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Aerobic Fitness and Cognitive Function in Midlife: An Association Mediated by Plasma Insulin

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Abstract

Insulin resistance in midlife increases the risk of dementia in late-life. In contrast, habitual aerobic exercise is an established strategy to ameliorate insulin resistance which may translate into better cognitive outcome.

Purpose—To determine the role of plasma insulin in mediating the relation between cardiorespiratory fitness and cognitive function.

Methods—Fifty-eight adults completed assessments of plasma insulin levels, maximal oxygen consumption (VO₂max), and neuropsychological test performance.

Results—Endurance-trained subjects demonstrated better cognitive outcome (total composite z-score: 0.21±0.08 versus -0.26±0.10, P=0.001) and lower concentrations of plasma insulin (12.6±0.6 versus 21.3±1.5 uIU/mL, P<0.001) than sedentary subjects. Greater VO₂max was significantly associated with higher memory performance (β =0.37, P=0.01) and lower plasma insulin levels (β =-0.68, P<0.001). The significant association between VO₂max and memory performance was abolished when the indirect effect of plasma insulin was statistically removed (β =0.24, P=0.19).

Conclusion—Fitness-related cognitive enhancement may be mediated, at least in part, by plasma insulin levels.

Keywords

physical activity; glycemic control; memory; middle-age

Introduction

Alzheimer's disease, the most prevalent form of dementia, lacks an established treatment, and its strongest risk factors (i.e., age and genetic predisposition) are not modifiable in

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Conflicts of interest

The authors declare that they have no conflict of interest.

nature (Querfurth et al. 2011). Thus, it is critical to focus on the primary prevention of cognitive decline at midlife before the onset of irreversible neuronal damage. The pathological phenotype of the Alzheimer's brains is closely associated with metabolic abnormalities (Biessels et al. 2006; Haley et al. 2012), including insulin resistance and hyperinsulinaemia. Insulin resistance and hyperinsulinaemia are often interrelated but represent different clinical conditions. With insulin resistance, the cells in the body fail to respond to insulin. In contrast, with hyperinsulinaemia, the blood concentration of insulin rises as a result of hyperglycemia and the elevated pancreatic release.

Habitual aerobic exercise is an efficacious lifestyle modification to ameliorate impairments in insulin-mediated glucose metabolism, which may further translate into better cognitive outcome (Mayer-Davis et al. 1998; Colcombe et al. 2003). As an initial step to address the role of plasma insulin in mediating the association between aerobic fitness and cognitive function, we performed a cross-sectional study involving middle-aged sedentary and endurance-trained adults. Specifically, we hypothesized that endurance-trained subjects would demonstrate lower levels of plasma insulin at rest and better cognitive function than sedentary subjects. Moreover, we predicted that plasma insulin concentration would indirectly mediate the association between higher aerobic fitness and cognitive function. Middle-aged men and women were studied because midlife is an important age group to start lifestyle interventions that may reduce the future risk of cognitive impairment (Jack et al. 2013).

Methods

Twenty-six sedentary and 32 endurance-trained subjects were studied. All subjects were vigorously screened and excluded for smoking, hypertension ($>140/90$ mm Hg), diabetes (fasting blood glucose concentration >126 mg/dL), and vascular or neurological disease. Subjects who were taking cardiovascular-acting medications, including hormone replacement therapy, were excluded. Endurance-trained subjects reported engaging in a moderate to vigorous aerobic exercise training for 7.6 ± 0.6 hours/week whereas sedentary subjects reported no participation in regular exercise over the past year. Aerobic fitness of all subjects was further confirmed by maximal oxygen consumption (VO_2max) test. The Human Research Committee reviewed and approved all procedures, and written informed consent was obtained from all subjects.

A modified Bruce protocol was used to assess VO_2max . Aerobic fitness percentile was also calculated based on the age- and sex-adjusted regression established by the American College of Sports Medicine (Armstrong et al. 2006). Whole blood samples were drawn from the antecubital vein after 12 hours of fasting and 24 hours of abstinence from alcohol, caffeine, and exercise. Plasma insulin was measured in duplicate using a commercially available RIA kit (MP Biomedicals, Orangeburn, NY). Homeostatic assessment of insulin resistance (HOMA-IR) was calculated using the equation described in detail elsewhere (Matthews et al. 1985).

