulla oblongata (rCBF). As shown in Table 2, nicorandil decreased rAR in a dose-dependent manner and increased rCBF at the higher dose. Nitroglycerin failed to produce a significant change in rAR and decreased rCBF. Nicardipine decreased rAR and increased rCBF to an extent similar to that induced by the higher dose of nicorandil.

Cerebroprotective effects

Changes in BRS following ischaemia and vagotomy were as shown in Figure 1. There was no statistically significant

Table 1 Effects of nicorandil, nitroglycerin and nicardipine on arterial blood pressure and heart rate

	Blood pressure (mmHg)								
	Systolic		*Mean*		*Diastolic*		*Heart rate* (beats min^{-1})		
Drugs	*Before*	*Change*[a]	*Before*	*Change*[a]	*Before*	*Change*[a]	*Before*	*Change*[a]	*(Max)*
Saline									
10 $\mu l\,kg^{-1}\,min^{-1}$	154 ± 8	− 4 ± 3	130 ± 6	− 3 ± 2	113 ± 5	− 1 ± 2	160 ± 7	1 ± 3	
Nicorandil									
10 $\mu g\,kg^{-1}\,min^{-1}$	167 ± 8	− 24 ± 5	139 ± 7	− 17 ± 3	124 ± 7	− 12 ± 1	158 ± 8	9 ± 2	(11 ± 2)
30 $\mu g\,kg^{-1}\,min^{-1}$	163 ± 6	− 56 ± 7**††	134 ± 6	− 45 ± 6**††	118 ± 6	− 38 ± 5**††	161 ± 9	− 2 ± 5	(10 ± 2)
Nitroglycerin									
3 $\mu g\,kg^{-1}\,min^{-1}$	162 ± 9	− 35 ± 6**	134 ± 6	− 23 ± 5*‡	117 ± 5	− 14 ± 5‡‡	150 ± 8	9 ± 4	(16 ± 3)
Nicardipine									
0.3 $\mu g\,kg^{-1}\,min^{-1}$	162 ± 8	− 19 ± 6‡‡	136 ± 7	− 27 ± 4**	123 ± 6	− 32 ± 5**†	157 ± 9	16 ± 5‡	(19 ± 4)

Results from 6 animals in each group are indicated as means ± s.e.mean.
[a]Change at the end of infusion period. Numbers in parentheses indicate the maximum increase in heart rate during infusion.
*$P<0.05$; **$P<0.01$; significantly different from saline.
†$P<0.05$; ††$P<0.01$; significantly different from the lower dose of nicorandil.
‡$P<0.05$; ‡‡$P<0.01$; significantly different from the higher dose of nicorandil.

Table 2 Effects of nicorandil, nitroglycerin and nicardipine on regional cerebral blood flow (rCBF) and regional arterial resistance (rAR) in the dorsal medulla oblongata

	Change in rCBF (%)	*Change in rAR (%)*
Saline		
10 μg kg^{-1} min^{-1}	0.1 ± 3.4	− 2.3 ± 3.2
Nicorandil		
10 μg kg^{-1} min^{-1}	0.2 ± 1.8	− 12.5 ± 2.3**
30 μg kg^{-1} min^{-1}	25.1 ± 7.8*	− 45.2 ± 4.7**
Nitroglycerin		
3 μg kg^{-1} min^{-1}	− 10.0 ± 3.3*	− 7.2 ± 4.3
Nicardipine		
0.3 μg kg^{-1} min^{-1}	17.9 ± 5.2*	− 30.6 ± 2.2**

Changes at the end of infusion are indicated as means ± s.e.mean of results from 6 animals in each group. *$P<0.05$; **$P<0.01$; statistically significant changes.

difference in pre-ischaemic BRS values and mean residual blood flow during ischaemia between the five groups. In animals which received saline or nicardipine prior to ischaemia, BRS during the reperfusion period was about 50% of the value before ischaemia. Subsequent vagotomy failed to affect BRS in these animals, indicating that the vagal component of BRS had been functionally abolished and that nicardipine failed to exert a cerebroprotective effect in the present experimental model. On the other hand, there was no significant decrease in BRS following ischaemia in animals which received nicorandil or nitroglycerin. Vagotomy decreased BRS in these animals, indicating that nicorandil and nitroglycerin protected the vagal component of BRS from ischaemia.

