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Abstract

A non-selective antihistamine, dimebon, has recently emerged as a potential treatment for Alzheimer's disease and Huntington's disease. Dimebon exerts several effects in addition to its anti-histaminergic effect, and of particular interest is its ability to enhance cognitive function in several models. The mechanism underlying this is unknown though it has been suggested that it may be associated with its anti-cholinergic action. Dimebon has also been reported to be neuroprotective, perhaps as a result of its ability to stabilize mitochondria. We considered that these effects might impact on the well-described age-related impairment in spatial learning and therefore examined the effect of repeated administration of dimebon on performance of young and aged animals in the Morris water maze. Whereas a clear age-related deficit was observed, dimebon failed to exert any effect on performance. Similarly, dimebon exerted no effect on the age-related increase in hippocampal expression of several markers of microglial and astroglial activation. We conclude that, despite its cognitive enhancing effects in some models, dimebon failed to modulate the deficit in spatial learning in aged rats and the evidence suggests that the drug does not possess anti-inflammatory properties.

Keywords (separated by '-')	Age - Dimebon - Microglia - Astrocytes - Spatial learning - Hippocampus
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ORIGINAL PAPER

The Age-related Gliosis and Accompanying Deficit in Spatial Learning are Unaffected by Dimebon

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Abstract A non-selective antihistamine, dimebon, has recently emerged as a potential treatment for Alzheimer's disease and Huntington's disease. Dimebon exerts several effects in addition to its anti-histaminergic effect, and of particular interest is its ability to enhance cognitive function in several models. The mechanism underlying this is unknown though it has been suggested that it may be associated with its anti-cholinergic action. Dimebon has also been reported to be neuroprotective, perhaps as a result of its ability to stabilize mitochondria. We considered that these effects might impact on the well-described age-related impairment in spatial learning and therefore examined the effect of repeated administration of dimebon on performance of young and aged animals in the Morris water maze. Whereas a clear age-related deficit was observed, dimebon failed to exert any effect on performance. Similarly, dimebon exerted no effect on the age-related increase in hippocampal expression of several markers of microglial and astroglial activation. We conclude that, despite its cognitive enhancing effects in some models, dimebon failed to modulate the deficit in spatial learning in aged rats and the evidence suggests that the drug does not possess anti-inflammatory properties.

Keywords Age · Dimebon · Microglia · Astrocytes · Spatial learning · Hippocampus

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Introduction

Dimebon is a non-selective anti-histamine agent which was originally used for the treatment of allergies in Russia where it was developed. However in 2001, it was reported to rescue cultured neurons from the neurotoxic effects of amyloid-beta (Aβ) [1] and, in a rat model of AD, where cholinergic transmission is depleted by the neurotoxin AF64A, a single injection of dimebon improves learning in an active avoidance task [18]. The neuroprotective effects may derive from its ability to stabilize mitochondria and therefore attenuate the damaging effects of Aβ or MPP^+ in neurons [3]; it also blocks voltage-gated calcium channels and has non-selective cholinesterase activity [31].

Dimebon has been shown to improve performance in active avoidance tests in animals treated with AF64A [1]; one proposal is that short-term memory improvements may result from its antagonist effects on 5-HT_6 receptors [23], although it also inhibits activation of 5-HT_{2c} and 5-HT_{5A}, as well as HT_6 receptors [31]. Its ability to antagonize histamine, H_1 and H_2, receptors and α-adrenergic receptors has been demonstrated [31] as has its inhibitory effect on NMDA receptors [31]; the latter may be a consequence of an action on the polyamine site of the NMDA-receptor located in the NR2B subunit, which is also a target for histamine [14]. Consistent with these findings, dimebon attenuates NMDA-induced seizures [1].

Results from a phase II clinical trial has revealed beneficial effects of dimebon in patients with Alzheimer's disease (AD) and Huntington's disease (HD). However despite the optimism with which dimebon was initially greeted [9], the results of a recent multinational phase 3 trial failed to identify any significant improvement in dimebon-treated patients with mild to moderate Alzheimer's disease, compared with the placebo group [16, 22].