On a separate visit, participants completed a comprehensive battery of neuropsychological assessments with established reliability and validity. The Mini-Mental State Exam (MMSE)

and the Wechsler Test for Adult Reading (WTAR) were employed to assess global cognitive function and IQ, respectively. To reduce the number of multiple comparisons, all other neuropsychological measures were grouped into one of the two cognitive domains: memory or attention-executive function. For the domain score calculations, raw scores were converted to z-scores based on the study sample's mean and standard deviation. Timed-test scores were multiplied by -1 so that higher scores indicate better performance. Domain scores were calculated for each participant by averaging the following tests: 1) *memory*: California Verbal Learning Test (CVLT)-II immediate recall and delayed recall, and recognition discrimination and 2) *attention-executive function*: Trail making A and B time to completion, Controlled Oral Word Association Test (COWAT), and Wechsler Adult Intelligence Scale (WAIS)-III Digit Span Subtest. In addition, a total cognitive composite score was calculated by averaging the z-scores of all individual tests. All tests were administered and scored by a trained research assistant using standard administration and scoring criteria.

The variable distributions were examined using the Shapiro-Wilk test of normality. Chi-squared tests were used to evaluate group differences in categorical variables. Group differences in continuous variables were assessed by Mann-Whitney U tests or independent t-tests as appropriate. Analysis of covariance (ANCOVA) examined group differences in cognitive function after controlling for age, sex, and education. Linear regression analysis examined the associations among VO₂max, plasma insulin, and cognitive function. Age, sex, and education were included as covariates in the models with cognitive function, whereas only age and sex were entered into the models with physiological data alone (e.g., VO₂max and plasma insulin). The direct and indirect effects of VO₂max on cognitive function through plasma insulin were tested using both the traditional causal steps approach (Baron et al. 1986) and a non-parametric bootstrapping procedure (Preacher et al. 2008). The non-parametric bootstrapping procedure was performed using the INDIRECT macro for SPSS provided by Preacher and Hayes (Preacher et al. 2008). 95% bias corrected confidence intervals (CI) were obtained from a resample procedure with 5,000 bootstrap samples. As recommended by Preacher and Hayes, indirect effects were interpreted as significant if zero was not included in the 95% CI (Preacher et al. 2008). All statistical analyses were performed using SPSS 19 (SPSS inc., Chicago, IL). An α -level of 0.05 was set as the criterion for statistical significance. All data are expressed as means $\pm$ SE.

Results

Endurance-trained subjects demonstrated lower body mass index and higher VO₂max and aerobic fitness percentile than sedentary subjects (all $P < 0.001$) (Table 1). While fasting blood glucose concentration was not different between the groups ($P = 0.51$), plasma insulin concentration and HOMA-IR were lower in endurance-trained subjects than in sedentary subjects (both $P < 0.001$), indicating that lower level of insulin resistance in endurance-trained subjects is primarily driven by reduced plasma insulin concentrations. Table 2 shows the results from the neuropsychological assessment. As compared with sedentary subjects, endurance-trained subjects demonstrated higher cognitive performance in total composite ($P < 0.01$), memory ($P < 0.01$), and attention-executive function ($P = 0.04$) domains, independent of age, sex, and education. However, these group differences in cognitive

function were abolished by the inclusion of plasma insulin as a covariate (total composite: $P=0.06$, memory: $P=0.10$, and attention-executive function: $P=0.26$).

Higher VO_{2max} was associated with better cognitive performance in the total composite ($F(49, 53)=6.75$, $P<0.001$, $\beta=0.43$, $P<0.01$) and memory domains ($F(49, 53)=4.09$, $P<0.01$, $\beta=0.37$, $P=0.01$), after controlling for age, sex, and education. There was no significant association with the attention-executive function domain ($F(49, 53)=3.45$, $P=0.02$, $\beta=0.29$, $P=0.052$), after controlling for covariates. Based on these results, we examined plasma insulin as mediator of the association between VO_{2max} and memory performance by testing each path illustrated in Figure. Plasma insulin concentration was related to both VO_{2max} (path a: $F(54, 57)=12.95$, $P<0.001$, $\beta=-0.68$, $P<0.001$) and memory performance (path b: $F(49, 53)=3.97$, $P<0.01$, $\beta=-0.32$, $P=0.02$). The association between VO_{2max} and memory performance was attenuated by the addition of plasma insulin to the model (path c': $F(48, 53)=3.58$, $P<0.01$, $\beta=0.24$, $P=0.19$), indicating successful mediation. This result was further confirmed by the non-parametric bootstrapping procedure, which demonstrated significant indirect effects of plasma insulin on memory performance (95% CI: 0.0044 – 0.0274).

