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Dopamine D_2 receptor agonists protect against ischaemia-induced hippocampal neurodegeneration in global cerebral ischaemia

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Abstract

To characterise the role played by dopamine receptors in ischaemic brain damage, we have evaluated the effects of pergolide, bromocriptine and lisuride (dopamine D_2 receptor agonists), haloperidol (a dopamine D_2 receptor antagonist), 2,3,4,5-tetrahydro-7,8,di-hydroxy-1-phenyl-1*H*-3-benzazepine (SKF 38393; a dopamine D_1 receptor agonist) and (*R*)-(+)-8-chloro 2,3,4,5-tetra-hydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol (SCH 23390; a dopamine D_1 receptor antagonist) in the gerbil model of global cerebral ischaemia. Ischaemia was induced by 5 min of bilateral carotid artery occlusion under halothane anaesthesia. Sham operated animals were used as controls. Pergolide (0.5 or 1.0 mg/kg i.p), bromocriptine (0.5 or 1.0 mg/kg i.p.), lisuride (0.5 or 1.0 mg/kg i.p.), SCH 23390 (0.1 or 1.0 mg/kg i.p.), haloperidol (0.5, 1.0 or 2 mg/kg i.p.) and SKF 38393 (1.0 or 2 mg/kg i.p.) were administered 1 h before occlusion. Five-minute-occluded animals had extensive damage in the CA1 region of the hippocampus 5 days after surgery. Pergolide 0.5 and 1.0 mg/kg i.p. provided significant ($P < 0.05$ and $P < 0.01$, respectively) neuroprotection against the ischaemia-induced hippocampal damage. Bromocriptine and lisuride also provided significant ($P < 0.05$) neuroprotection, but only at the higher 1.0 mg/kg dose. In contrast, the dopamine D_2 receptor antagonist (haloperidol), the dopamine D_1 receptor agonist (SKF 38393) and the dopamine D_1 receptor antagonist (SCH 23390) failed to provide any neuroprotection in the model. These results support studies indicating that dopamine is important in ischaemic situations. The results also indicate that dopamine D_2 receptor agonists are neuroprotective against ischaemia-induced brain injury and may play a role in neurodegenerative disorders.

Keywords: Cerebral ischaemia; Pergolide; Bromocriptine; Dopamine D_1/D_2 receptor; SCH 23390; SKF 38393; Lisuride

1. Introduction

It has been shown that there is a large increase in glutamate, dopamine and other neurotransmitters during ischaemia (Benveniste et al., 1984; Globus et al., 1988; Bentué-Ferrer et al., 1993). Glutamate, through an action on *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and metabotropic receptors, allows calcium to enter the cell and leads to the production of diacylglycerol and inositol tri-phosphate, which activate enzymes and lead to the release of calcium from intracellular stores (Choi, 1992; McCulloch, 1992). This large increase in calcium leads to activation of proteases, nucleases, phospholipases, nitric oxide synthase and other degradative enzymes that lead to free radical production and cell death (Siesjö, 1992). Many recent studies have indicated that apoptotic mechanisms may also contribute to the cell death observed following cerebral ischaemia (Johnson et al., 1995). In agreement with these mechanisms, it has been shown that many compounds acting at excitatory amino acid receptors have beneficial effects against ischaemic insults (Gill et al., 1987; Sheardown et al., 1990; McCulloch, 1992; Bullock et al., 1994). Agents that prevent free radical production such as recombinant human superoxide dismutase (Tagaya et al., 1992), 21-amino steroids or 'lazaroids' (Clark et al., 1995; Hall, 1995), LY 231617 (2,6-bis(1,1 dimethylethyl)-4-[[(1-ethyl)amino]methyl]phenol, hydrochloride) (Clemens et al., 1993; O'Neill et al., 1997) and nitric oxide

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synthase inhibitors (Buisson et al., 1993; O'Neill et al., 1996, 1997) have also provided protection in animal models of cerebral ischaemia.

However, it has also been shown using microdialysis that as well as producing increases in glutamate, ischaemia causes a large increase in dopamine and serotonin levels (Brannan et al., 1987; Globus et al., 1988; Damsma et al., 1990; Bentué-Ferrer et al., 1993, 1994). In fact, Globus et al. (1988) reported that 20 min of four-vessel occlusion caused a seven-fold increase in glutamate, but a 500-fold increase in dopamine content. The group also demonstrated that prior substantia nigra lesioning prevented the ischaemia-induced release of dopamine and attenuated the release of glutamate (Globus et al., 1987). Further studies indicated that there is also a large increase in dopamine after focal ischaemia in rats and that this is also completely blocked by substantia nigra lesioning (Buisson et al., 1991). The authors also reported an attenuation in the glutamate release and a reduction in the infarct volume. Therefore, dopamine appears to play an important role in mediating ischaemic brain damage. It has also been demonstrated that dopamine increases ischaemia-induced cell damage

