



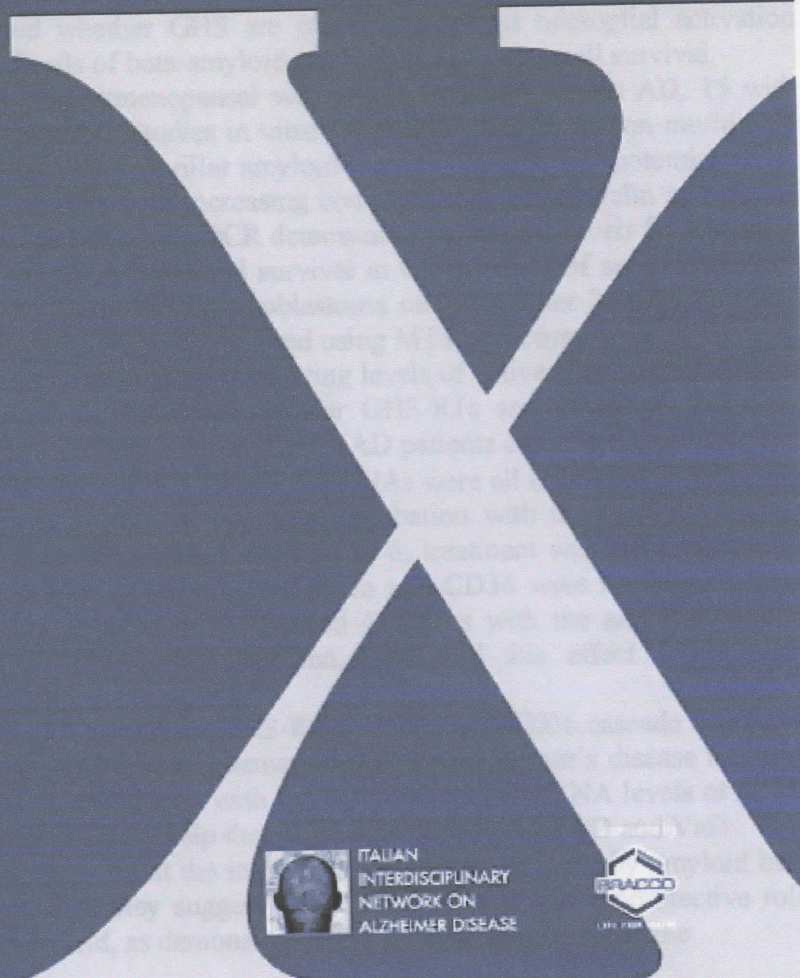
ITALIAN INTERDISCIPLINARY NETWORK ON ALZHEIMER DISEASE - X ANNUAL MEETING

ABSTRACTS BOOK

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ITALIAN
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ALZHEIMER DISEASE





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ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA: POSSIBLE ANTI-INFLAMMATORY AND NEUROPROTECTIVE ROLE OF GHRELIN AND GROWTH HORMONE SECRETAGOGUES (GHS)

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Background: Alzheimer's disease (AD) and cerebrovascular disease (VaD) are the most frequent cause of dementia in elderly individuals. Alzheimer's disease (AD) is characterized by the presence in the brain of amyloid plaques composed mainly of fibrils of beta-amyloid peptide, dystrophic neurites, activated microglia and astrocytes. The fibrillar forms of beta amyloid bind the CD36, a class B scavenger receptor, and initiate a signalling cascade that regulates microglial recruitment and activation. The CD36 is also able to bind synthetic growth hormone secretagogues (GHS), a family of peptides that stimulates growth hormone secretion. In this study we explored whether alterations in ghrelin and/or GHS-R1a and CD36 expression could be involved in the development of AD and VaD and if they may be used as tool for the differential diagnosis of the two type of dementia. Moreover we investigated whether GHS are capable to inhibit microglial activation induced in vitro by incubation with fibrils of beta-amyloid peptide, and promote cell survival.

Methods: Human studies involved 40 postmenopausal women: 13 outpatients with AD, 15 with VAD and 12 healthy age-matched controls. Studies in vitro were performed in part on murine N9 microglial cells activated by incubation with fibrillar amyloid peptide (25-35). The potential effect of GHS was studied coincubating the cells with increasing concentrations of hexarelin and one of its analogues. Cell activation was estimated by RT-PCR determining the mRNA levels for IL-1beta, IL-6 and TNF-alpha and CD36 in N9 cells. Neuronal survival in the presence of amyloid peptide and GHS was evaluated on SH-SY5Y, a human neuroblastoma cell line, after 24 and 48 hours incubation with amyloid beta fibrils and GHS and measured using MTT reduction assay.