Figure 2 shows the effects of drugs on the correlation between the severity of ischaemia and the extent of the

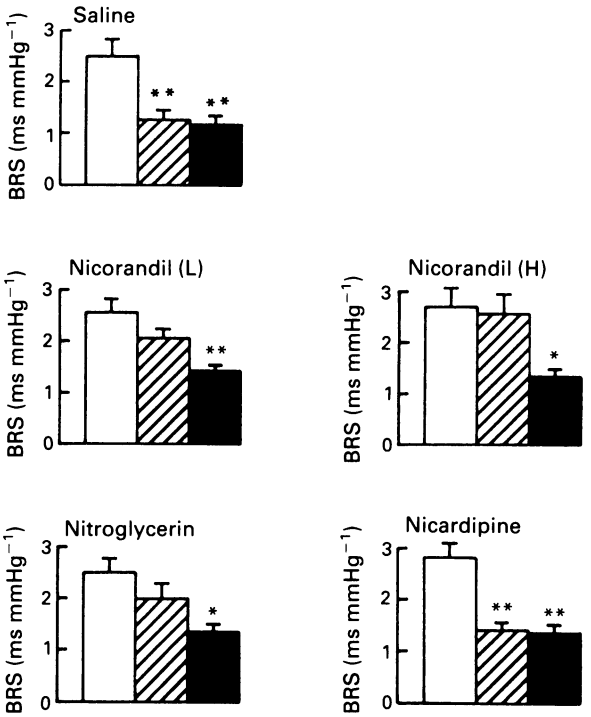

Figure 1 Effects of pretreatment with drugs on changes in baroreflex sensitivity (BRS) following 5 min global cerebral ischaemia. Open, hatched and closed columns indicate the BRS values ± s.e.mean before ischaemia, during reperfusion (before vagotomy) and after vagotomy, respectively ($n = 6$ for each group). The doses of the drugs are as indicated in Table 1. Nicorandil (L); the lower dose, Nicorandil (H); the higher dose. *$P<0.05$; **$P<0.01$; significantly different from the value before ischaemia.