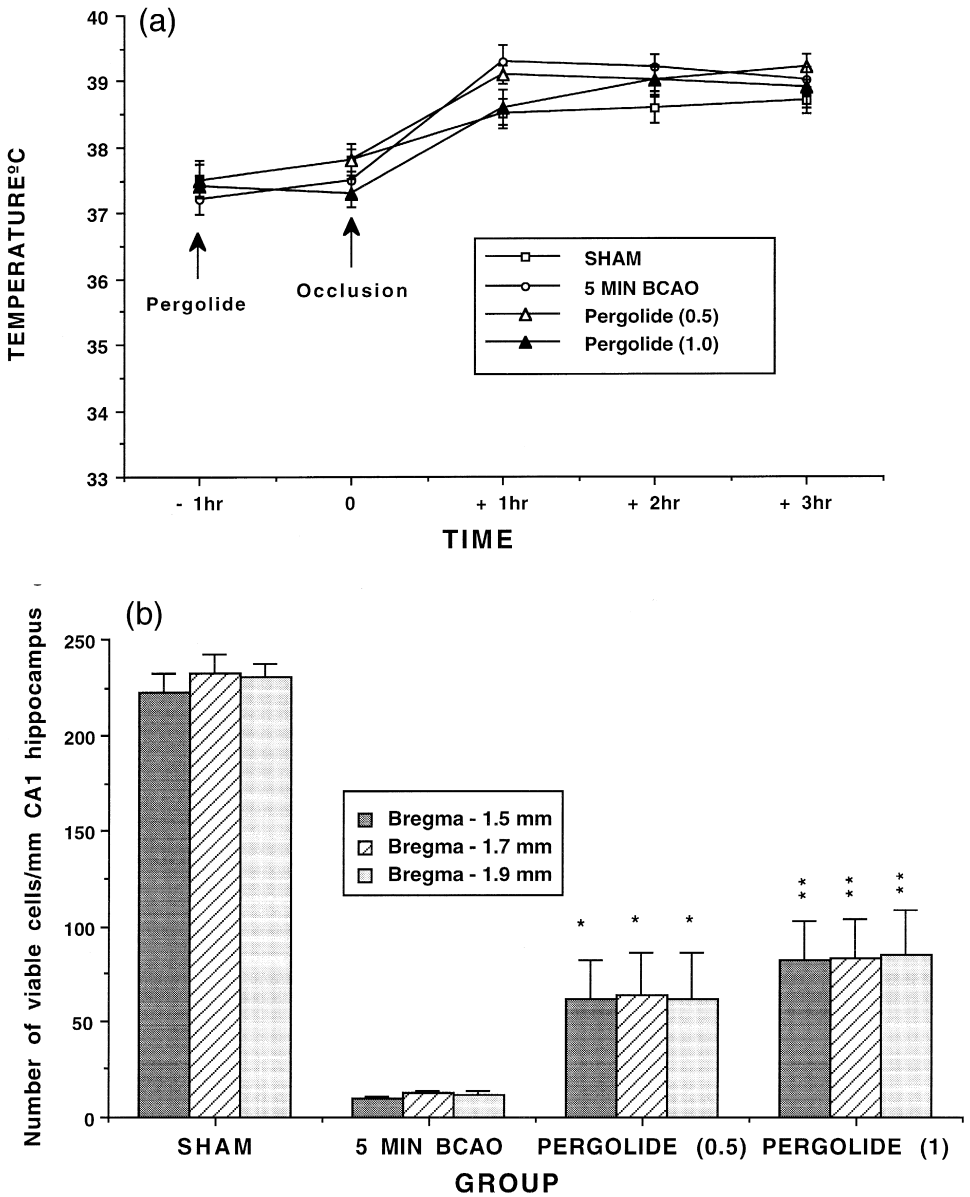

Fig. 1. The effects of pergolide administered 1 h before 5 min bilateral carotid artery occlusion (BCAO) on rectal temperatures (a) and on the neuronal density in the CA1 region of the hippocampus 5 days after surgery (b). Histological results are expressed as mean ± S.E.M. viable cells/mm CA1 hippocampal region ($n = 8$ animals per group). Five-minute BCAO produced a severe loss in neurones in the CA1 region ($P < 0.0001$; Student's *t*-test). Pergolide (0.5 and 1 mg/kg i.p.) provided significant neuroprotection ($P < 0.05$ and 0.01, respectively; Student's *t*-test) against the ischaemia-induced cell death in the hippocampus.

(Hashimoto et al., 1994) and that brain extracellular levels of dopamine and serotonin are related to the severity of ischaemic insult (Richards et al., 1993a).

Dopamine receptor agonists are extensively used in the treatment of Parkinson's disease and it has been suggested that these agonists may suppress dopamine release via dopamine autoreceptors. It is well established that in Parkinson's disease there is a progressive loss of nigrostriatal dopaminergic neurones (Javoy-Agid, 1992). It has been shown that this nigrostriatal degeneration involves oxygen radical and iron-dependent lipid peroxidation (Jenner et al., 1992) which are also evident in ischaemia-induced brain injury (Clemens et al., 1993). Therefore, it is possible that dopamine receptor agonists may also prevent ischaemia-induced neuronal cell death. In agreement with this, recent studies have demonstrated that bromocriptine protects against hippocampal damage in global cerebral ischaemia (Liu et al., 1995). The dopamine D_2/D_3 receptor agonist pramipexole has also been shown to protect degeneration of nigrostriatal neurones after ischaemia (Hall et al., 1996).

