

Investigating the effect of ghrelin on improving memory and learning ability in animals: A systematic review

Mohaya Farzin^{1,2,*}, Parastoo Jafarzade¹, Niloofar Faraji², Seyedeh Maral Mousavi², Mostafa Yousefi³

¹Department of Physiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

²Razi Clinical Research Development Unit, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

³Department of Biology, Faculty of Sciences, University of Guilan, Rasht, Iran

Abstract

Ghrelin does an important role in neurological functions such as memory, learning, and cognition as well. There is some evidence that ghrelin can improve memory. This study aimed to evaluate the effects of ghrelin on rat memory. A systematic search was conducted to identify papers published by Iranian authors in the Web of Science, PubMed, Scopus, Embase, and Google Scholar electronic databases from January 2010 to December 2019 with the PRISMA statement. Totally, 547 animals were listed in our systematic review. All of the animals were male Wistar rats with a mean weight of 250 ± 280 g. The Morris Water Behavior behavioral test and the passive avoidance task were performed to evaluate memory. Truly, injection of ghrelin appears to enhance the compactness of the synapse dendritic spines in the hypothalamus. These findings indicate that ghrelin has a prospective role to recover learning and memory ability in animal models, suggesting it as a candidate therapy for memory.

Keywords: Ghrelin, Memory, Depression, Memory disorders

1. Introduction

Ghrelin is a 28-amino acid orexigenic peptide that was identified as an endogenous ligand for the growth hormone secretagogue receptor (GHSR)-1a, performing a significant role in nutrition intake, control of obesity, and plays an important role in homeostasis [1]. Based on the findings, it showed that the hippocampus plays an important role in cognitive function and is a vital structure for memory [2]. The presented in different brain tissues for example the hypothalamus and pituitary, ghrelin control brain purposes by entering or highly mainly as GHS-R1a mRNA in hippocampal neurons [3]. Studies have shown that ghrelin is present in hypothalamic neurons, which are located next to the third ventricle between the abdominal, dorsal, ventricular, and

arched nuclei [4]. Notably, ghrelin neurons are located in the hypothalamus and cortex, also the ghrelin neuron fibers in the hypothalamus are straightly thrust to the dorsal vagal complex (DVC) [5]. The above-mentioned ghrelin-induced synaptic growth causes better spatial learning and memory while meddling in ghrelin gene expression diminished the spine synapses density and cholinergic fibers in the hippocampal CA1 which caused reasoning and memory performance to lessen [6]. Moreover, intra amygdaloid ghrelin management enhances learning and memory procedures in aversive circumstances in male rats, as studied in the Morris water maze (MWM) patterns [6].

Intra-hippocampal injection increases long-term memory [7]. It suggests a modulatory performance of

* Corresponding author:

Mohaya Farzin, Ph.D
Razi Clinical Research Development Unit, Razi Hospital,
Guilan University of Medical Sciences, Rasht, Iran
Tel/Fax: +98 13 33542460
Email: mf99155@yahoo.com
<https://orcid.org/0000-0003-4739-2454>

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ghrelin in memory acquisition/consolidation over processes that could contain the promotion of synaptic plasticity and concentration of hippocampal cholinergic fibers [8]. The particular role of ghrelin in depression and anxiety is ambiguous by now, as it has shown, either advanced and lighten depressive and anxiety-behavior in animal studies are with an overweight of indication proposing antidepressant special effects. But a few human investigations demonstrate an interruption of the ghrelin system in a patient with dementia [9]. This study aims to provide a concise yet comprehensive overview of ghrelin's role in memory. Ghrelin consistently showed protective and memory-enhancing effects, as well as reducing psychopathology in animal models of dementia. Some human investigations demonstrate an interruption of the ghrelin system in a patient with dementia.

2. Materials and Methods

2.1 Search strategies

A systematic search from January 2010 to December 2019 on the Web of Science, Google Scholar, Scopus, PubMed, and Embase electronic

databases was carried out. The Guidelines used for this literature review were from the preferred reporting items for systematic reviews and meta-analyses (PRISMA). The search was conducted by two reviewers who independently screened the databases through the following terms: “Ghrelin” AND “Alzheimer's disease” OR “Memory corruption” OR “Improve memory” OR “Memory disorder” OR “Cognition disorders” OR “Neurodegenerative diseases” AND Iran. Any discrepancies were resolved by consensus with a third reviewer. Studies were included without language restrictions.

2.2 Inclusion criteria

The following articles are included in the study (1) Ghrelin was used as a treatment, (2) The tests used in the articles include the Maurice Water Table and the Shuttle Box, (3) All studies investigating ghrelin in animals.

