Neurological Sciences (2019) 40:1145–1150
https://doi.org/10.1007/s10072-019-03781-y

ORIGINAL ARTICLE

Irisin and BDNF serum levels and behavioral disturbances in Alzheimer's disease

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Received: 9 October 2018 / Accepted: 19 February 2019 / Published online: 27 February 2019

Abstract
Behavioral dysfunctions (BPSD) represent the most important problem in Alzheimer's dementia (AD) management. We assessed the serum levels of two myokines in AD patients, preliminary investigating, as secondary aim, their role as potential biomarkers for agitation/aggression (AA) and aberrant motor behavior (AMB): irisin, since it is able to modify the motor pattern, and BDNF, since it was transcribed following irisin stimulation. Forty AD patients were recruited and characterized according to the expressed neuropsychiatric syndrome. Myokines were measured by ELISA. Irisin serum levels were slightly elevated in AA+ patients (+ 10.0%; $p < 0.05$) and correlated with the duration of AA ($r = 0.74$, $p < 0.03$). BDNF failed to show such differences. We propose that these selected myokines are not useful as surrogate markers for agitation in AD, but might represent interesting secondary outcomes when testing drugs for those BPSD implying elevated motor activity.

Keywords Alzheimer's disease · BPSD · Myokines · Irisin · BDNF

Introduction

Behavioral and psychological symptoms of dementia (BPSD) represent one of the most important problems in dementia management, implying extremely elevated economic and social costs for both families and the health system. Alzheimer's disease (AD) patients virtually all express BPSD to some extent during the disease, and the need for effective treatments is stronger than ever. In the USA, no drugs are approved for treating BPSD and in most countries few options are available, leading to a widespread off-label use of prescriptions, including antipsychotics, antidepressants, anticonvulsants, benzodiazepines, cholinesterase inhibitors (AChEI), and Memantine. Guidelines suggest to consider non-pharmacological options first, such as changes in the surrounding environment or management issues, but some BPSD, as agitation/aggression or aberrant motor behavior, are perceived by caregivers as so much disruptive to force treating physicians to propose potentially harmful pharmacological mixtures [1, 2].

Given these premises, one of the most puzzling issues is probably represented by the fracture existing between the mainly negative results obtained by evidence-based randomized controlled trials and the — perhaps partial — anecdotic evidence of efficacy in the real world practice. Among the reasons for this contrast are both inadequate measuring tools and scant knowledge regarding BPSD pathophysiology. Measuring tools, in particular, are inevitably centered on the main caregiver, potentially implying an accuracy bias. To overcome this problem, few Authors have been proposing cognate biomarkers, probably given the manifest lack of knowledge on the mechanisms generating non-cognitive symptoms, in particular, agitation, in dementia [3–5].

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Irisin is the cleavage product of the ectodomain of fibronectin type III domain-containing protein 5 (FNDC5). This peptide is produced by muscles following exercise and circulates in the blood. For this reason, it is more properly tagged as a myokine, although it plays additional roles in metabolism, increasing cortical bone mass and modifying the activity of fat cells. Even more interestingly, this "exercise hormone" seems more properly to play a bidirectional role, because it also induces locomotor activity when injected into the CNS of mice [6]. Due to these multiple roles, irisin role has been investigated not only mainly into metabolic diseases but also in neuropsychiatric ones, such as eating disorders [7].

Furthermore, irisin is known to contribute to the transcription of the brain-derived neurotrophic factor (BDNF), a neurotrophin and myokine as well, whose lack or reduction has been repeatedly claimed to be involved in neurodegeneration [8]. Specifically, this is one of the mechanisms claimed to potentially mediate the increasingly known beneficial effects of exercise in AD [9]. Further irisin-mediated mechanisms include the promotion of hippocampal neurogenesis, oxidative stress reduction, the enhancement of glucose homeostasis, and of synaptic plasticity [9].