To further characterise the role of dopamine in ischaemic brain damage we have evaluated the effects of pergolide, bromocriptine and lisuride (dopamine D_2 recep-

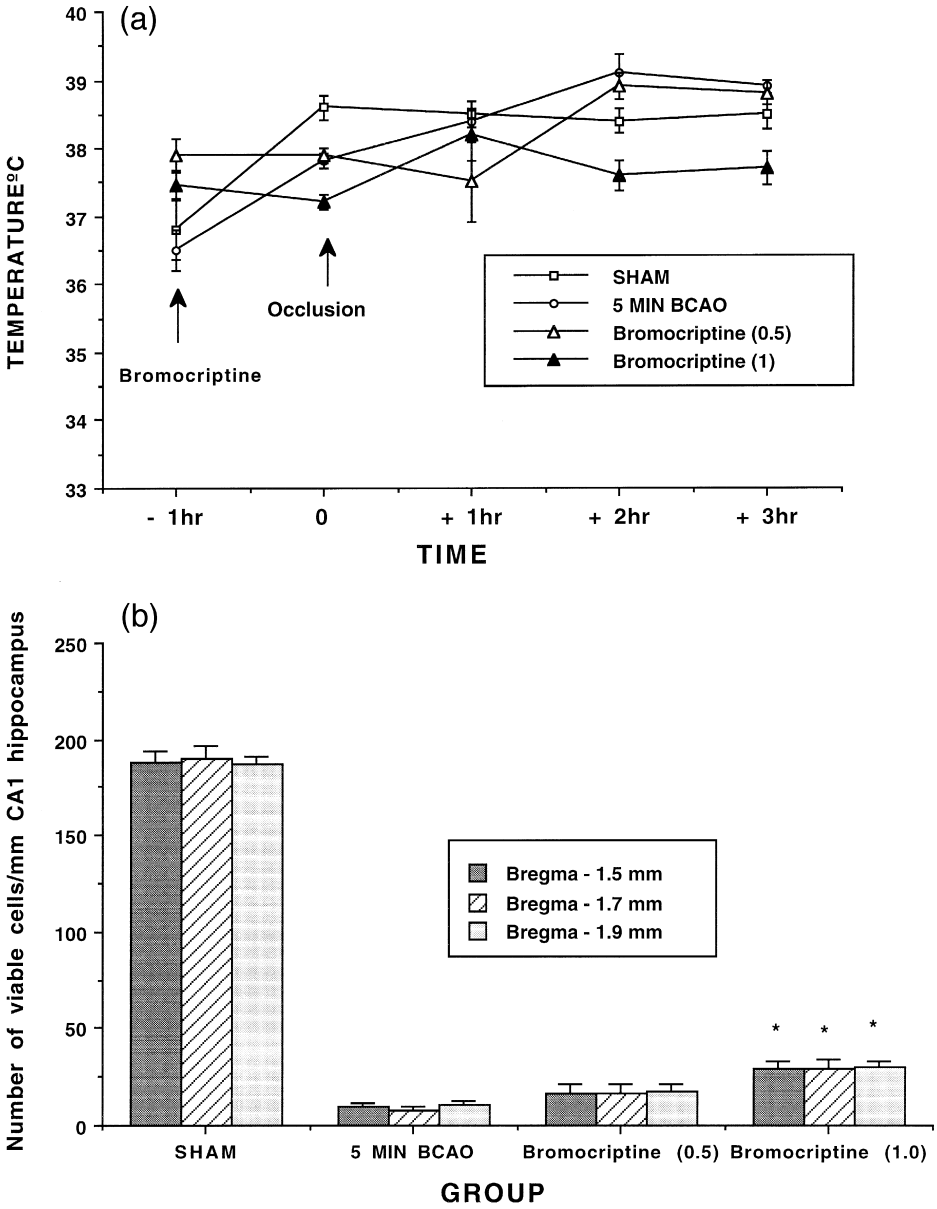

Fig. 2. The effects of bromocriptine administered 1 h before 5 min bilateral carotid artery occlusion (BCAO) on rectal temperatures (a) and on the neuronal density in the CA1 region of the hippocampus 5 days after surgery (b). Histological results are expressed as mean ± S.E.M. viable cells/mm CA1 hippocampal region ($n = 8$ animals per group). Five-minute BCAO produced a severe loss in neurones in the CA1 region ($P < 0.0001$; Student's *t*-test). The lower dose (0.5 mg/kg i.p.) failed to provide any neuroprotection, while the higher dose (1 mg/kg i.p.) provided a small, but significant neuroprotection ($P < 0.05$; Student's *t*-test) against the ischaemia-induced cell death in the hippocampus.

tor agonists), haloperidol (dopamine D_2 receptor antagonist), SKF 38393 (dopamine D_1 receptor agonist) and SCH 23390 (dopamine D_1 receptor antagonist) in the gerbil model of global cerebral ischaemia.

2. Materials and methods

2.1. Animals and surgery

Male Mongolian gerbils (Bantin and Kingman, Hull, UK) at least 3 months old and weighing in excess of 60 g were used. They were delivered to the laboratory at least 1 week before commencement of experiments and housed five per cage. The animals were maintained at a constant temperature of 21 ± 1°C and standard lighting conditions and food and water were available ad libitum.

The animals were anaesthetised with a 5% halothane/oxygen mixture and maintained using 2% halothane delivered with oxygen at 1 l/min via a face mask throughout the operation. Through a midline cervical incision, both common carotid arteries were exposed and freed from surrounding connective tissue, taking care not to damage the vagus or sympathetic nerves running close