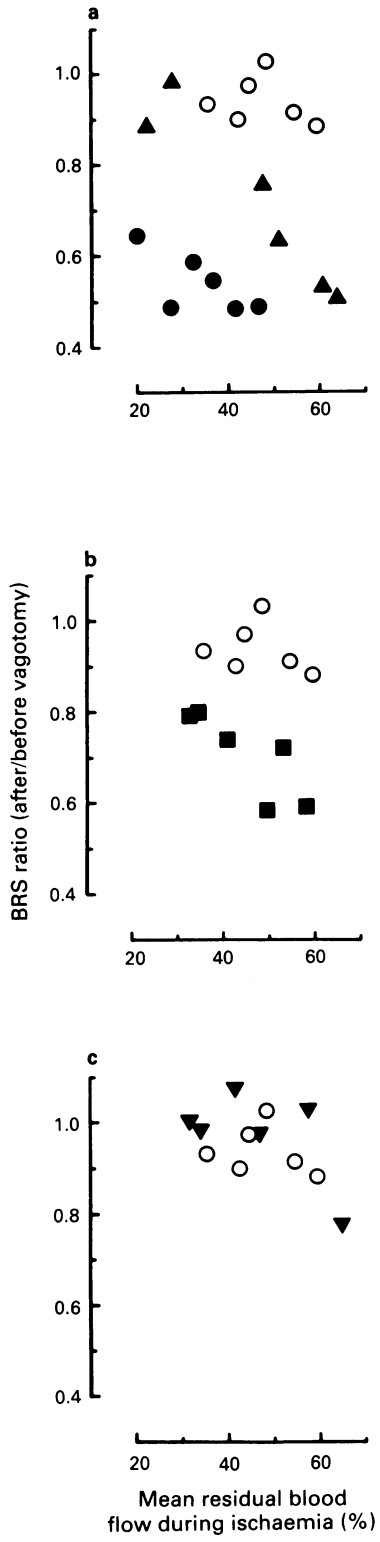

Figure 2 Correlation between the severity of ischaemia and the extent of post-ischaemic dysfunction of the vagal baroreflex. The data from animals treated with the lower (▲ in a) and higher (● in a) dose of nicorandil, nitroglycerin (■ in b) and nicardipine (▼ in c) are compared with those from saline-treated animals (○ in a, b and c). Abscissa scale; severity of ischaemia is indicated as the mean residual blood flow in the dorsal medulla oblongata during ischaemia. Thus, the severity of ischaemia increases as the value decreases. Ordinate scale: the extent of the influence of vagotomy is indicated as the ratio of the baroreflex sensitivity after vagotomy to that before vagotomy. Thus, the value 1 indicates that the vagal component of baroreflex is virtually absent. Additionally, the BRS ratio in sham-operated animals, which suffered no ischaemic insult, has been shown to be about 0.5 on average (see Kurihara *et al.*, 1990b).

post-ischaemic dysfunction of the vagal baroreflex. The data from saline-treated animals were consistent with a previous result that an ischaemic insult which reduced the mean residual blood flow by more than about 50% abolished the vagal component of baroreflex (Kurihara *et al.*, 1990b). The cerebroprotective effect of nitroglycerin was similar to that of the equihypotensive dose of nicorandil ($10\,\mu g\,kg^{-1}\,min^{-1}$, i.v.). In both cases, the extent of cerebral protection was dependent on the severity of ischaemia; the drugs were less effective against the severe ischaemia. The effect of nicorandil was dose-dependent. The higher dose of nicorandil was considered to be able to protect the vagal component of the baroreflex completely from the reduction in mean residual blood flow to about 30%, as the BRS ratio in sham-operated animals, which suffered no ischaemic insult, has been shown to be about 0.5 (Kurihara *et al.*, 1990b). In contrast, the data from nicardipine-treated animals shows that nicardipine failed to provide cerebral protection even against a mild ischaemia. Additionally, it was confirmed in preliminary experiments with sham-operated animals that nicorandil ($30\,\mu g\,kg^{-1}\,min^{-1}$, i.v.), nitroglycerin ($3\,\mu g\,kg^{-1}\,min^{-1}$, i.v.) and nicardipine ($0.3\,\mu g\,kg^{-1}\,min^{-1}$, i.v.) failed to affect the BRS ratio during the period from 60 min after the cessation of the 60 min infusion (data not shown).

Discussion

In the present study, nicorandil prevented the post-ischaemic dysfunction of the central vagal baroreflex system at doses similar to those shown to protect the heart from ischaemia/reperfusion injuries in dogs (Lamping *et al.*, 1984; Shimshak *et al.*, 1986; Gross *et al.*, 1987; Grover *et al.*, 1990; Auchampach *et al.*, 1992). The protective effect of nicorandil was dose-dependent and was dependent on the severity of ischaemia. In addition, the present study demonstrates that nicorandil produces cerebral vasodilatation and increases blood flow in the dorsal medulla oblongata. The latter results are consistent with those obtained by Nakagawa *et al.* (1979), who observed that nicorandil increased cerebral venous outflow in dogs. Nicardipine increased cerebral blood flow to an extent similar to that observed with the higher dose of nicorandil, while it failed to prevent the post-ischaemic cerebral dysfunction. On the other hand, nitroglycerin exerted a cerebroprotective effect similar to that of the lower dose of nicorandil, producing a small decrease in cerebral blood flow. Therefore, the observed cerebral protection by nicorandil and nitroglycerin may be independent of their effects on cerebral circulation, but rather ascribed to a direct protective effect.