Despite these premises, no data are currently available on serum levels of irisin in AD, while BDNF serum levels seem to be protective against cognitive impairment [10]. A recent report proposed both irisin and BDNF, together with the kynurenine pathway, as putative biomarkers in elderly adults at risk of dementia undergoing to either physical training, cognitive training, or a wait-list control condition [11]. In this experimental setting, global cognition and episodic memory were significantly associated with irisin and BDNF serum concentrations, and only BDNF tended to increase following physical training [11].

In the present study, we aimed at investigating serum levels of irisin and BDNF in AD patients versus controls, including as secondary aim, the evaluation of a potential relationship with BPSD expression, focusing, in particular, on those behaviors implying elevated motor — and potentially muscular activity, such as agitation/aggression and aberrant motor behavior.

Subjects and methods

Subject recruitment

Following Ethical Committee approval and informed consent, 40 consecutive AD outpatients were recruited at the Manzoni Lecco Hospital (Italy). AD specialists diagnosed probable AD according to the NINCDS-ADRDA criteria [12] and alternative diagnoses were excluded by MR brain imaging and a routine extensive neuropsychological test battery. Patients were recruited only if the main caregiver was available for the interview. For each patient, current scores at the Mini-Mental State Examination (MMSE), the Caregiver Burden Inventory (CBI), and the Neuropsychiatric Inventory-10 (NPI-10) were collected. A post hoc patient stratification was conducted according to five distinct neuropsychiatric syndromes: apathetic (NPI-AP), affective (anxiety and depression, NPI-AF), psychomotor (agitation/aggression, irritability, and aberrant motor behavior, NPI-PM), psychotic (delusions and hallucinations, NPI-PS), manic (disinhibition and euphoria, NPI-MA), or none of them (NPI-00) [13] (see Fig. 1**A**).