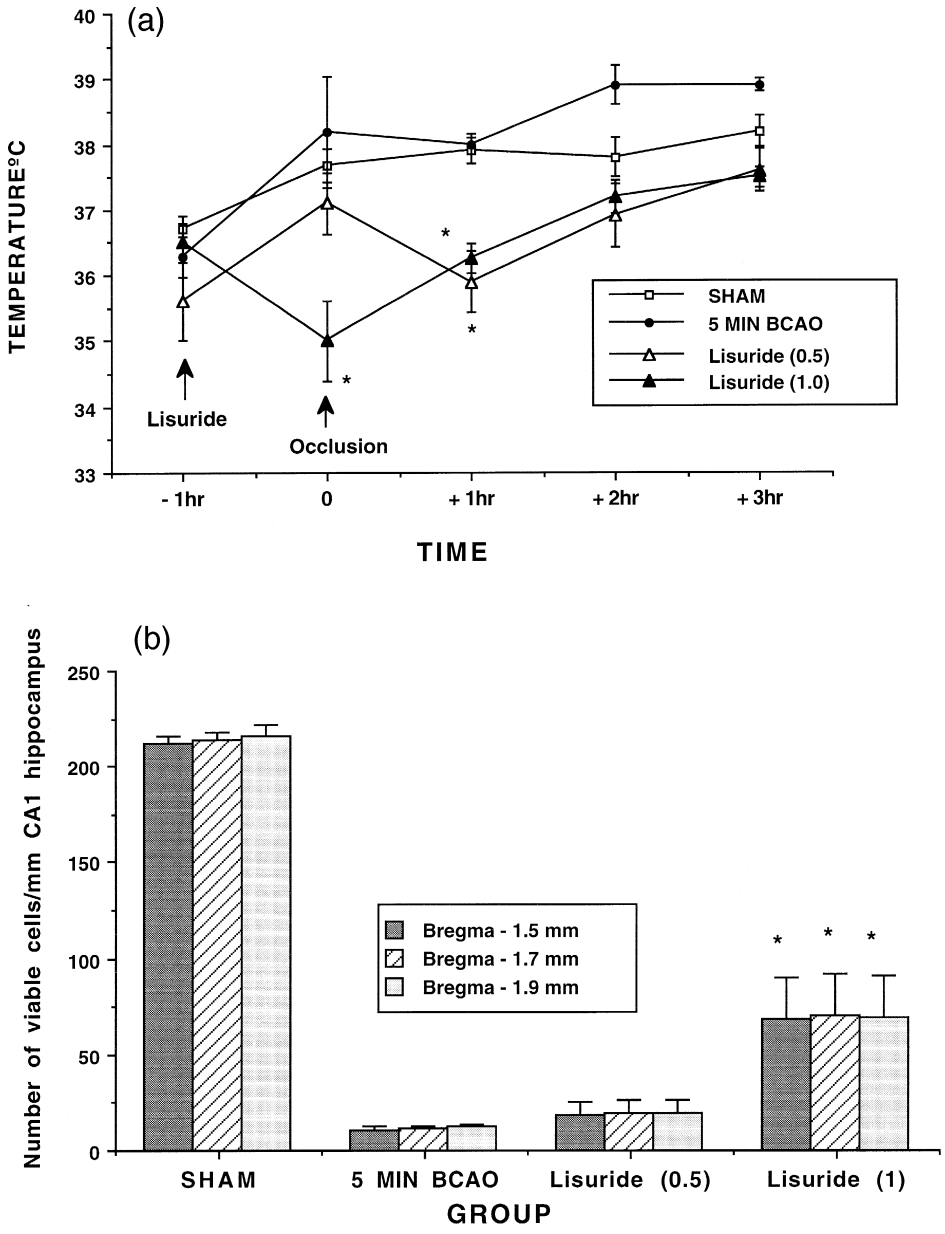

Fig. 3. The effects of lisuride administered 1 h before 5 min bilateral carotid artery occlusion (BCAO) on rectal temperatures (a) and on the neuronal density in the CA1 region of the hippocampus 5 days after surgery (b). Both doses of lisuride produced some hypothermic effects. Histological results are expressed as mean ± S.E.M. viable cells/mm CA1 hippocampal region ($n = 8$ animals per group). Five-minute BCAO produced a severe loss in neurones in the CA1 region ($P < 0.0001$; Student's t-test). The lower dose (0.5 mg/kg i.p.) failed to provide any neuroprotection, while the higher dose (1 mg/kg i.p.) provided significant neuroprotection ($P < 0.05$; Student's t-test) against the ischaemia-induced cell death in the hippocampus.

by. In animals to be rendered ischaemic, both carotid arteries were clamped for 5 min. At the end of the occlusion, blood flow was re-established. In sham operated animals the arteries were exposed but not occluded. The wound was then sutured and the animals allowed to recover. The temperature was maintained at 37°C throughout surgery using a 'K-temp' temperature controller/heating pad (International Market Supply, Cheshire, UK) and rectal temperatures were measured. The animals were allowed to recover in a thermacage (Beta Medical and Scientific, UK) which consisted of a four-compartmental chamber in which the environmental temperature was maintained at 28°C and rectal temperatures were monitored for 6 h post-occlusion.

2.2. Drugs

All drugs were dissolved in 0.89% saline and administered via the intraperitoneal route. Pergolide (LY 127809, synthesised at Lilly), bromocriptine (Semat, UK) and lisuride (Semat) were administered at 0.5 or 1 mg/kg i.p. 1 h before occlusion. SCH 23390 ((*R*)-(+)-8-chloro 2,3,4,5-tetra-hydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol, Semat) was administered at 0.1 or 1.0 mg/kg 1 h before occlusion. Haloperidol (Semat) was administered at 0.5, 1