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Despite this, further phase III trials for both AD and HD are underway.

Because of its ability to act as a cognitive enhancing agent, we considered that dimebon may attenuate the age-related decrease in spatial learning [6]. The evidence indicates that at least one factor which contributes to the deficit in spatial learning is the neuroinflammation which has been shown consistently in the hippocampus of aged animals [6]. Therefore we set out to examine the effect of treating aged and young rats with dimebon for 7 days and to evaluate any potential effect on the well-described age-related glial activation [19]. The data indicate that dimebon failed to modulate the age-related deficit in learning in the Morris water maze, and the age-related increase in expression of markers of activation of microglia and astrocytes.

Methods

Young (3 months; 200–360 g) and aged (20–22 months; 550–800 g) male Wistar rats (Bantham and Kingham, UK) were injected daily i.p with dimebon (1 mg/kg) or vehicle (1 ml/kg; 0.9 % NaCl) starting 2 days before and for the duration of training in the Morris water maze. The water maze regime consisted of 8 trials on day 1 and 6 trials/day for 5 days (maximum trial length 60 s; 15 s on the platform) as described previously [17]. Rats were led to the hidden platform if they failed to find it after 60 s.

On the last day of behavioural analysis, rats were anaesthetised by intraperitoneal injection of urethane (ethyl carbamate: 1.5 g/kg) and killed by decapitation. The brain was rapidly removed and a sagittal portion proximal to the midline was used to prepare cryostat sections (10 μm) for analysis of GFAP and CD11b immunoreactivity [7]. To visualize CD11b by light microscopy, sections were fixed in ice-cold methanol, blocked in 10 % normal horse serum (in Tris-buffered saline (TBS); pH 7.5, containing 4 % w/v bovine serum albumin (BSA; Sigma, UK) for 30 min, incubated overnight at 4 °C with CD11b antibody (1:200 in 2 % w/v BSA/TBS), washed and incubated for 2 h in biotin-conjugated secondary antibody (horse anti-mouse antibody; 1/200 in 2 % w/v BSA/TBS; Vector, UK). Endogenous peroxidases were blocked by incubation in the presence of 0.3 % hydrogen peroxide/TBS for 15 min. Sections were incubated in a pre-made avidin:biotinylated enzyme complex, diaminobenzidine solution (Vector, UK) for 10 min then rinsed, counterstained with haematoxylin (RA Lamb, UK), rinsed again, dehydrated through a series of graded alcohols and cleared by immersion in Xylene (Sigma, UK). Coverslips were mounted using DPX (RA Lamb, UK) and examined by light microscopy. To assess GFAP, sections were permeabilized with 0.1 % Triton X-100™ (Sigma-Aldrich, Ireland) in PHEM buffer (60 mM PIPES, 25 mM HEPES, 10 mM EGTA, 2 mM $MgCl_2$; Sigma-Aldrich, Ireland), washed with PHEM buffer, fixed in ice-cold methanol, washed and blocked for 2 h at room temperature in 10 % goat serum/4 % BSA in PHEM. The polyclonal rabbit anti-GFAP (1:1,500; Dako Diagnostics, Ireland) were prepared in blocking buffer and incubated overnight at 4 °C; anti-IgG was used as a negative control. Sections were washed and incubated with Alexa488 secondary antibody (1:4,000 goat anti-rabbit IgG; Invitrogen, UK), washed and mounted (Vectashield® with Dapi, Vector, UK). Sections were viewed with a Zeiss 510 Meta confocal laser microscope at ×40 magnification. Dapi staining of nuclei was visualized using the 543 nm helium neon laser.

The contralateral hippocampus was flash-frozen in liquid nitrogen for analysis of mRNA by Q-PCR [7]. The assay IDs for the genes examined were as follows: CD11b (Rn00709342_m1), CD68 (Rn01495631_m1), MHC II (Rn01768597_m1), GFAP (Rn00566603_m1), S100β (Rn00566139_m1) and RANTES (Rn00579590_m1).

All data were analysed by 2-way ANOVA with age and dimebon treatment as factors, except where indicated.