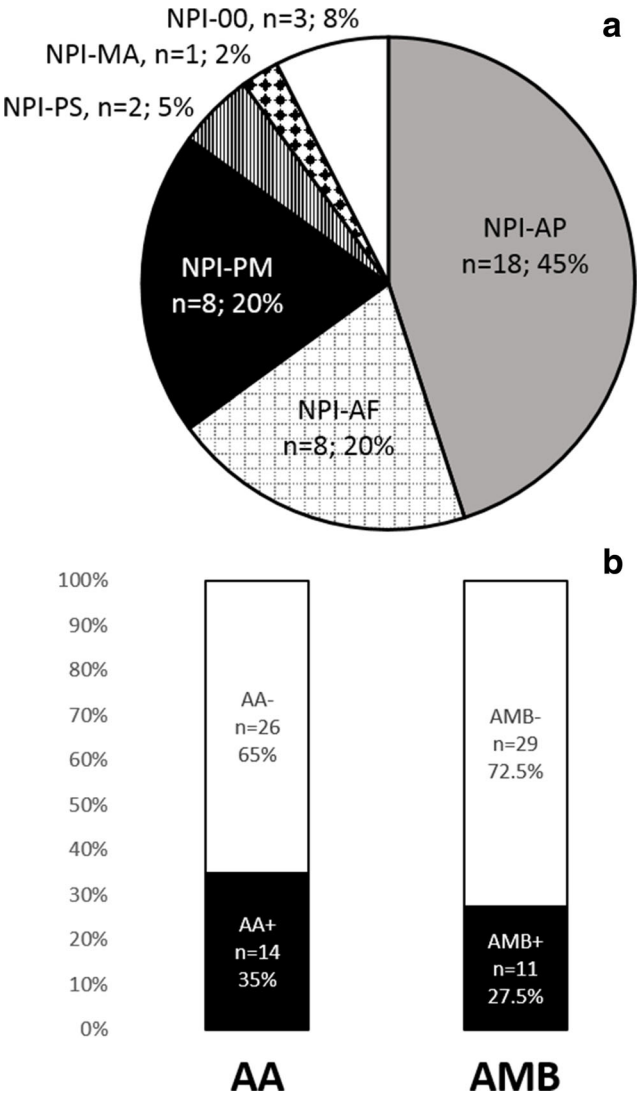

Fig. 1
Behavioral dysfunctions expressed by the recruited AD patients. ($n = 40$). **A** Stratification according to five distinct neuropsychiatric syndromes: apathetic (NPI-AP), affective (anxiety and depression, NPI-AF), psychomotor (agitation/aggression, irritability, and aberrant motor behavior, NPI-PM), psychotic (delusions and hallucinations, NPI-PS), manic (disinhibition and euphoria, NPI-MA), or none of them (NPI-00) [13]. **B** Proportion of patients expressing two selected behavioral phenotypes: agitation/aggression (AA) and aberrant motor behavior (AMB)

Average NPI scores (severity × frequency) were calculated for each neuropsychiatric syndrome and patients were allocated to the one expressing higher scores (equal scores in two or more NPI syndromes were never observed in this work). Furthermore, two separate dichotomic post hoc analyses were conducted according to the presence vs. absence of scoring in a single pre-selected area: "aberrant motor behavior" (AMB+, $n = 11$) area or "agitation/aggression" (AA+, $n = 14$) (see Fig. 1B). For those patients scoring within the area AA, the caregiver was also required to estimate the first onset of AA and the lag between disease Onset and AA appearance was calculated (O/AA-lag). This data was acquired regardless of the subsequent expression over time of the AA behavior: some patients, in fact, had relapsing-remitting courses, while some other patients presented with more chronic, sub-continuous courses. Haloperidol equivalents (HE) were calculated as well based on current therapeutic regimens [2]. Liver, kidney, and electrolyte tests for all patients were within the provided reference ranges.

Twenty age- and sex-comparable healthy controls (CTRL) were recruited as well among patients' spouses, without personal or family history of neurological or psychiatric disorders; lack of cognitive impairment in CTRL was established by a clinical interview, including a MMSE score > 26. Either patients or controls, with recent infections or surgery (6 months) or under anti-inflammatory, corticosteroid, or immunosuppressive drug treatments, or affected by kidney or liver failure were excluded. Clinical and demographic data are shown in Table 1. All the recruited subjects had a sedentary lifestyle and did not practice any sport or regular physical activity. Furthermore, none of the recruited subjects was a current smoker. Two AD patients and none of CTRL subjects had diabetes mellitus in comorbidity and were taking oral antidiabetic drugs.

Table 1 Clinical and demographic data

	AD $n = 40$	CTRL $n = 20$
Sex, M (%)	17 (42.5%)	9 (45.0%)
Age, years	77.6 ± 5.6 (69–88)	78.7 ± 5.7 (70–89)
Disease duration, months	38.9 ± 24.6 (4–96)	–
MMSE, score	18.7 ± 5.7 (4–27)	Always > 26
NPI-10, score	17.7 ± 18.9[b] (0–82)	N/P
CBI, score	24.1 ± 18.8 (0–61)	N/P
AA duration, months[a]	19.0 ± 12.9 (4–45)	–
O/AA-lag, months[a]	27.1 ± 28.3[c] (0–79)	–
AChEI/memantine/combined/none, *n*	26/15/8/7	–
Neuroleptics, *n* (%)	9 (22.5%)	–
Haloperidol equivalents (HE)	0.69 ± 0.41 (0.16–1.48)	–
ApoE genotype	4/4, $n = 5$ (12.5%) 3/4, $n = 18$ (45%) 3/3, $n = 16$ (40%) 2/2, $n = 1$ (2.5%)	N/P

[a] $n = 14$ AA+ patients

[b] Median, interquartile range 10, 3.5–32

[c] Median, interquartile range 19, 0–56

Data are reported as mean ± SD (range)

AA agitation/aggression, *AChEI* cholinesterase inhibitors, *CBI* caregiver burden inventory, *MMSE* mini-mental state examination, *N/P* not performed, *NPI-10* neuropsychiatric inventory-10 items, *O/AA-lag* lag between disease onset and AA appearance

Serum sample preparation and ApoE genotyping

The ApoE genotype was acquired since some studies report a possible relationship with agitation [14]. Blood samples (10 mL) were collected from the antecubital vein after overnight fasting always between 08.00 and 09.00 a.m., to obtain serum by centrifugation at 3600*g* for 15 min. All samples were processed within 30 min of withdrawal and stored at − 80 °C until assay that was performed within 3 months in blind on coded aliquots. To analyze ApoE genotype, total DNA was extracted from peripheral blood using a commercial DNA extraction kit (Qiagen) and DNA amplification was performed using specific primers as previously reported [15].