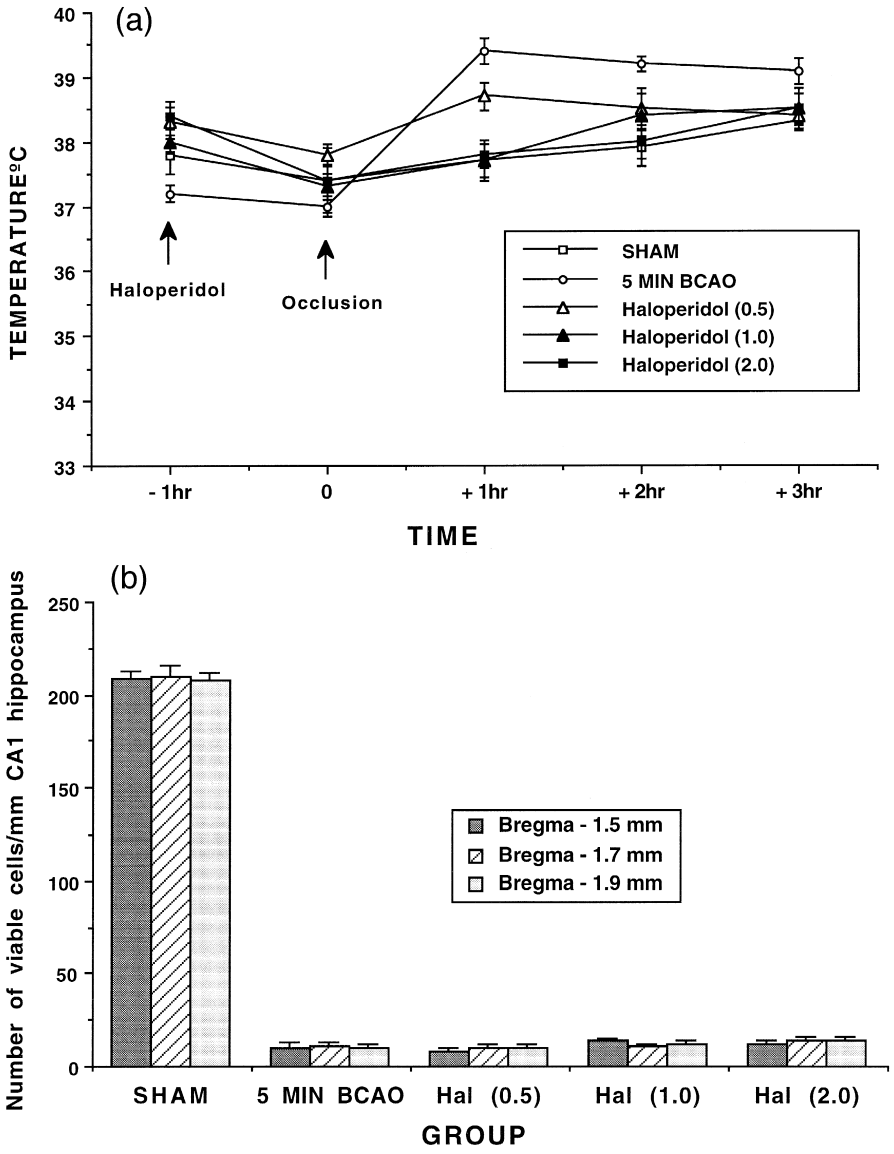

Fig. 4. The effects of haloperidol administered 1 h before 5 min bilateral carotid artery occlusion (BCAO) on rectal temperatures (a) and on the neuronal density in the CA1 region of the hippocampus 5 days after surgery (b). Histological results are expressed as mean ± S.E.M. viable cells/mm CA1 hippocampal region ($n = 8$ animals per group). Five-minute BCAO produced a severe loss in neurones in the CA1 region ($P < 0.0001$; Student's *t*-test). Haloperidol (0.5, 1 or 2 mg/kg i.p.) failed to protect against the ischaemia-induced cell death in the hippocampus.

or 2 mg/kg and SKF 38393 HCl (2,3,4,5-tetrahydro-7,8,dihydroxy-1-phenyl-1*H*-3-benzazepine, HCl, Semat) were administered at 1 or 2 mg/kg 1 h before occlusion.

2.3. Histology

5 days after surgery, the animals were perfused transcardially with 30 ml of 0.9% saline followed by 100 ml of 10% buffered formalin solution. The brains were removed and placed in 10% formalin for 3 days, processed and embedded in paraffin wax. 5 μm coronal sections were taken at 1.5, 1.7 and 1.9 mm caudal to the bregma in the anterior hippocampus using a sledge (Leitz 1400) microtome. The slices were stained with haematoxylin and eosin and the neuronal density in the CA1 subfield of the hippocampus was measured using a microscope with grid lines (0.05 mm × 0.05 mm). The neuronal density is expressed as neuronal density per mm CA1 hippocampus.

2.4. Statistics

Statistical analysis of histological data was carried out using analysis of variance (ANOVA) followed by Student's *t*-test using $P < 0.05$ as the level of significance.