2.3 Exclusion criteria

Articles were excluded if the following standards were encountered: (1) Duplicate publications, (2)

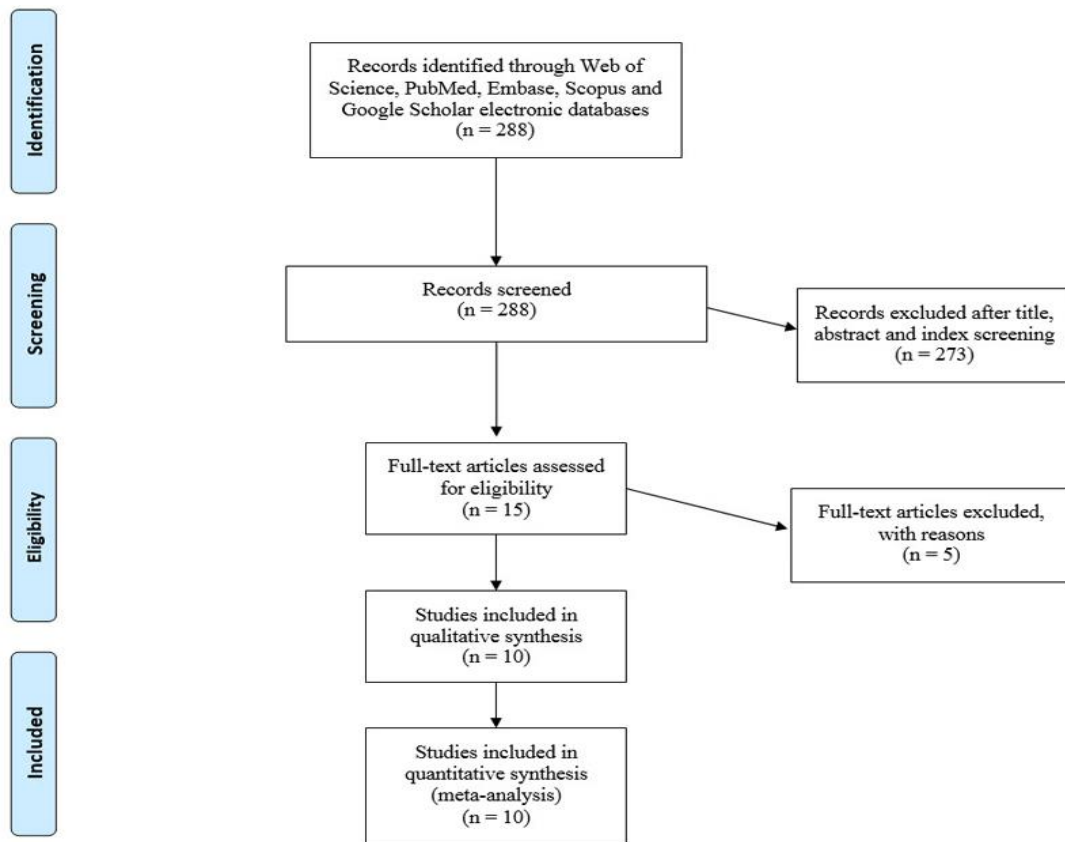


Figure. 1 PRISMA flow diagram showing a selection of articles for review

articles that compared diverse techniques, (3) Studies with a non-control group, (4) Intraperitoneal ghrelin injection in mice.

2.4. Data extraction

The following details were extracted for each of the included studies: the first author's name, publication date, the study location, sample size, animal details, treatments, and outcome.

3. Results

Ghrelin increases memory and improves map memory performance by becoming longer and richer. Ghrelin seems to have a beneficial effect on memory disorders in animals. This will make the memory have better quality. Finally, it appears to affect synaptic flexibility in areas involved in memory and has been shown to improve memory capacity in rodents. A total of 15 potential articles were identified. After checking duplicates, reviewing titles, abstracts, and full text, 10 eligible articles were included, which detailed characteristics of them are specified in Table 1. The flow diagram outlining the searching procedures is presented in Figure 1.

Over levels of screening, 547 animals were listed in our systematic review. All of the animals were male Wistar rats. The weight of all the animals was over 250 ± 280 . The Morris Water Behavior behavioral test and the passive avoidance task were performed to evaluate memory. Truly, injection of ghrelin appears to enhance the compactness of the synapse dendritic spines in the hypothalamus. According to both types of research by Babri, et al. ghrelin can increase memory level [10]. Also, other studies by the simultaneous use of narcotics and ghrelin indicated that ghrelin can improve memory level [11, 12]. Using the shuttle box and ghrelin block, Zahiriri et al. and Beheshti, et al. showed that the level of memory increased by ghrelin [2]. Moreover, Eslami, et al. by use of ghrelin blocking demonstrated that it can enhance memory level [6].