Irisin and BDNF measurement

Serum irisin concentration was measured in duplicate using an Enzyme-linked Immunosorbent Assay (ELISA) kit (Phoenix Pharmaceuticals, Burlingame, CA), according to manufacturer's specifications. Briefly, samples were diluted 1:5 and the peptide standard solutions were prepared by using serial dilutions. Twenty-five microliters of primary antibody, 25 μL of biotinylated peptide, and 50 μL of diluted samples or standards were incubated for 2 h. After the washing step, 100 μL of streptavidin-horseradish peroxidase solution was added to each well for 1 h. Then, 100 μL of substrate solution (TMB: 3,3′,5,5′-tetramethylbenzidine) was added to each well for a further 1 h. The reaction was stopped by adding 100 μL of HCl and then the 450 nm absorbance was recorded by Microtiter Plate Reader (Synergy™ HT). The minimum detectable concentration (sensitivity) was 1.78 ng/mL; the linear range was 1.78–26.0 ng/mL, the range was 0.1–1000 ng/mL, intra-assay variation was < 10%, and inter-assay variation was < 15%. To quantify the sample concentrations, a four-parameter logistic equation was used.

Samples were assessed for BDNF in duplicate by ELISA (Promega, E-max® ImmunoAssay System) according to the manufacturer's specifications. Samples were diluted 1:100 using a kit buffer, to obtain a final concentration of BDNF within the linear part of the standard curve (range, 15.6–500 pg/mL). Two ELISA kits belonging to the same batch were used, duplicating several samples for calculating intra-assay variability that was always below 10%, which was considered acceptable and not further considered as a source of bias. The range value of control samples was similar to what was previously reported [16].

Statistical analyses

Data are shown as mean ± standard deviation (SD). Statistical analysis was performed with GraphPad Prism, version 4.00 program. Two-tailed Student's *t* test was used for computing difference between two groups, while either Kruskal-Wallis or analysis of variance (ANOVA) was used as appropriate for three or more groups, the latter followed by the Newman-Keuls post hoc test. Correlations were computed by the Pearson's *r* test and differences of frequency distribution by the χ^2 test.

Results

Neuropsychiatric symptoms in the recruited AD population

Thirty-seven patients (92.5%) expressed a positive score at the NPI. The stratification according to the prevalent neuropsychiatric syndrome is shown in Fig. 1**A**. Most patients were included in the NPI-AP category ($n = 18$, 45.0%), while only $n = 8$ in the NPI-PM one (20.0%). At the dichotomic analysis, 14 patients were AA+ (35.0%) and 11 were AMB+ (27.5%) (Fig. 1B).

NPI-10 scores correlated with caregiver burden (CBI, $r = 0.60$ $p < 0.0001$) and MMSE ones ($r = -0.48$ $p < 0.005$) but failed to do so with the O/AA-lag or the other collected clinical and demographic parameters.

As shown by Table 1, 9 AD patients ($n = 22.5\%$) were taking neuroleptic medications (7 AA+ vs. 2 AA−, χ^2 9.1 $p < 0.003$; HE 0.69 ± 0.41, range 0.16–1.48; AA+ 0.75 ± 0.42, range 0.33–1.48 vs. AA− 0.16 and 0.82), while 26 (65.0%) were taking cholinesterase inhibitors (AChEI) at therapeutic dose, and 15 (37.5%) Memantine 20 mg o.d., with eight patients in combined regimen (20.0%).

Besides neuroleptic medications in AA+, all these drugs failed to segregate significantly with any of the pre-specified BPSD category.