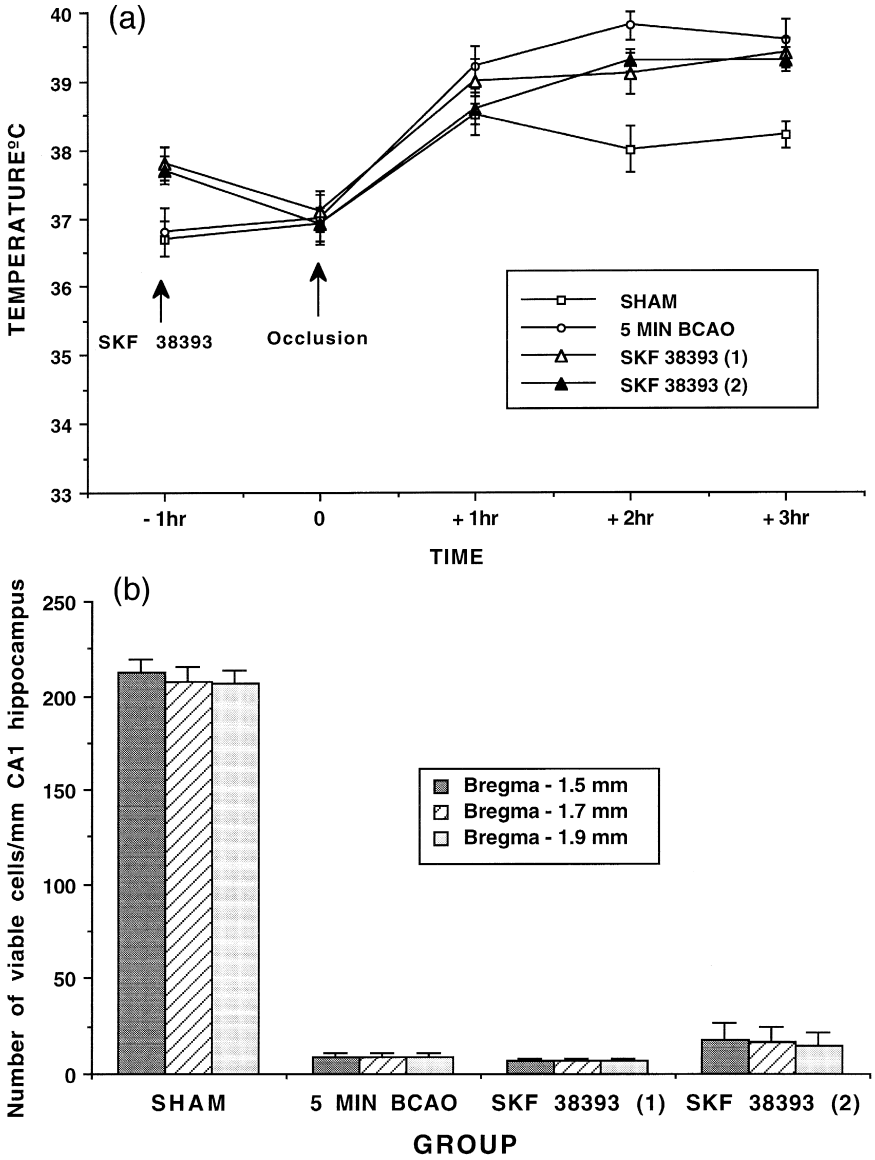

Fig. 5. The effects of SKF 38393 administered 1 h before 5 min bilateral carotid artery occlusion (BCAO) on rectal temperatures (a) and on the neuronal density in the CA1 region of the hippocampus 5 days after surgery (b). Histological results are expressed as mean ± S.E.M. viable cells/mm CA1 hippocampal region ($n = 8$ animals per group). Five-minute BCAO produced a severe loss in neurones in the CA1 region ($P < 0.0001$; Student's *t*-test). SKF 38393 (1 or 2 mg/kg i.p.) failed to protect against the ischaemia-induced cell death in the hippocampus.

3. Results

5 μm sections taken 1.5–1.9 mm caudal to the bregma in the anterior hippocampus were examined under a microscope with grid lines. The CA1 pyramidal neurones were found to be degenerated in the 5 min occluded animals (Fig. 1). The neuronal death involved nearly all the pyramidal neurones and this neurodegeneration was not evident in any other forebrain region. Pergolide had no effect on rectal temperatures (Fig. 1a) but provided significant protection against the ischaemia-induced cell death in the CA1 region of the hippocampus (Fig. 1b).

Bromocriptine also did not have any effect on rectal temperatures (Fig. 2a). The lower dose (0.5 mg/kg) failed to provide any protection, while the higher dose (1 mg/kg) provided a small, but significant neuroprotection (Fig. 2b).

The lower dose of lisuride caused a slight drop in temperature and this was significant at the higher dose of lisuride (Fig. 3a). The lower dose (0.5 mg/kg) failed to provide any protection, while the higher dose (1 mg/kg) provided significant ($P < 0.05$) neuroprotection (Fig. 3b).

Haloperidol (0.5–2 mg/kg i.p.) had no effect on rectal temperature post-occlusion (Fig. 4a). Haloperidol also failed to provide any neuroprotection against the ischaemia-induced neurodegeneration in the CA1 region of the hippocampus (Fig. 4b).

SKF 38393 (1 or 2 mg/kg i.p.) caused no changes in rectal temperature (Fig. 5a). The compound failed to pro-