Neichi *et al.* (1980) demonstrated that nicorandil increased prostacyclin (PGI_2) formation in the coupled system of platelets and aortic microsomes. PGI_2 has been shown to be cerebroprotective (Pluta, 1985; Masuda *et al.*, 1986) and our previous study demonstrated that beraprost, a chemically stable PGI_2 analogue, possesses a protective effect in the same experimental model as used in the present study (Kurihara *et al.*, 1990a). These results may indicate a contribution of PGI_2 to the cerebroprotective effect of nicorandil in the present study. However, at least in a canine model of myocardial ischaemia, it has been shown that nicorandil failed to increase PGI_2 release into coronary venous blood and that indomethacin failed to affect the cardioprotective effect of nicorandil (Gross *et al.*, 1989). Furthermore, the protective effect of beraprost in our previous study (Kurihara *et al.*, 1990a) was observed only at a dose higher than that required to inhibit platelet aggregation. Therefore, it seems to be unlikely that the cerebroprotective effect of nicorandil is due to an increase in PGI_2 formation.

The mechanism of the cytoprotective effect of nicorandil, which is independent of its haemodynamic effect, has been investigated in several models of myocardial ischaemia/reperfusion injuries (Gross *et al.*, 1989; Ohta *et al.*, 1991; Auchampach *et al.*, 1992). The recent study by Auchampach *et al.* (1992) clearly demonstrated that glibenclamide blocked the protective effect of nicorandil against myocardial stunning induced by ischaemia/reperfusion in dogs, suggesting that activation of the ATP-sensitive K^+ channel (K^+_{ATP} channel) may be the dominant mechanism of the cardioprotective effect of nicorandil. Since a similar K^+_{ATP} channel seems to be present in the brain (Ashford *et al.*, 1988; Mourre *et al.*, 1989; Krnjević, 1990), it is possible that nicorandil might protect the brain through activation of K^+_{ATP} channels with a resultant inhibition of excessive excitation of neurones during ischaemia, providing nicorandil readily penetrates the blood-brain barrier. According to unpublished data of the Chugai Pharmaceutical Co., Ltd., the ratio of the concentration of nicorandil in cerebrospinal fluid to that in plasma reaches about 1 after a 1 h infusion of $30\,\mu g\,kg^{-1}\,min^{-1}$ i.v., to anaesthetized dogs. Thus, it can be expected that at least the higher dose of nicorandil used in the present study might be enough to activate K^+_{ATP} channels in the brain, although further study is necessary to confirm this.

On the other hand, the present study also suggests that the nitrate properties of nicorandil may contribute to cerebral protection, as the cerebroprotective effect of nicorandil was mimicked by nitroglycerin at an equihypotensive dose. This result is in contrast with that from the canine model of myocardial ischaemia (Gross *et al.*, 1989), in which nitroglycerin exerted only a minimal protective effect.

It has been shown that the pharmacological effects of nitroglycerin are mediated by nitric oxide (NO), which is released from its $-ONO_2$ moiety and subsequently increases cytosolic cyclic GMP through activation of soluble guanylate cyclase (Ahlner *et al.*, 1991). Nicorandil also possesses the $-ONO_2$ moiety and its vasodilator effect may be, at least in part, mediated through cyclic GMP (Holtzmann, 1983; Kukovetz *et al.*, 1991). Concerning the relationship between cyclic GMP and neuronal damage, Garthwaite & Garthwaite (1988) suggested that guanlyate cyclase/cyclic GMP may be part of a protective mechanism against oxygen free radicals in rat cerebellar slices. Since oxygen free radicals may play an important role in the development of neuronal damage by cerebral ischaemia/reperfusion (Siesjö *et al.*, 1989), one can speculate that the increase in cyclic GMP by nicorandil and nitroglycerin might be favourable for cerebral protection in the present study. In this context, Pieper & Gross (1992) recently suggested that the nitrate action could, at least in part, explain the inhibition by nicorandil of free radical production in neutrophils.

In conclusion, the present study suggests that nicorandil may exert a direct cerebroprotective effect at doses which effectively protect the heart from ischaemia/reperfusion injuries. Although the precise mechanism of cerebral protection by nicorandil is still obscure, its property as a nitrate might, at least in part, be important in addition to activation of K^+ channels.