Results: We report that VAD patients have reduced circulating levels of active ghrelin compared to controls and AD patients. Moreover, the mRNA levels for GHS-R1a and PPAR-gamma were significantly elevated in peripheral blood lymphocytes from VAD patients compared to control and AD. Ghrelin, COX-1, COX-2, PPAR-beta, and TNF-alpha mRNAs were all expressed in PBL, but their levels were similar in the three groups. In N9 cells, incubation with the amyloid peptide induced a significant rise of mRNA levels for IL-1beta and IL-6; treatment with hexarelin or its analogue blunted this effect. The mRNA levels of TNF-alpha and CD36 were not significantly modified by the different treatments. Incubation for 24 and 48 hours with the amyloid peptide induced a significant death in SH-SY5Y neuroblastoma cells, and this effect was clearly counteracted by the hexarelin analogue but not hexarelin.

Conclusions: Our data indicate that ghrelin and the GHS-R-PPAR-gamma-CD36 cascade may have a relevant role in the pathophysiology of vascular dementia but not Alzheimer's disease and low circulating levels of active and total ghrelin along with increased leucocyte mRNA levels of GHS-R1a, CD36 and PPAR-gamma may potentially help the differential diagnosis of AD and VaD.

Indeed these data indicate that GHS may blunt the inflammatory process induced by amyloid beta fibrils in N9 microglial cells. Moreover, they suggest that GHS may play a neuroprotective role against cell death induced by beta amyloid, as demonstrated in the neuroblastoma cell line



SH-SY5Y. These findings indicate that GHS may act against the inflammation and oxidative stress involved in the pathogenesis of the Alzheimer Disease.

COMORBILITA' MEDICA E DISABILITA' NEI SOGGETTI DEMENTI

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Scopo della ricerca: Relativamente pochi studi hanno esaminato la prevalenza delle condizioni mediche concomitanti nei soggetti dementi. In questo studio epidemiologico trasversale abbiamo esaminato la prevalenza della comorbilità e il suo impatto funzionale nei soggetti anziani con deficit cognitivi e con demenza.

Materiali e Metodi: Sono stati analizzati i dati provenienti dal Progetto ReGAL (Rete Geriatrica Alzheimer della SIGG). Sono stati analizzati i dati relativi a 4075 soggetti, valutati in 44 centri italiani specializzati in problemi di memoria dal gennaio 2001 al novembre 2005. Ciascun paziente è stato valutato accuratamente secondo un protocollo standardizzato. Per quantificare la comorbilità è stata usata la Cumulative Illness Rating Scale (CIRS). Lo stato funzionale è stato valutato mediante la ADL (Activity Daily Living): da 0 (dipendenza completa) a 6 (indipendenza).

Risultati: La popolazione presa in esame è formata da 2640 femmine (età media $77,4 \pm 7,4$ anni, scolarità $5,26 \pm 3,4$ anni e punteggio medio al MMSE $19,16 \pm 6,4$) e 1435 maschi (età media $76,01 \pm 7,28$ anni, scolarità $7 \pm 4,4$ anni e punteggio medio al MMSE $21,14 \pm 6,6$). In base alla diagnosi principale la popolazione risulta così suddivisa: controlli 17,7%, MCI 9,5%, demenza di Alzheimer (AD) 50,3%, Demenze vascolari (VaD) 18,23% e altre demenze 4,3%. I soggetti con AD hanno una comorbilità significativamente più bassa rispetto agli altri tipi di demenza, al MCI ed ai soggetti cognitivamente integri ($p < 0,001$). Le differenze più importanti sono soprattutto con i VaD. Correggendo per sesso, età, scolarità e MMSE, la severità della comorbilità e la comorbilità complessiva (numero di sintomi con punteggio ≥ 3) aumentano il rischio di disabilità grave (almeno una ADL persa) in tutte le classi diagnostiche considerate.

La tabella mostra gli effetti relativi della coesistenza di patologie diverse dalla demenza sulla probabilità di disabilità funzionale grave (almeno 1 ADL persa), corretta per età, sesso e scolarità.

Demenza	Comorbilità sintomatica	≥ 1 ADL persa
-	-	1
-	+	3,47 (1,9-6,1)
+	-	5,75 (3,2-10,2)
+	+	9,0 (5,2-15,6)

Conclusioni: I soggetti con demenze di tipo degenerativo hanno la tendenza ad avere una comorbilità significativamente più bassa rispetto ai soggetti con forme vascolari o miste e ai soggetti con MCI e cognitivamente integri. Inoltre intervenire sulla comorbilità potrebbe ridurre la disabilità nei soggetti anziani con deterioramento cognitivo.