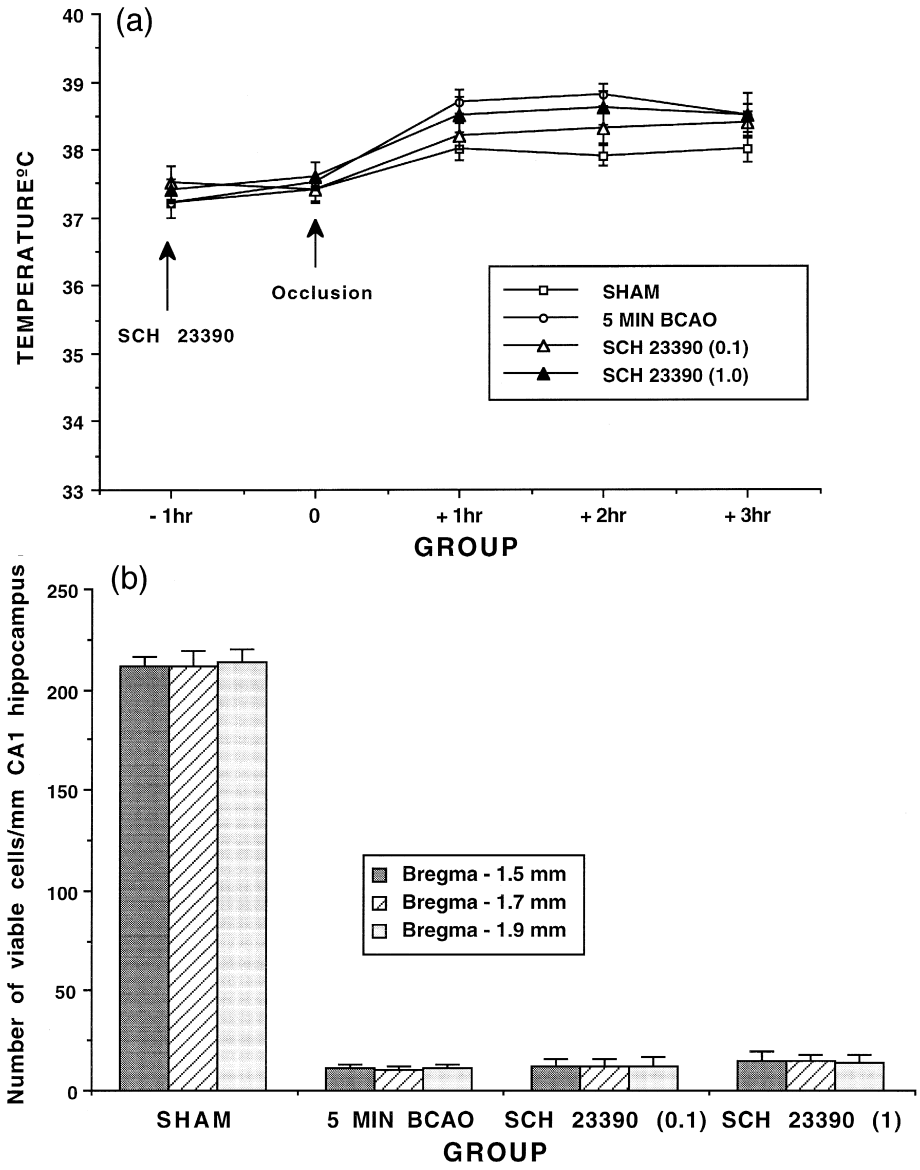

Fig. 6. The effects of SCH 23390 administered 1 h before 5 min bilateral carotid artery occlusion (BCAO) on rectal temperatures (a) and on the neuronal density in the CA1 region of the hippocampus 5 days after surgery (b). Histological results are expressed as mean ± S.E.M. viable cells/mm CA1 hippocampal region ($n = 8$ animals per group). Five-minute BCAO produced a severe loss in neurones in the CA1 region ($P < 0.0001$; Student's *t*-test). SCH 23390 (0.1 or 1 mg/kg i.p.) failed to protect against the ischaemia-induced cell death in the hippocampus.

vide any neuroprotection against the ischaemia-induced hippocampal damage (Fig. 5b).

In the final experiment we observed no changes in rectal temperature with SCH 23390 at either dose tested (Fig. 6a). SCH 23390 also failed to provided any neuroprotection against the ischaemia-induced neurodegeneration in the CA1 hippocampal region (Fig. 6b).

4. Discussion

In the present experiments we have evaluated the effects of dopamine receptor agonists and antagonists in global cerebral ischaemia. The results indicate that D_2 receptor agonists are neuroprotective in the model. It has been shown using microdialysis that ischaemia causes a large increase in dopamine and serotonin levels (Globus et al., 1988; Phebus and Clemens, 1989; Baker et al., 1991; Bentué-Ferrer et al., 1993). It has also been demonstrated that prior substantia nigra lesioning prevented the ischaemia-induced release of dopamine and attenuated the release of glutamate in global (Globus et al., 1988) and focal (Buisson et al., 1993) cerebral ischaemia. Therefore, dopamine appears to play an important role in mediating ischaemic brain damage. Other studies have shown that dopamine increases ischaemia-induced cell damage (Hashimoto et al., 1994) and that brain extracellular levels of dopamine and serotonin are related to the severity of ischaemic insult (Richards et al., 1993a,b). It has been reported that pre-treatment with α-methyl-*para*-tyrosine attenuates ischaemia-induced dopamine release in gerbils (Brannan et al., 1987), other workers have demonstrated that rats treated with α-methyl-*para*-tyrosine show an 80% decrease in dopamine levels 6 h later and this protects striatal neuronal death induced by four-vessel occlusion (Marie et al., 1992). In addition to this it has been demonstrated that dopamine depletion produced by 6-hydroxydopamine protects striatal neurones from ischaemia-induced cell death (Clemens and Phebus, 1988).

In the present study pergolide provided good neuroprotection and produced no effect on rectal temperature indicating that the protection observed was probably not due to hypothermia. There are several possible explanations for the neuroprotection: (1) pergolide activates the dopamine autoreceptor and therefore inhibits dopamine synthesis in striatal synaptosomes (Tissari and Lillgäls, 1993). It is possible that pergolide downregulates dopamine receptors allowing much less dopamine release during ischaemia (2) pergolide and deprenyl induce CuZn superoxide dismutase activity in vivo (Glover et al., 1993). Further studies by Clow et al. (1993) demonstrated that low doses of pergolide (0.04 mg/kg i.p.) induce CuZn superoxide dismutase in the rat striatum. This may also explain the neuroprotective effects observed with pergolide in 6-hydroxydopamine lesioned animals (Asanuma et al., 1995). Further support for the importance of superoxide dismutase in cerebral ischaemia comes for studies that indicate that recombinant human superoxide dismutase (Tagaya et al., 1992) and polyamine-modified superoxide dismutase (Wengenack et al., 1997) are neuroprotective in global cerebral ischaemia and that mice overexpressing CuZn superoxide dismutase have smaller infarct volumes after focal ischaemia (Chan et al., 1994), (3) pergolide can scavenge nitric oxide radicals (Nishibayashi et al., 1996). It is know that high concentrations of nitric oxide are toxic and nitric oxide synthase inhibitors are neuroprotective in global (O'Neill et al., 1996, 1997) and focal (Buisson et al., 1993; Yoshida et al., 1994) cerebral ischaemia, (4) pergolide has anti-inflammatory effects (Bendele et al., 1991) and (5) a combination of the above effects.