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References

AHLNER, J., ANDERSSON, R.G.G., TORFGARD, K. & AXELSSON, K.L. (1991). Organic nitrate esters: Clinical use and mechanisms of actions. *Pharmacol. Rev.*, **43**, 351–423.

ASHFORD, M.L.J., STURGESS, N.C., TROUT, N.J., GARDNER, N.J. & HALES, C.N. (1988). Adenosine-5′-triphosphate-sensitive ion channels in neonatal rat cultured central neurones. *Pflügers Arch.*, **412**, 297–304.

AUCHAMPACH, J.A., CAVERO, I. & GROSS, G.J. (1992). Nicorandil attenuates myocardial dysfunction associated with transient ischemia by opening ATP-dependent potassium channels. *J. Cardiovasc. Pharmacol.*, **20**, 765–771.

FURUKAWA, K., ITOH, T., KAJIWARA, M., KITAMURA, K., SUZUKI, H., ITO, Y. & KURIYAMA, H. (1981). Vasodilating actions of 2-nicotinamidoethyl nitrate on porcine and guinea-pig coronary arteries. *J. Pharmacol. Exp. Ther.*, **218**, 248–259.

GARTHWAITE, G. & GARTHWAITE, J. (1988). Cyclic GMP and cell death in rat cerebellar slices. *Neuroscience*, **26**, 321–326.

GROSS, G.J., WARLTIER, D.C. & HARDMAN, H.F. (1987). Comparative effects of nicorandil, a nicotinamide nitrate derivative, and nifedipine on myocardial reperfusion injury in dogs. *J. Cardiovasc. Pharmacol.*, **10**, 535–542.

GROSS, G., PIEPER, G., FARBER, N.E., WARLTIER, D. & HARDMAN, H. (1989). Effects of nicorandil on coronary circulation and myocardial ischemia. *Am. J. Cardiol.*, **63**, 11J–17J.

GROVER, G.J., SLEPH, P.G. & PARHAM, S. (1990). Nicorandil improves postischemic contractile function independently of direct myocardial effects. *J. Cardiovasc. Pharmacol.*, **15**, 698–705.

HOLTZMANN, S. (1983). Cyclic GMP as possible mediator of coronary arterial relaxation by nicorandil (SG-75). *J. Cardiovasc. Pharmacol.*, **5**, 364–370.

KRNJEVIĆ, K. (1990). Adenosine triphosphate-sensitive potassium channels in anoxia. *Stroke*, **21**, suppl. III, III–190–III–193.

KUKOVETZ, W.R., HOLTZMANN, S., BRAIDA, C. & PÖCH, G. (1991). Dual mechanism of the relaxing effect of nicorandil by stimulation of cyclic GMP formation and by hyperpolarization. *J. Cardiovasc. Pharmacol.*, **17**, 627–633.

KURIHARA, J., NISHIMURA, H,. ODA, N. & KATO, H. (1989a). Deterioration of baroreceptor reflex by transient global cerebral ischemia in dogs. *Jpn. J. Pharmacol.*, **49**, 255–265.

KURIHARA, J., ODA, N. & KATO, H. (1989b). Effect of flunarizine on the attenuation of baroreflex by transient cerebral ischemia. *Eur. J. Pharmacol.*, **165**, 147–150.

KURIHARA, J., SAHARA, T. & KATO, H. (1989c). Deterioration of baroreflex by transient global cerebral ischemia: Its correlation with the degree of ischemia or post-ischemic hypoperfusion in the medulla oblongata. *Jpn. J. Pharmacol.*, **51**, 493–499.

KURIHARA, J., SAHARA, T. & KATO, H. (1990a). Protective effect of beraprost sodium, a new chemically stable prostacyclin analogue, against the deterioration of baroreceptor reflex following transient global cerebral ischaemia in dogs. *Br. J. Pharmacol.*, **99**, 91–96.