Results

We assessed the escape latency as a measure of spatial learning and found that aged rats took significantly longer to find the hidden platform in the water maze than young animals ($^{**}p < 0.01$; young vs. aged rats; days 4 and 5; ANOVA; Fig. 1a). Dimebon exerted no effect on the mean escape latency in either young or aged rats. The distance swam and the swim speed did not vary with age or dimebon treatment (Fig. 1b, c).

We evaluated microglial activation by evaluating CD11b immunoreactivity and mRNA expression of CD11b, MHCII and CD68. Immunoreactivity of CD11b was increased in hippocampus of aged, compared with young, rats (Fig. 2a); dimebon did not ameliorate that age-related increase in CD11b. CD11b mRNA expression was significantly increased in hippocampus of aged, compared with young, rats ($^{***}p < 0.001$; ANOVA; Fig. 2b) but dimebon exerted no effect in either young or aged animals. In addition to the changes in CD11b expression with age, the data showed that there was a significant age-related increase in CD68 mRNA ($^{***}p < 0.001$; ANOVA; Fig. 3b). There was a significant interactive effect of age and dimebon treatment on MHCII mRNA expression ($^{\dagger}p < 0.05$; ANOVA; Fig. 3b).

These data indicate that there was an age-related increase in microglial activation but an age-related increase in astrogliosis has also been reported [6]. Here we demonstrate that GFAP fluorescence was markedly increased in sections of hippocampus prepared from aged, compared

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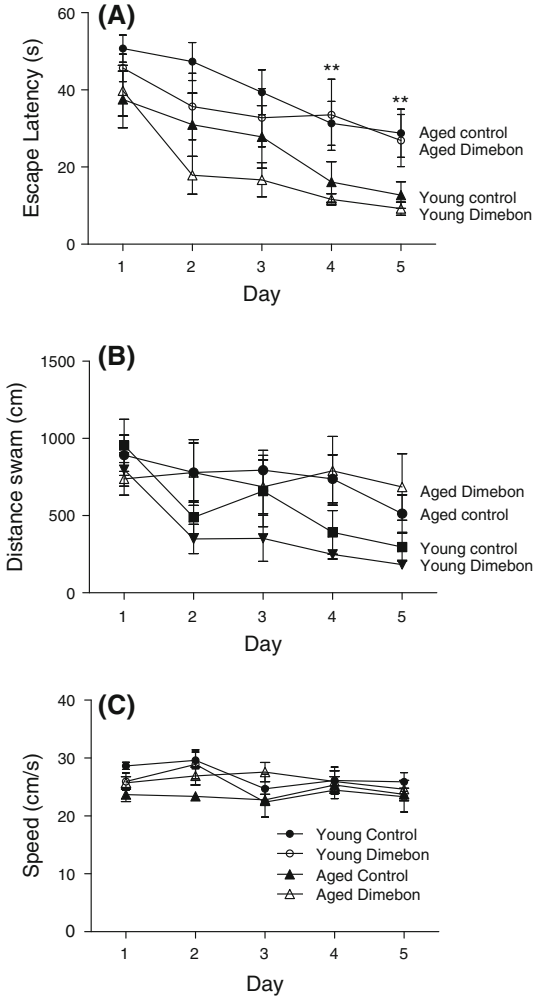

Fig. 1 The age-related deficit in spatial learning is unaffected by dimebon. **a** Aged rats took significantly longer than young rats to find the hidden platform on days 4 and 5 (**$p < 0.01$; ANOVA); dimebon had no effect. **b**, **c** There was no significant difference in the distance swam or swim speed between young and aged, control- or drug-treated groups

