Preliminary Evidence of Midazolam Effect in Brain Microstructure using Diffusional Kurtosis Imaging

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TARGET AUDIENCE: For those interested in diffusion MRI and the effect of sedatives in the brain

PURPOSE: Benzodiazepines (BZD) are widely prescribed among older adults, often for anxiety, depression and insomnia[1]. Also, in patients in the intensive care unit (ICU) who needs to undergo certain procedures (such as intubation, CT or MRI scans) moderate sedation is required[2]. Midazolam (MDZ) is the most commonly used BZD premedication for sedation and in the intensive care unit (ICU) because of its short elimination half-life, combined with its water solubility and its suitability for continuous infusion[2]. However, the mechanisms of a possible MDZ neuroprotection[3] or neurotoxicity[4] effects on brain microenvironment are not fully understood. This study investigates if short-term MDZ administration in middle-aged rodents causes changes in the cerebral microenvironment as defined by diffusional kurtosis imaging (DKI) measures[5].

METHODS: Twelve, 9-11 months old Fischer 344 rats (normal control; n=6) and (exposed to MDZ; n=6) were studied. MDZ dose (1mg/kg, ip, twice a day) 2 days before undergoing diffusion MRI was chosen to mimic a clinical model of anxiolysis. DKI experiments were performed using a 7 Tesla Bruker scanner. A two shot spin-echo echo planar imaging (EPI) diffusion sequence with 30 diffusional directions, 2 excitations and 4 b-values (0, 650, 1300, 2000 s/mm2) were used. Other imaging parameters: repetition time/echo time = 4750/32.5 ms, field-of-view = 30 × 30 mm2, image resolution = 0.23 x 0.23 x 1.00 mm3, acquisition time ≈ 31 minutes. All diffusion metrics were derived from one DKI data set using Diffusional Kurtosis Estimator (DKE)[6]. Region-of-interests (ROIs) were manually drawn in the cortex, striatum, thalamus and hippocampus using ImageJ. Unpaired student's t-test was performed to compare the means of the groups for all the metrics. Following MRI, all animals underwent cognitive testing over 12 days in a water radial arm maze, which measures spatial and working reference memory. Postmortem hippocampal tissue was collected to assess changes in mitochondria-related protein expression (VDAC1 and VDAC2).

RESULTS: In the MDZ-treated rats we detected DK metrics increase in the cortex ($K_{//}$; *p= 0.02*), striatum (MK; *p=0.04*), thalamus (MK, $K_{//}$, $K_{\perp}$; *p=0.001*-(Fig.1)), and ventral hippocampus ($K_{//}$; p=0.001-(Fig.2C)). These rats presented with changes in working memory (Fig. 2A) and elevated mitochondria-related protein expression (VDAC2) in the hippocampus (Fig. 2B).

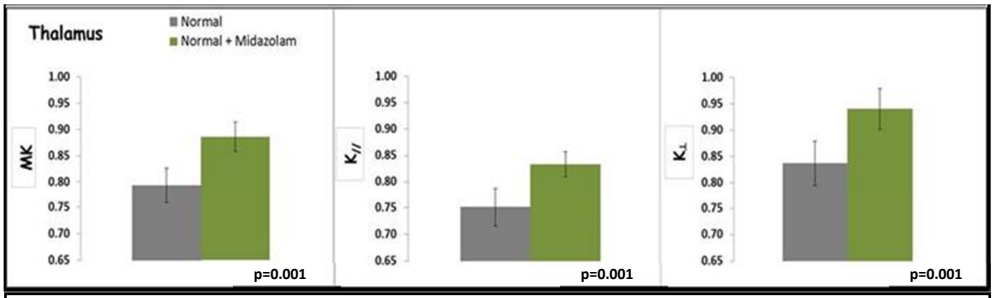
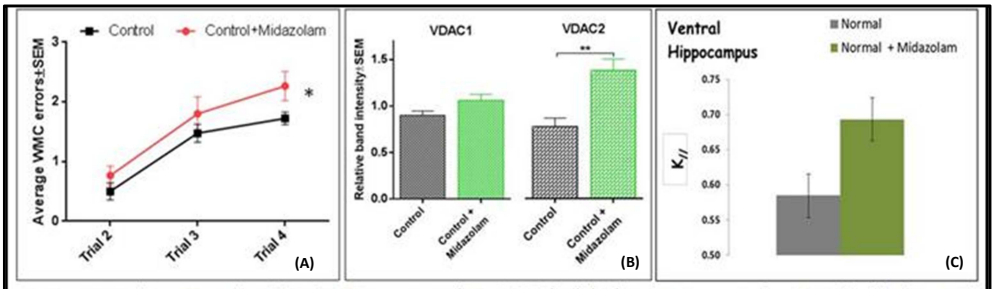


Figure 1: Thalamus: DK metrics showing changes between the control group (grey) and midazolan group (green); mean kurtosis (MK); axial kurtosis ($K_{//}$); radial kurtosis ($K_{\perp}$).

DISCUSSION & CONCLUSION: We have detected changes in the cerebral microenvironment of the cortex, striatum, thalamus and hippocampus of middle-aged rats exposed to MDZ. The overall increase in kurtosis metrics may be related to the increase in mitochondrial membrane permeability, mitochondrial swelling and axonal and synapse degeneration due to the exposure to MDZ[7]. It is not clear if the increase in DK metrics reflects a deleterious effect in the brain, but based on the fact that the increase of $K_{//}$ in the hippocampus was accompanied by negative behavior changes, it is most likely that the MDZ is also causing a negative effect on the brain morphology.



Rats exposed to MDZ had higher incidence of working memory errors due to impaired spatial memory, compared to control. WM (working memory); 2-way ANOVA followed by Bonferroni comparisons; statistically significant * (p<0.015).

Rats exposed to MDZ had higher mitochondria-related protein VDAC1 and VDAC 2 expression, statistically significant for VDAC2 (p<0.03) using unpaired Student's t-test.

Rats exposed to MDZ had higher axial kurtosis (K//) in the ventral hippocampus; statistically significant using unpaired Student's t-test p = 0.001.

Figure 2

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