Discussion

The primary findings from the present study were as follows. First, as compared to sedentary age-matched controls, the endurance-trained subjects demonstrated better cognitive performance in the total composite, memory, and attention-executive function domains as well as lower concentrations of plasma insulin. Second, higher aerobic fitness was associated with lower plasma insulin levels and better cognitive performance in the total cognitive composite and memory domains. Third, group differences in cognitive function were attenuated by the inclusion of plasma insulin in the model. Moreover, the non-parametric bootstrapping procedure revealed an indirect role of plasma insulin in mediating the association between VO_{2max} and memory performance. To the best of our knowledge, this is the first study to demonstrate that plasma insulin may be involved in mediating the association between cardiorespiratory fitness and cognitive function in healthy middle-aged adults.

There are several potential physiological mechanisms that may explain the associations among aerobic fitness, plasma insulin, and cognitive function. First, exercise-related improvements in insulin resistance may ameliorate impairments in cerebral glucose metabolism. Regular aerobic exercise promotes angiogenesis which enhances blood flow and the delivery of glucose to skeletal muscle, upregulates the synthesis of insulin-dependent glucose transporter proteins (i.e., GLUT-4), and increases the activity of mitochondrial and oxidative enzymes (Houmard et al. 1993). Habitual aerobic exercise also upregulates the translocation of GLUT-4 to the cellular surface and promotes insulin-mediated glucose uptake (Brozinick et al. 1993). Collectively, these physiological adaptations attenuate insulin resistance, a factor associated with cerebral glucose hypometabolism (Mayer-Davis et al. 1998; Baker et al. 2011). Baker et al. demonstrated that insulin resistance is inversely associated with the metabolic rate of cerebral glucose in pre-diabetic and diabetic patients (Baker et al. 2011). Furthermore, the observed reduction in cerebral glucose metabolism spatially coincided with the regions where Alzheimer's disease

patients typically manifest cerebral hypometabolism (Baker et al. 2011). However, further studies are needed to elucidate a causal or mechanistic relation between insulin resistance and cerebral hypometabolism in Alzheimer's disease (Luchsinger et al. 2011). Second, an elevated level of plasma insulin may compromise the ability of insulin-degrading enzyme (IDE) to clear cerebral amyloid- β (A β) from the extracellular space. IDE is highly expressed in the brain and degrades substrates, including insulin and A β (Qiu et al. 2006). It has recently been hypothesized that insulin may outcompete the binding of A β to IDE in the hyperinsulinaemic condition, thereby reducing the rate of A β clearance and promoting the deposition (Qiu et al. 2006).

In conclusion, the present study demonstrated that plasma insulin mediates the association between higher cardiorespiratory fitness and memory performance. Future studies should determine the impact of exercise-related reductions in plasma insulin on the neuroimaging markers of cognitive impairment and dementia (e.g., fluorodeoxyglucose or amyloid PET). Moreover, the results from the present study necessitate further investigations using a prospective interventional study design with a larger sample size in order to establish a causal relation.

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References

1. Armstrong, L.; Balady, GJ.; Berry, MJ., et al. ACSM's Guidelines for Exercise Testing and Prescription. Baltimore Md: Lippincott Williams & Wilkins; 2006.
2. Baker LD, Cross DJ, Minoshima S, et al. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Archives of Neurology*. 2011; 68:51–57. [PubMed: 20837822]
3. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*. 1986; 51:1173–1182. [PubMed: 3806354]
4. Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006; 5:64–74. [PubMed: 16361024]
5. Brozinick JT Jr, Etgen GJ Jr, Yaspelkis BB 3rd, et al. Effects of exercise training on muscle GLUT-4 protein content and translocation in obese Zucker rats. *Am J Physiol*. 1993; 265:E419–E427. [PubMed: 8214051]
6. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003; 14:125–130. [PubMed: 12661673]
7. Haley AP, Gonzales MM, Tarumi T, et al. Subclinical vascular disease and cerebral glutamate elevation in metabolic syndrome. *Metab Brain Dis*. 2012; 27:513–520. [PubMed: 22552897]
8. Houmard JA, Shinebarger MH, Dolan PL, et al. Exercise training increases GLUT-4 protein concentration in previously sedentary middle-aged men. *American Journal of Physiology*. 1993; 264:E896–E901. [PubMed: 8333515]
9. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013; 12:207–216. [PubMed: 23332364]