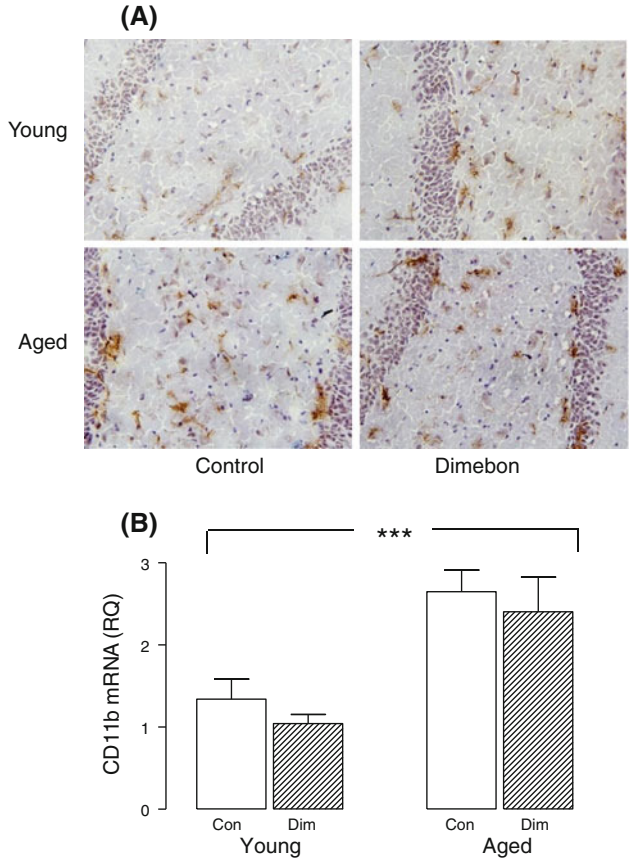

Fig. 2 Microgliosis in aged rats is not alleviated by dimebon **a** CD11b immunoreactivity was markedly increased in hippocampus of aged, compared with young, rats and dimebon failed to attenuate this change in aged animals. **b** CD11b mRNA was significantly increased in hippocampus of aged, compared with young, rats (***$p < 0.001$; ANOVA) but no treatment-related changes were observed

with young, rats (Fig. 4a) but treatment of aged rats with dimebon failed to attenuate this change; measurement of relative fluorescence intensity indicated a significant age-related increase (*$p < 0.05$; ANOVA; Fig. 4b) that was not affected by dimebon. Expression of GFAP, RANTES and S100β mRNA was significantly increased in hippocampal tissue prepared from aged, compared with young, rats (*$p < 0.05$; **$p < 0.01$; ANOVA; Fig. 5a, b, c). Analysis of GFAP mRNA expression revealed a significant interaction of age and dimebon ($^{\dagger\dagger}p < 0.01$; ANOVA) and a comparison of the data obtained from aged animals alone, indicated that GFAP mRNA was significantly reduced in tissue prepared from dimebon-treated, compared with control-treated, rats ($^{++}p < 0.01$, student's t test for independent means).

Discussion

Dimebon has been reported to enhance memory in a mouse model of senescence [13] and improve learning after a single dose in rats with a cholinergic model of AD [18]. We set out to assess whether it might also ameliorate the deficit in spatial learning in aged rats. The data indicated that it failed to modulate the age-related deficit in behaviour in the Morris water maze and we also demonstrate that dimebon exerted minimal effects on markers of glial activation in the hippocampus of aged rats.

The present observation that performance of aged animals in the Morris water maze was significantly worse than young animals supports the findings of several earlier studies. Thus an age-related deterioration in cognitive function and a particular deficit in hippocampal-dependent tasks has been consistently reported [4, 17, 21, 26, 29]. The significant finding here is that dimebon failed to exert any effect on performance, despite previous evidence of its cognitive enhancing effects in other models [1]. It has also

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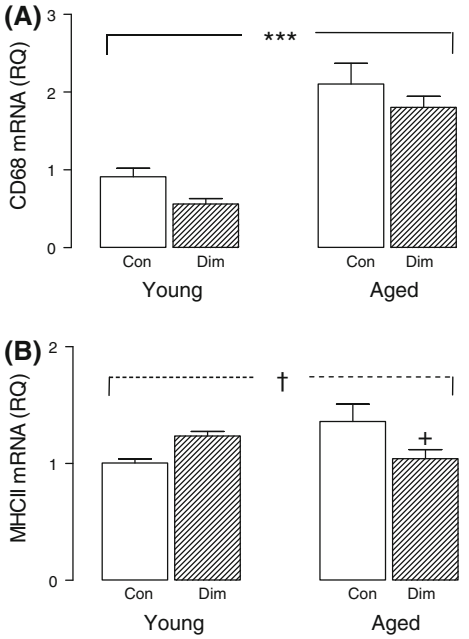