Irisin and BDNF serum levels in AD

Both irisin and BDNF serum levels were unchanged considering the whole sample of AD patients when compared to CTRL (see Fig. 2). Furthermore, no correlation was found between them ($p = 0.27$) and both serum peptides failed to correlate with sex, age, disease duration, NPI-10, CBI, or MMSE scores, nor differences emerged when considering AChEI or Memantine use (data not shown).

After stratification of patients according to the five pre-specified neuropsychiatric syndromes, no significant differences emerged for both serum irisin ($p = 0.52$; data not shown), and BDNF ($p = 0.46$; data not shown).

When considering separately the AA area of the NPI, AA+ patients displayed slightly but significantly increased (+10.0%) irisin levels with respect to AA− ones (20.5 ± 3.4 vs. 18.6 ± 2.1, AA+ vs. AA−, respectively, $p = 0.037$, two-tailed Student's *t* test, $t = 2.152$ df = 38).

However, irisin serum levels correlated with the duration of AA ($r = 0.74$, $p < 0.03$), but not with the O/AA-lag. Conversely, BDNF serum levels were not different between AA+ and AA− patients (22.7 ± 4.8 vs. 22.9 ± 6.2 ng/mL, respectively, $p = 0.92$), nor correlated with AA-related parameters.

Finally, AMB+ patients failed to show differences with respect to AMB− patients regarding both irisin (18.9 ± 1.9 vs. 19.4 ± 3.0 ng/mL, AMB+ vs. AMB−, respectively, $p =$

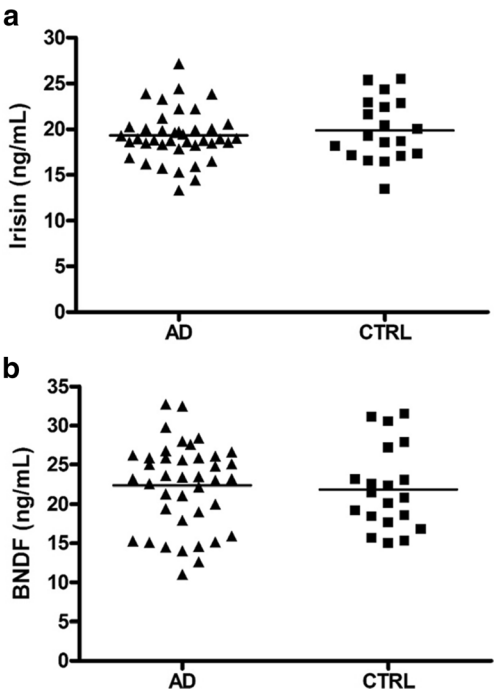

Fig. 2
Irisin (**A**) and BDNF (**B**) serum levels were unchanged in the whole sample of AD patients with respect to matched controls (CTRL). Cohen's *d* 0.096 and 0.089, respectively.

0.60) or BDNF serum levels (21.8 ± 6.1 vs. 23.2 ± 5.7 ng/mL, AMB+ vs. AMB−, respectively, $p = 0.51$).

The APOE4 allele was carried by 57.5% of AD patients (see Table 1) and failed to show any relationship either with serum irisin or BDNF levels or with clinical and demographic scores.

Discussion

Our primary aim consisted in assessing irisin serum levels in AD patients versus non-demented controls: with regard to this, no differences were found. However, this cross-sectional study secondarily attempted to explore novel markers of BPSD in AD, searching for direct measures not relying on caregivers' reports. In particular, this aim was pursued by evaluating the circulating levels of the myokines irisin and BDNF in AD patients that were stratified according to the BPSD profile, favoring those behaviors implying increased motor activity. The main finding of the present study is that serum irisin is slightly but significantly increased in AA+ AD patients and correlates with the duration of AA. These differences were not found for BDNF. Certainly, sample size was quite small for dichotomic analyses, assigning to these results — at the moment — a merely exploratory meaning. In any case, we are currently expanding this project by recruiting patients for a larger study, also able to specifically address possible confounders that modify irisin production and that were only marginally considered in the present exploratory work (e.g., exercise, cold exposure, metabolic alterations including diabetes, drugs) [9].