KURIHARA, J., SAHARA, T., ODA, N., TOMITA, H. & KATO, H. (1990b). Selective dysfunction of the vagal component of the baroreflex following cerebral ischemia: protection by ifenprodil and flunarizine. *Eur. J. Pharmacol.*, **190**, 23–30.

KURIHARA, J., TOMITA, H., OCHIAI, N. & KATO, H. (1992). Protection by halothane of the vagal baroreflex system from transient global cerebral ischemia in dogs. *Jpn. J. Pharmacol.*, **60**, 63–66.

LAMPING, K.A., CHRISTENSEN, C.W., PELC, L.R., WARLTIER, D.C. & GROSS, G.J. (1984). Effects of nicorandil and nifedipine on protection of ischemic myocardium. *J. Cardiovasc. Pharmacol.*, **6**, 536–542.

MASUDA, Y., OCHI, Y., OCHI, Y., KARASAWA, T., HATANO, N., KADOKAWA, T. & SHIMIZU, M. (1986). Protective effect of prostaglandin D_2, E_1 and I_2 against cerebral hypoxia/anoxia in mice. *Naunyn-Schmied. Arch. Pharmacol.*, **334**, 282–289.

MOURRE, C., BEN-ARI, Y., BERNARDI, H., FOSSET, M. & LAZDUNSKI, M. (1989). Antidiabetic sulfonylureas: Localization of binding sites in the brain and effects on the hyperpolarization induced by anoxia in hippocampal slices. *Brain Res.*, **486**, 159–164.

NAKAGAWA, Y., TAKEDA, K., KATANO, Y., TSUKADA, T., KITAGAWA, Y., OTORII, T. & IMAI, S. (1979). Effects of 2-nicotinamidoethyl nitrate on the cardiovascular system. *Jpn. Heart J.*, **20**, 881–895.

NAKAYAMA, K., FAN, Z., MARUMO, F., SAWANOBORI, T. & HIRAOKA, M. (1991). Action of nicorandil on ATP-sensitive K^+ channel in guinea-pig ventricular myocytes. *Br. J. Pharmacol.*, **103**, 1641–1648.

NEICHI, T., TOMISAWA, S., KUBODERA, N. & UCHIDA, Y. (1980). Enhancement of PGI_2 formation by a new vasodilator, 2-nicotinamidoethyl nitrate in the coupled system of platelets and aortic microsomes. *Prostaglandins*, **19**, 577–586.

OHTA, H., JINNO, Y., HARADA, K., OGAWA, N., FUKUSHIMA, H. & NISHIKORI, K. (1991). Cardioprotective effects of KRN2391 and nicorandil on ischemic dysfunction in perfused rat heart. *Eur. J. Pharmacol.*, **204**, 171–177.

PIEPER, G.M. & GROSS, G.J. (1987). Salutary action of nicorandil, a new antianginal drug, on myocardial metabolism during ischemia and on postischemic function in a canine preparation of brief, repetitive coronary artery occlusions: comparison with isosorbide dinitrate. *Circulation*, **76**, 916–928.

PIEPER, G.M. & GROSS, A.G. (1992). Anti-free-radical and neutrophil-modulating properties of the nitrovasodilator, nicorandil. *Cardiovasc. Drugs Ther,*. **6**, 225–232.

PLUTA, R. (1985). Influence of prostacyclin on early morphological changes in the rabbit brain after complete 20-min ischemia. *J. Neurol. Sci.*, **70**, 305–316.

SHIMSHAK, T.M., PREUSS, K.C., GROSS, G.J., BROOKS, H.L. & WARLTIER, D.C. (1986). Recovery of contractile function in post-ischaemic reperfused myocardium of conscious dogs: influence of nicorandil, a new antianginal agent. *Cardiovasc. Res.*, **20**, 621–626.

SIESJÖ, B.K., AGARDH, C.-D. & BENGTSSON, F. (1989). Free radicals and brain damage. *Cerebrovasc. Brain Metab. Rev.*, **1**, 165–211.

TAIRA, N. (1989). Nicorandil as a hybrid between nitrates and potassium channel activators. *Am. J. Cardiol.*, **63**, 18J–24J.

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