T2 relaxation time is decreased in hippocampus of aged rats: analysis of the effect of the peroxisome proliferator-activated receptor γ agonist rosiglitazone

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Introduction: Rosiglitazone is a selective ligand of peroxisome proliferator-activated receptor γ (PPARγ) widely used in the treatment of diabetes mellitus (Avandia, GlaxoSmithKline). It has also been shown to have an anti-inflammatory effect in the brain, decreasing concentrations of interleukin-1β in hippocampus and restoring the age-related deficits in long-term potentiation (LTP), a putative model of learning and memory. It has also been found to attenuate learning and memory deficits in a mouse model of Alzheimer's disease (1). It is therefore of interest to investigate its effect on areas of the brain intimately involved in memory formation, such as the hippocampus. Relaxometry measurements were chosen as there have been recent reports in the literature linking T1 and T2 relaxation times to astrocytic activation (2) and microglial activation (3) respectively.

Methods: Groups of male Wistar rats aged 3 and 18 months (n=5-6 per group) were pre-treated for 56 days, either with 3mg/day p.o. rosiglitazone maleate or with vehicle only. The animals were anaesthetised with isofluorane and MR images were obtained using a 7 Tesla spectrometer (Bruker BioSpin) using purpose-built transmit and receive coils. Images of the coronal slice of interest were acquired using a fast imaging with steady-state precession (FISP) protocol (4) with TE=1.5ms TR=3ms, 180^0 phase advance, matrix 128x128, resolution 0.23x0.23x1.6mm, acquisition time 5 min. From this, T2 relaxation time maps were generated using an in-built macro in ParaVision software (Bruker). Slices were selected to give optimal regions of interest in the dorsal hippocampus (Fig. 1). The animal was positioned so the appropriate slice was in the isocentre of the magnet, to minimize image artifacts.
Additionally, groups (n=6) of untreated young (3 months), middle aged (14 months) and aged (18-20 months) Wistar rats were scanned using the same FISP protocol, and also using an echo-train multi-slice multi-echo (MSME) sequence with TE=8ms TR=2s, matrix 128x128, resolution 0.23x0.23x1.6mm, 5 slices, 12 echoes. T2 maps were generated from the signal decay curve using a script written in IDL language (ITTVIS). Data were analysed using IDL and ImageJ software.
One- or two-way analyses of variance (ANOVA) with Fischers post-test or Tukey post-test were used to statistically assess the data.

Results: T2 relaxation times in hippocampus and cortex, as measured by FISP (Fig. 2) and MSME (Figs. 3 & 4), were significantly decreased with age (*p < 0.05; **p < 0.01); no significant changes were observed in thalamus or corpus callosum. Rosiglitazone increased T2 relaxation time in hippocampus of aged, but not young rats (*p < 0.05; Fig. 5). T2 times were systematically overestimated when measured by FISP compared with MSME, as previously suggested (4).

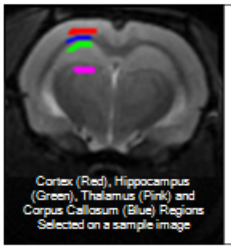


Fig. 1: Regions of Interest

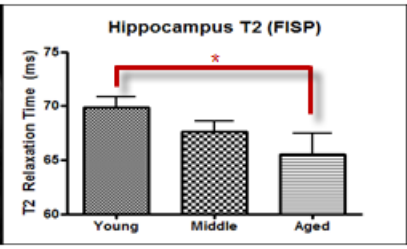


Fig. 2: T2 times for hippocampus by FISP method

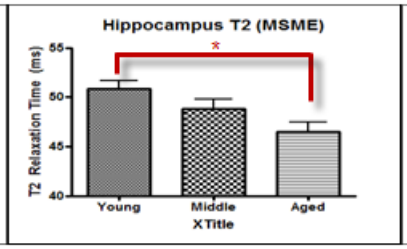


Fig. 3: T2 times for hippocampus by MSME method

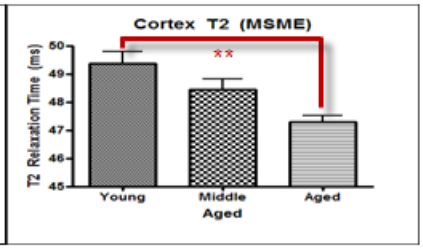
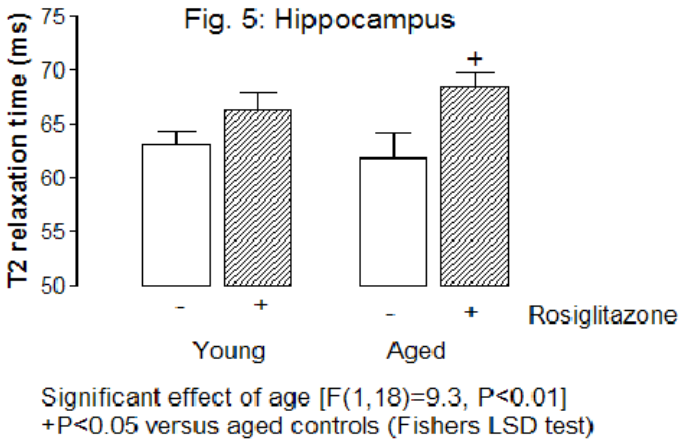


Fig. 4: T2 times for cortex by MSME method



Discussion: The data demonstrate an age-related decrease in T2 relaxation time in hippocampus and cortex; this correlates with an increase in microglial activation (data not shown). We also report that treatment of aged rats with rosiglitazone increases T2 relaxation time in hippocampus. Consistent with the present findings, previous research (5) failed to show a significant decrease in T2 relaxation time between 3- and 12-month old rats, indicating that changes occur later in life, where chronic neuroinflammation is a feature.

References: (1)Pedersen *et al.* 2006 Exp Neurol **199**(2):265-7. (2)Sibson *et al.* 2008 J Cereb Bl Fl Metab **28**(3):653-63. (3)Justicia *et al.* 2008 Stroke **39**:1541-7. (4)Schmitt *et al.* 2004 Magn Res Med **51**:661-7. (5) Heiland *et al.* 2002 Neurosci Lett **334**:157-160.