Previous attempts in this sense with a different approach were performed with actigraphy, whose parameters were shown to correlate with the Cohen-Mansfield Agitation Inventory [17]. Interestingly, actigraphic recordings of patients' motor activity correlated with the response to treatments of agitation, albeit failing to correlate with NPI scores, reinforcing the idea that the two methods are estimating BPSD from totally different points of view [18]. Considering blood-based biomarkers of BPSD, and agitation in particular, very few have been proposed, mostly without further validation in larger independent cohorts [3, 5].

Here we chose two candidate biomarkers among myokines, i.e., cytokines directly released by myocytes into the bloodstream in response to muscular contraction. In particular, we hypothesized that the serum levels of these myokines could mark the presence vs. the absence of symptoms implying elevated motor activity, such as agitation/aggression or aberrant motor behavior. The same was done when considering the predominant neuropsychiatric syndrome, hypothesizing a sort of continuum of muscular activation from the apathetic syndrome to the psychomotor one. Irisin, in particular, was chosen among the various available myokines because of its bidirectional role. In fact, this protein is produced by movement in the periphery and is able to induce movement acting in the CNS. This represents the premise for a recursive mechanism sustaining motor activity that, in a demented person, can find its expression into aberrant motor behavior (AMB), or perhaps, into agitation (AA). The other myokine studied, BDNF, is linked to irisin production, since it is also expressed in the hippocampus upon stimulation by peripherally-borne irisin, accounting, at least in part, for the proposed neuroprotective effects of exercise [19].

Our results, as mentioned above, show that irisin is moderately but significantly increased in AA+ AD patients and that the duration of AA clearly correlates with irisin serum levels. This data seems to support the idea that longer duration of agitated behaviors might lead to increased secretion of selected myokines, implying the possibility of using such markers in pharmacological trials. In any case, a final validation of irisin as a clinical biomarker in AD awaits further studies. Surprisingly, however, no association was found with the AMB+ status or the NPI-PM syndrome. This may be due to some limitations of this study: (a) the low number of patients in each subgroup obtained after post hoc splitting of patients into these categories and (b) the lack of assessment of the severity of the symptoms. Then, future studies should selectively explore one target behavioral domain (e.g., AA or AMB) with a semi-quantitative approach, extend these observations to larger cohorts, and include the monitoring of individual physical activity by portable devices. Conversely, serum BDNF failed to show such pattern but this might not be surprising when considering that multiple mechanisms regulate BDNF production and release into the bloodstream [16, 20]. Certainly, we need to keep in mind that the half-life and the exact dynamics of production of these two myokines by skeletal muscles are not completely clear.

In our samples, both irisin and BDNF failed to correlate with the MMSE score, albeit global cognition was previously found to correlate with serum levels of both in elderly subjects at risk of dementia [11]. Differences in terms of collected cognitive measures (extensive neuropsychological battery versus MMSE) and of patient types (subjects at risk of dementia versus AD patients) can account for this inconsistency, and future studies might clarify this issue.

Finally, in the neuroscience field, besides having been studied in eating disorders [7], serum irisin was recently assessed by our group in another degenerative disorder, amyotrophic lateral sclerosis (ALS), reporting an increase [21] and a decrease of serum BDNF with increasing disease severity [16]. The prominent muscular involvement observed in this neurodegenerative disorder is the probable reason for this discrepancy.

Conclusion

We report here the mild segregation of irisin serum levels with the phenotype agitation/aggression associated with AD and we propose that: (a) these selected myokines do not appear useful as surrogate markers for acute agitation in AD, but (b) might be tested as secondary outcomes in drug studies testing novel compounds for BPSD that imply elevated motor activity.

Future studies also should test the potential role of other myokines, looking for a possible combination that might mark closely the response of target phenotypes to psychoactive drugs.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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