We failed to see any protective effect with the 0.5 mg/kg dose of bromocriptine, however the 1 mg/kg dose provided some neuroprotection without any effect on temperature. This is in agreement with a study by Liu et al. (1995), reporting that bromocriptine protects against hippocampal damage in the gerbil. The authors reported that doses as low as 0.3 mg/kg provided significant neuroprotection against 3 min of occlusion. However, as expected 3 min of occlusion is less severe (our results indicate that 3 min of occlusion produce 60–70% loss in CA1 neurones, whereas 5 min produce 95% loss in CA1 neurones) and the number of viable cells/mm CA1 hippocampus was much higher than observed with the 5 min period of occlusion in the present study, which would explain that we needed a dose of 1 mg/kg to see neuroprotection. These authors also suggested that the mechanism of neuroprotection may be related to the preservation of superoxide dismutase (Liu et al., 1995). Other recent studies indicate that bromocriptine is a free radical scavenger in vitro (Yoshikawa, 1993; Yoshikawa et al., 1994) and protects against 3-acetylpyridine-induced neurodegeneration in vivo (Sethy et al., 1997).

Lisuride also provided good neuroprotection at the higher dose, but this dose also caused a significant drop in rectal temperature. The lower dose failed to provide any neuroprotection in the model. Previous studies have reported that chronic treatment with lisuride prevents ischaemia-induced changes in dopamine and dopamine metabolites in the gerbil brain (Hirata et al., 1992). More recent studies have reported that lisuride attenuates behavioural deficits and histological damage (Caldwell et al., 1996) and attenuates the increase in extracellular dopamine induced by transient global cerebral ischaemia in the rat (Caldwell et al., 1997). It has been suggested that low doses of lisuride act preferentially at the auto receptor and inhibit dopamine synthesis, while higher doses activate post-synaptic receptors (Nisoli et al., 1993). It is also known that lisuride has is a 5-HT_{1A} receptor agonist and it has been reported that 5-HT_{1A} receptor agonists are neuroprotective in rodent models of cerebral ischaemia (Prehn et al., 1991, 1993). In the present study lisuride produced a significant drop in rectal temperature at the neuroprotective dose and several studies have indicated that hypother-

mia is neuroprotective in several models of cerebral ischaemia (Green et al., 1992; Xue et al., 1992). However, in the present studies we also saw hypothermia at the lower dose which failed to provide neuroprotection. Although the amount of hypothermia observed with either dose of lisuride was small, we cannot rule out that this may account for the observed neuroprotection.

Recently, it has been suggested that when dopamine receptors are occupied by agonists the activity of the neurons will be decreased by a feedback mechanism (decreasing release and uptake of dopamine), thereby providing less dopamine for oxidation by monoamine oxidase and decreasing the amount of hydroxyl radical production (Mizuno et al., 1994). It is also interesting to note that pergolide induces CuZn superoxide dismutase activity at lower doses than bromocriptine and that 50% inhibitory concentrations against nitric oxide generation are 23 and 250 μM for pergolide and bromocriptine, respectively. It is of interest to note that the neuroprotection with pergolide is greater than that observed with bromocriptine and this is in agreement with clinical treatment of Parkinson's in which higher doses of bromocriptine are used. However, the half life of pergolide is also much longer and this may account for differences in neuroprotection.

In contrast, the dopamine D_2 receptor antagonist haloperidol failed to provide any neuroprotection in the model. Haloperidol is a typical antipsychotic that has been shown to attenuate MK-801 and phencyclidine (PCP) induced behavioural effects in mice. The dopamine D_1 receptor agonist SKF 38393 and the dopamine D_1 receptor antagonist SCH 23390 failed to provide any neuroprotection against the ischaemia-induced neurodegeneration. The present results suggest that dopamine D_2 receptor agonists can attenuate hippocampal damage produced by global cerebral ischaemia.

We are currently carrying out further research with dopamine D_2 receptor agonists in a rat four-vessel occlusion model, and are using intracerebral microdialysis to monitor extracellular neurotransmitter levels following ischaemia. Our preliminary results indicate that lisuride decreases dopamine release and prevents learning and memory impairment induced by 4 vessel occlusion in the rat (Caldwell et al., 1997). In future experiments we intend to examine the effects of dopamine D_2 receptor agonists on ischaemia-induced striatal damage in rats and gerbils. Recent studies have shown that longer periods (10 min) of bilateral carotid artery occlusion in the gerbil produces striatal damage that is attenuated by pre-treatment with D_2/D_3 agonist pramipexole (Hall et al., 1996). It would also be valuable to examine the effects of post-administration of these compounds on ischaemia-induced neuronal damage in gerbils and this may help elucidate the mechanism by which these compounds provide neuroprotection. In conclusion, it is clear that dopamine receptors play a role in cerebral ischaemia and that dopamine D_2 receptor agonists may be useful as neuroprotective agents.

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