Fig. 3 Dimebon fails to modulate the age-related increases in expression of CD68 or CD68 mRNA. **a** CD68 mRNA was significantly increased in hippocampus of aged, compared with young, rats (***$p < 0.001$; ANOVA); no effect of dimebon was observed. **b** A significant interaction of age and dimebon was observed for MHCII mRNA ($^{\dagger}p < 0.05$; ANOVA)

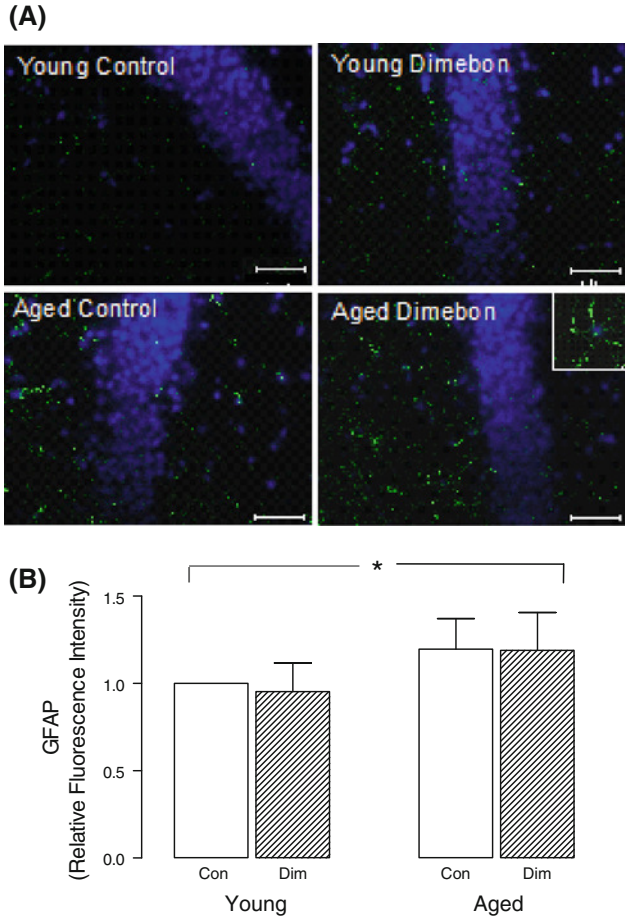

Fig. 4 Astrogliosis in aged rats is not alleviated by dimebon. GFAP immunoreactivity **a** was increased with age; measurement of relative fluorescence intensity **b** indicated a significant age-related increase (*$p < 0.05$; ANOVA) that was not affected by dimebon

been reported that a single dose of dimebolin improves performance of both adult and aged monkeys in a delayed matching-to-sample test [30], and cognition in a novel object recognition task in rats [11] whereas intraperitoneal administration with dimebon for 5 days improved learning in the Y maze in rats [27]. However no mechanism of action was identified in these studies.

Neuroinflammatory changes, with accompany upregulation of markers of microglial and astroglial activation, are characteristic of age [5, 7, 8]. These changes have been associated with a deficit in synaptic plasticity as revealed by the impairment in long-term potentiation [5, 8]. The present data indicate that the deficit in spatial learning was accompanied by age-related increases in microglial activation as indicated by upregulation of CD11b, MHCII and CD68 but treatment of aged animals with dimebon failed to attenuate any of these age-related changes. Dimebon is a non-selective anti-histaminergic agent and in this context it is interesting that injection of histamine into the substantia nigra triggers microglial activation [28]. Data from a recent in vitro study, suggest that histamine-induced microglial activation (specifically migration) was dependent on H4 receptor activation, though histamine was also able to inhibit LPS-induced microglial activation [10]. Significantly, in parallel with the well-described increase in microglial activation with age, an age-related increase in histamine receptor expression [25] has been reported and, perhaps predictably, an age-related increase in the cataleptogenic effect of histamine has also been described [15].