10. Luchsinger JA, Small S, Biessels GJ. Should we target insulin resistance to prevent dementia due to Alzheimer disease? *Arch Neurol*. 2011; 68:17–18. [PubMed: 21220672]
11. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28:412–419. [PubMed: 3899825]
12. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, et al. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA*. 1998; 279:669–674. [PubMed: 9496984]
13. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods*. 2008; 40:879–891. [PubMed: 18697684]
14. Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiol Aging*. 2006; 27:190–198. [PubMed: 16399206]
15. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2011; 362:329–344. [PubMed: 20107219]

Figure.

A model illustrating that plasma insulin mediates the relation between maximal oxygen consumption and memory performance. Greater maximal oxygen consumption was associated with better memory performance (path c) and lower plasma insulin level (path a). Lower plasma insulin level was related to better memory performance (path b). Finally, the significant association between maximal oxygen consumption and memory performance was abolished after controlling for plasma insulin level (path c'). Covariates entered: path a=age and sex, paths b & c=age, sex, and education, and path c'=age, sex, education, and plasma insulin.

Table 1

Selected subject characteristics

	Sedentary	Endurance-trained	P-values
Males/Females (n)	10/16	11/21	0.75
Age (years)	53 ± 1	52 ± 1	0.50
Education (years)	16 ± 1	17 ± 1	0.25
Height (cm)	170 ± 2	167 ± 1	0.32
Body mass index (kg/m ²)	27 ± 1	23 ± 1	<0.001
VO ₂ max (mL/min/kg)	25.7 ± 1.1	42.8 ± 1.5	<0.001
Aerobic fitness percentile (%)	12 ± 4	93 ± 5	<0.001
Plasma glucose (mg/dl)	91 ± 2	93 ± 2	0.51
Plasma insulin (uU/mL)	21.3 ± 1.5	12.6 ± 0.6	<0.001
HOMA-IR (AU)	4.85 ± 0.40	2.87 ± 0.14	<0.001

Values are means±SEMs. HOMA-IR=homeostatic assessment model of insulin resistance and VO₂max= maximal oxygen uptake.

Table 2

Neuropsychological assessment

	Sedentary	Endurance-trained	P-values (model 1)	P-values (model 2)	P-values (model 3)
Total cognitive composite score (z score)	-0.26 ± 0.10	0.21 ± 0.08	0.001	<0.01	0.06
MMSE	28.6 ± 0.3	29.0 ± 0.2	0.26		
WTAR	41.6 ± 1.7	44.5 ± 0.8	0.33		
Memory (z score)	-0.35 ± 0.17	0.29 ± 0.12	<0.01	<0.01	0.10
CVLT-II immediate recall	10.3 ± 0.6	12.4 ± 0.4			
CVLT-II delayed recall	10.5 ± 0.6	12.7 ± 0.4			
CVLT-II discriminability index	2.7 ± 0.2	3.5 ± 0.4			
Attention-executive function (z score)	-0.21 ± 0.11	0.17 ± 0.11	0.02	0.04	0.26
Trail Making Test A	32.2 ± 1.8	28.6 ± 1.4			
Trail Making Test B	70.8 ± 4.2	58.2 ± 3.4			
COWAT	43.0 ± 1.7	46.7 ± 2.6			
WAIS-III Digit Span Subtest	18.1 ± 0.7	18.9 ± 0.7			

Model 1: no covariate entered; Model 2: adjusted for age, sex, and education; Model 3: adjusted for age, sex, education, and plasma insulin.

Values are means±SEMs. COWAT=Controlled Oral Word Association Test, CVLT-II=California Verbal Learning Test-II, MMSE=Mini-Mental State Exam, WAIS-III=Wechsler Adult Intelligence Scale-III, and WTAR=Wechsler Test for Adult Reading.