The Impact of Ageing on [^{11}C]meta-Hydroxyephedrine Uptake in the Rat Heart

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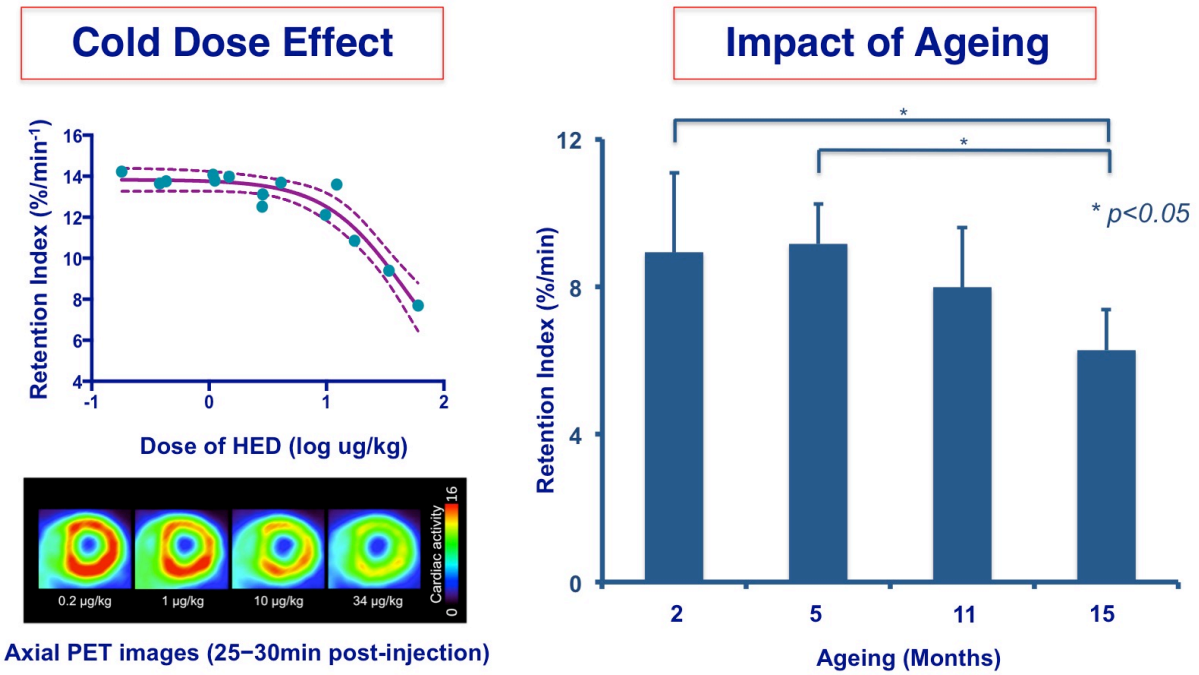
Objectives: An extensive body of evidence has reported on physiological age-related changes in autonomic nervous system function. The influence of ageing on myocardial sympathetic innervation remains to be fully understood. We aimed to elucidate the impact of physiological ageing on [^{11}C]meta-Hydroxyephedrine ([^{11}C]HED) uptake in the rat heart.

Methods: First, to confirm specific uptake via the neural norepinephrine transporter, the effect of specific activity on cardiac [^{11}C]HED uptake was evaluated: [^{11}C]HED was synthesized by N-methylation of (−)-metaraminol as the free base (radiochemical purity > 95%). [^{11}C]HED (48.7+/-9.7MBq, ranged 0.2–60.4µg/kg cold mass) was injected via tail vein in 14 healthy male Wistar Rats. Dynamic 23-frame PET images were obtained over 30 min. Time activity curves were generated for the blood input function and myocardial tissue. Cardiac [^{11}C]HED retention index (%/min) was calculated as myocardial tissue activity at 20-30 min divided by the integral of the blood activity curves. After confirming the specificity of [^{11}C]HED handling in the nerve terminal, the impact of ageing on myocardial [^{11}C]HED uptake was investigated longitudinally: PET studies at different ages (month (M) 2, 5, 11 and 15) were conducted by injecting of 55 MBq [^{11}C]HED (specific activity, 370–740 GBq/µmol) and the retention index (%/min) was assessed (n=7, respectively).

Results: [^{11}C]HED dynamic PET with different tracer specific activities showed rapid blood clearance and clear delineation of the myocardium in all animals. A dose-dependent reduction of cardiac [^{11}C]HED uptake was observed. The estimated retention index as a marker of norepinephrine function decreased at lower specific activity (higher amount of cold mass): Retention indices were 11.7, 11.7, 11.4, 11.7, 10.6, 10.9, 9.9, 8.8, 7.9 and 6.8 (%/min) for total injected cold masses (µg/kg) of 0.2, 0.4, 1, 1.5, 3, 4, 10, 17, 34 and 60, respectively. The EC50 value (95% CI) was 46.6 (32.3-67.1) µg/kg. This high affinity of [^{11}C]HED to the neural norepinephrine transporter triggered a subsequent study: In a longitudinal setting, the [^{11}C]HED retention index (%/min) decreased with increasing age (month 2: 8.9±2.1, M5:

9.2±1.09, M11: 7.9±1.64, M15: 6.3±1.1; M2 and M5 vs. M15, p<0.05, respectively).

Conclusions: We could observe specific uptake of [^{11}C]HED via the neural norepinephrine transport system in the rat heart. Second, the herein reported impact of physiological ageing on myocardial [^{11}C]HED uptake in rats is consistent with the generalized decrease of peripheral somatic nerve function in the ageing population.



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