Supplementary Online Content

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eAppendix. Further Details Regarding STRAW Criteria, Image Acquisition, and Additional Results

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Further Details Regarding STRAW Criteria, Image Acquisition, and Additional Results

Introduction

The STRAW consensus criteria[1] for perimenopause apply the criterion of menstrual cycle length greater than one week as a key measure of change for the onset. Secondary measures include variability of plasma FSH, elevation in plasma FSH and vasomotor symptoms. Perimenopause averages about 5 years in length, starting from meeting the cutoff for onset criteria to the end being the first year of cessation of the menstrual cycle. Based upon this definition, for 80% of perimenopause, menstrual cycles are present, albeit of longer duration, more variable duration, and sometimes with skipped cycles. Menopause (as applied in this study) may be defined as the second and subsequent years after cessation of the menstrual cycle.

Methods

Image Acquisition and Analysis. PET images were acquired using an HRRT PET camera (in-plane resolution; full width half maximum, 3.1mm; 207 axial sections of 1.2mm; Siemens Molecular Imaging, Knoxville, Tennessee, U.S.A.) as previously described.[2] The frames consisted of 15 frames of 1 minute followed by 15 frames of 5 minutes. [^{11}C] harmine doses were of high specific activity (mean: 2153.38 mCi/μmol, standard deviation 918.56 mCi/μmol and high radiochemical purity (mean: 99.2%, standard deviation: 1.22%). Our regions of interest are based upon the neuroanatomy atlas of Duvernoy[3]. For each region MAO-A V_T was measured. MAO-A V_T represents the total distribution volume of [^{11}C]harmine and it is an index of tissue binding at equilibrium, of which 85% is specific binding to MAO-A. Therefore, changes in MAO-A V_T may be interpreted as representing changes in [^{11}C]harmine binding to MAO-A. The V_T can be expressed in terms of kinetic rate parameters of a 2-tissue compartment model: $V_T = (K_1/k_2) \times (k_3/k_4) + (K_1/k_2)$, where K_1 and k_2 are the influx and efflux rate constants for radiotracer passage across the blood brain barrier and k_3 and k_4 describe the radioligand transfer between the free and nonspecific compartment and the specific binding compartment. K_1/K_2 is similar among different individuals.[2]

Measure of Crying. Crying was a psychological symptom of interest. One reason was that it is highly prevalent in healthy women in perimenopause. During perimenopause, report of crying spells which require some level of severity as compared to increased crying, occur at a substantial prevalence of 33%.[4,5] The second is greater MAO-A V_T has been previously associated with predisposition to cry after recent estrogen decline since, in early postpartum, at the time of postpartum blues, MAO-A V_T is highly elevated.[6] While mood severity was also of interest, we had screened out subjects based upon the Hamilton Depression Rating Scale score of 7, which ensured recruitment of healthy subjects but limited our assessment of the relationship of MAO-A V_T to MDE symptoms.

Results

As would be expected, since MAO-A V_T is correlated across different brain regions, elevation in MAO-A V_T in the other brain regions was correlated with tendency to cry at uncorrected significance in most regions (r=0.51 to 0.54, p=0.007 to 0.014) and trend level effect in the hippocampus and midbrain (r= 0.34 and 0.41 respectively). Other measures in the STRAW criteria such as presence of vasomotor symptoms (as measured by the "Vasomotor" subscale of Greene Climacteric Scale[7]) and plasma FSH level were not correlated with MAO-A V_T in the perimenopause age group (MANCOVA, vasomotor symptoms: $F_{(2,21)} = .689$, $P = .51$; FSH level: $F_{(2,20)} = .392$, $P = .68$).

Through our screening process, we excluded women with a Hamilton Depression Rating Scale score greater than 7, which creates some challenge in evaluating the relationship to mood symptoms. Interestingly, we observed, post-hoc, that 6/7 women (86%) in the upper quartile of MAO-A V_T (corresponding to a prefrontal cortex MAO-A V_T of greater than 29) reported at least one symptom on the HDRS whereas 5/19 women (26%) with lower MAO-A V_T reported at least one symptom. The proportion of women reporting at least one symptom was significantly greater in the subgroup with high MAO-A V_T (chi-squared test, X^2 (1, N = 26) = 7.39, p=0.007).

Discussion

The present study also has implications for monoamine metabolism across the lifespan in women. Since, MAO-A metabolizes monoamines and MAO-A levels correlate with MAO-A activity in health,[8,9] the present work implies that monoamines metabolized by MAO-A (such as serotonin, norepinephrine and dopamine)[10] follow a parallel course with lower metabolism in adulthood prior to age 40, greater metabolism during ages 41 to 50 and a lower metabolism during menopause, although not as low as during young age. The exception to this would be that monoamine metabolism by MAO-A may be elevated in early postpartum, when MAO-A V_T is also transiently elevated in health.[6]

It is interesting that estrogen levels are actually lower in postmenopause than perimenopause, yet MAO-A V_T was highest in perimenopause. The greatest evidence for the relationship between decline in estrogen and rise in MAO-A level, activity and mRNA is that the subsequent MAO-A effects occur shortly thereafter, and may have a variable level of persistence.[11-15] In such a model, repeated, strong, declines in estrogen, as observed during perimenopause would be expected to lead to more elevated MAO-A levels as compared to menopause, in which the stimulus of repeated, strong, declines in estrogen are no longer present.

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