Despite the lack of effect of dimebon on age-related changes, it has been reported to improve learning and decrease Aβ accumulation in a mouse model of AD, perhaps as a consequence of its ability to enhance autophagy [24]. However it has also been proposed that the beneficial actions of dimebon may be attributed to its ability to block the opening of the mitochondrial permeability transition pore [20] or to its calcium-stabilizing effects [31].

In addition to the age-related changes in microglia described here, markers of astrocytic activation, RANTES, GFAP and S100β, were also upregulated in hippocampus of aged animals. Treatment of aged rats with dimebon failed to modulate these changes, though a modest decrease in GFAP mRNA was observed in hippocampus of aged dimebon-treated, compared with aged control-treated, rats. It should be noted that dimebon has been reported to decrease astrogliosis in a transgenic mouse model in which γ-synuclein was overexpressed [2]. Thus these data link glial activation

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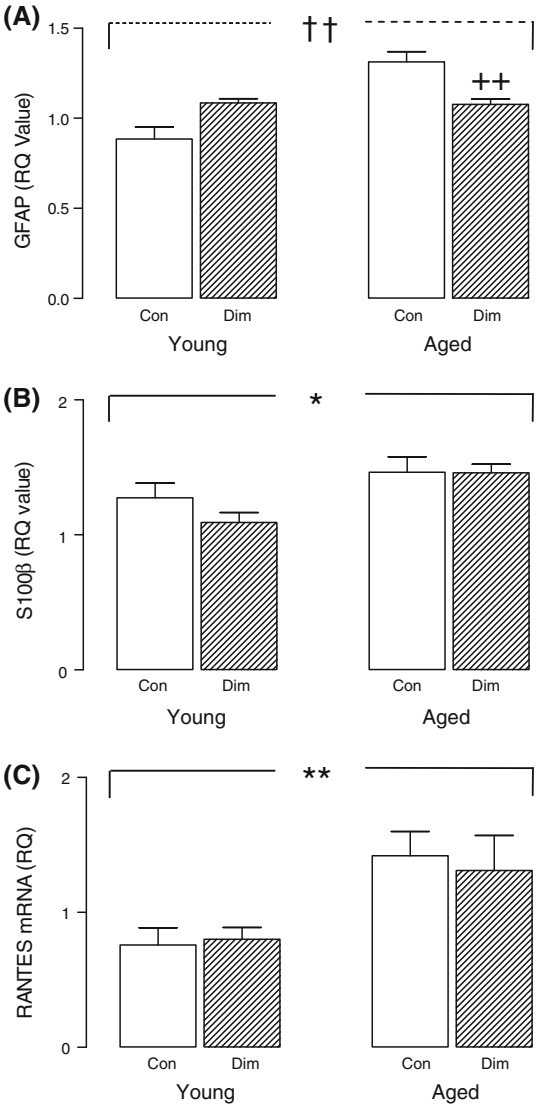

Fig. 5 Dimebon exerts a modest effect on the age-related increase in GFAP mRNA but no effect on the age-related increases RANTES mRNA or S100β mRNA. **a** GFAP mRNA shows a significant interaction of age and dimebon ($^{\dagger\dagger}p < 0.01$; ANOVA). Dimebon attenuated this age-related increase when assessed by a student's t test ($^{++}p < 0.01$; student's t test for independent means). **b**, **c** mRNA expression of RANTES **b** and S100β **c** was significantly increased in hippocampal tissue prepared from aged, compared with young, rats ($^{*}p < 0.05$, $^{**}p < 0.01$; ANOVA); dimebon exerted no effects on these age-related changes

with impaired spatial learning supporting earlier findings [12, 17]. However, this link is not universally accepted. For example, a recent study reported that, although an age-related change in glial activation was evident in 3 subregions of the hippocampus, there was no evidence of a difference in activation between cognitively-intact and cognitively-impaired aged animals, stratified according to their performance in the Morris water maze [26].

We conclude that dimebon does not affect glial activation suggesting that it is unlikely to possess anti-inflammatory effects, at least in hippocampus of aged rats, and that it fails to modulate the age-related impairment in spatial learning in the Morris water maze.

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