

Unique Thalamic Perfusion Abnormalities in Painful but not Painless Diabetic Peripheral Neuropathy.

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Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes with significant health and economic consequences. Chronic painful DPN is a serious condition that impacts on an individual's quality of life, limiting productivity and often leads to depression. Unfortunately currently available treatments lack efficacy and their use limited by unwanted side effects. A better understanding of the pathogenesis of painful DPN may aid the development of new therapies. DPN is not restricted to peripheral nerves but also affects the central nervous system. MRS has shown that thalamic sensory neuronal dysfunction occurs in painless but not painful DPN, suggesting that preservation of neuronal function maybe a prerequisite for the perception of pain. Although the pathogenesis remains unknown, it is likely that both vascular and metabolic aetiological factors are involved. This study tests the hypothesis that DPN is associated with thalamic perfusion abnormalities.

Methods

Eighteen right-handed, male subjects with type 1 diabetes (No-DPN = 6, Painful DPN = 5, Painless DPN = 7) and 5 healthy volunteers (HV) underwent detail clinical and neurophysiological assessments to grade DPN. Painful symptoms were graded using standard questionnaires.

MR perfusion imaging

MR examinations were performed on a 1.5T system (Eclipse, Philips Medical Systems, Cleveland, Ohio, USA). Parenchymal perfusion was assessed using a multi time point, single shot T2* weighted EPI sequence (TEeff = 60ms; TR = 1.4ms; acquisition matrix = 192 x 188, zero filled prior to Fourier transformation to 256 x 256; FOV = 25cm). Twelve 5mm thick contiguous axial slices sampled the cerebrum every 1.4s for a total imaging time of 98s, yielding 70 time points. Exogenous perfusion contrast was provided by a 20ml bolus of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA, Magnevist, Schering AG, Germany) which was followed by a 20ml saline flush, administered intravenously using a power injector (Spectris, Medrad, Netherlands) at a rate of 5ml/s starting at the 10th imaging time point. For each scan episode, the timing of the signal change within used defined regions of interest (ROI) were obtained with respect to those defined by the signal time [ST(t)] course of a circular ROI placed within the proximal intracranial internal carotid artery. Haemodynamic anatomical ROI's were applied to outline eight regions to outline major intracranial vascular territories (ACA, MCA and PCA) and deep brain nuclei (thalamus and caudate nucleus) (Fig. 1). The caudate nucleus served as an internal control for group comparisons.

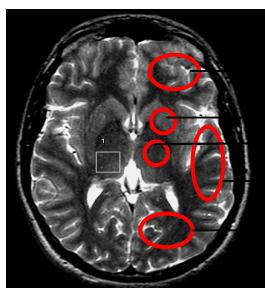


Figure 1: ROI

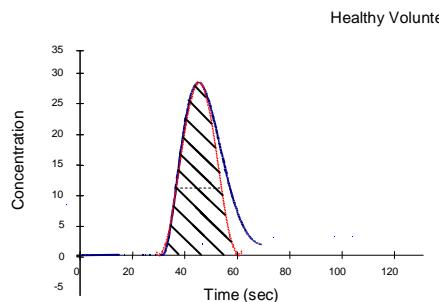


Figure 2 : Model A

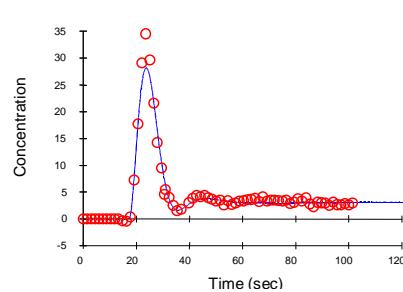


Figure 3: Model B

Data analysis

The concentration-time curve of the passage of gadolinium through our ROIs was analyses using two mathematical models (A and B).

Model A: $C(t) = -(k/TE_{eff}) \ln[S(t)/S(t=0)]$ (Fig. 2) This uses the standard dynamic susceptibility contrast (DSC) method to analyse the first pass bolus of Gd-DTPA. Using this model we compared the regional perfusion of the major cerebrovascular territories (MCA, ACA and PCA) between diabetic subjects and healthy volunteers. We then used this model to compare thalamic and caudate nucleus perfusion characteristics between No DPN, Painless DPN, Painful DPN and HV. Perfusion parameters assessed (ANOVA) included relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF) and first moment transit time (TT_{FM}).

Model B: Concentration Gd-DTPA = $A(1 - e^{-k_{el}(t-t_{lag})}) + C(e^{-k_{cos}(t-t_{lag})}) \times [1 - \cos((B(t-t_{lag}) + B2(t-t_{lag})))]$ (Fig. 3). Model B is based on the principles of pharmacokinetic mathematical modelling and consists of two components. The first, accounts for accumulation of gadolinium in the ROI that reaches a constant level after several peaks and the second represents the episodic concentration profile of Gd-DTPA until it becomes a smooth line. Seven biomarkers are used in this model which we propose are related to these variables: **A:** Combined effects of the size of the thalamus and the affinity of gadolinium to the tissue, K_{el} : the uptake rate of gadolinium, possibly determined by the ratio of organ size/affinity to its vascularity, **C:** the size of the initial pool for dilution of gadolinium in the body, K_{cos} : the rate of gadolinium mixing in the body, **B:** the constant for short circuiting and recirculation through the thalamus, **B2:** similar to B but in the absence of any short circuiting, t_{lag} : time it takes for the bolus to arrive at the thalamus. We used this model to further interrogate thalamic microcirculation in each of the three DPN subgroups and HV. Group comparison of the seven biomarkers was undertaken using ANCOVA with t_{lag} as a covariate in the analysis.

Results

In all three cerebrovascular territories, diabetic subjects had larger relative cerebral blood volume (rCBV) compared to HV [ACA mean (SD), 264.4(55.2) vs. 205.3(57.2), $p=0.05$; MCA 244.6(43.3) vs. 189.0(55.2), $p=0.03$; PCA 248.4(43.8) vs. 190.8(36.5), $p=0.01$]. Subjects with painful-DN had significantly higher thalamic rCBV (painful DN, 234.3(45.1), No-DN, 196.5(78.7), painless DN, 203.1(171.7); $p=0.045$) and the longest transit time (TT_{FM}). In contrast, subjects with painless DN had lowest thalamic relative cerebral blood flow (rCBF). There were no significant differences in caudate nucleus perfusion characteristics between study groups. Interrogating thalamic perfusion in more detail using Model B, we found a significant decrease in biomarker B2 in subjects with Painless DPN compared to Healthy Volunteers, No DPN and Painful DPN [Painless DPN 0.38(0.1), No DPN 0.42(0.2), Painful DPN 0.37(0.06) and HV 0.43(0.1); $p=0.04$]. There were no significant group differences in the other biomarkers assessed.

Discussion

Diabetic subjects had global increased rCBV in all major cerebral artery territories, suggesting impaired cerebral autoregulation with a persistent resting state vasodilation. Painful DPN is accompanied by increased thalamic relative blood volume and Painless DPN possessing the lowest relative thalamic blood flow, indicating greater microvascular impairment. This is supported by the significant decrease in biomarker B2 (Model B analysis), which represents recirculation of Gd-DTPA through the thalamus, in subjects with established DPN (Painful and Painless). In conclusion, we have demonstrated unique pathophysiological thalamic microvascular changes that may provide important clues to the pathogenesis of pain in diabetes.