4. Discussion

This study highlights the conclusion of ghrelin on ameliorating learning and memory aptitude. To our information, this study is a systematic review that discovers the efficacy of ghrelin on enhancing memory and learning in animal trials by the results of the Morris water maze test and shuttle box as the result measures in Iran. It recommends that ghrelin has a

possible role in enhancing learning and memory impairment in animal models.

Ghrelin appears to use a neuroprotective effect in various models over similar signaling pathways. Subsequently, ghrelin could be used to improve existing symptoms in multiple neurodegenerative and also neurological disorders as well as to make disease development slow. In the CA1 region of the hippocampus, ghrelin developed spatial memory and about the ghrelin secretion from the stomach through fasting, it can be theorized that ghrelin may have an ameliorating impact on learning and memory which exposed the enhancing the effect of higher doses of ghrelin on spatial memory in the PTZ-treated rats [10]. These findings indicate that the GHS-R1a blocking in the rat's brain using a selective antagonist impairs memory encoding and emphasis the idea of the signaling of endogenous ghrelin in the rat's brain is vital for memory attainment and merging [2]. A long-term schedule of ghrelin therapy can have a possible therapeutic value for impaired cognitive function and ghrelin treatment might improve spatial memory and reduce the apoptotic cell number in the hippocampus of methamphetamine-treated animals [6, 13]. Advantageous impacts of ghrelin are mediated fairly by the N-Methyl-D-aspartic acid (NMDA) receptor signaling and ghrelin in the amygdale dependent learning [14, 15]. Ghrelin in the dorsal hippocampal network avoids disrupting the influence of morphine in avoidance memory. Furthermore, ghrelin empowers the nicotine improving impact on morphine-induced impairment and also the hippocampal nicotinic receptors which are involved in this procedure [12]. Infusion of ghrelin into the lateral ventricle was identified to behave this potency to preventing morphine-induced memory impairment loss. The median septal area appears to mediate the ghrelin effects on morphine-induced amnesia [16]. Based on the co-administration of ghrelin and compound C highlighted the reductive effect of ghrelin on memory, and it could be considered that this presentation is at least in part, mediated via the AMP-activated protein kinase (AMPK) pathway [17].

As a limitation, these data must be interpreted with caution because our population was not large enough and we only evaluated studies conducted in a limited area. Further studies with larger numbers of articles are needed to confirm our results.

Table 1. Characteristics of studies included in the meta-analysis

Study	Publication year	City/Region	Weight (g)	Sample size	Outcome index	P-value	Drug	Control	Ref
Babri	2013	Tabriz	230–250	90	1. Escape latency 2. Total swimming distance	1. P < 0.05 2. P < 0.05	PTZ + GH	Saline	[10]
Beheshti	2015	Isfahan	230–280	72	1. STL 2. TDC 3. NST up to 600 s	1. P < 0.05 2. P < 0.05 3. P < 0.05	Bolok ghrelin(D-Lys-3-GHRP-6)	Saline	[2]
Eslami	2018	Tehran	250 ± 20	20	1. STL 2. PAL(STL, TLC, and TDC)	1. P < 0.01 2. P < 0.01	Treatment (Aβ+Ghr)	Sal+Ghr (ghrelin-control)	[6]
Fallahi	2019	Tabriz	220–250	60	1. Escape latency 2. Traveled distance parameters 3. STL up to 600 s	1. P < 0.05 2. P < 0.05 3. P < 0.001	Methamphetamine /Simultaneous Ghrelin (MeSG)	Saline/Saline group (SeS)	[13]
Goshadrou	2013	Tehran	200 + 20	32	1. STL 2. TDC	1. P < 0.05 2. P < 0.001	Different doses of ghrelin (200 ng/rat and 400 ng/rat) Ghrelin 200 ng/rat and MK 801	MK-801	[14]
Goshadrou	2012	Tehran	200–250	40	1. STL	1. P < 0.01	Sal + Ghr	Saline+ Saline	[15]
Mohaddes	2011	Tabriz	230–250	50	1. Escape latency 2. Total swimming distance	1. P < 0.05 2. P < 0.05	Ghrelin	Saline	[11]
Nazari-Serenjeh	2019	Tehran	220–250	35	1. STL	1. P < 0.001	Saline/Ghrelin/Nicotine/Morphine	Saline/Saline/Morphine	[12]
Shafieifar	2019	Arak	220–250	84	1. STL 2. TDC	1. P < 0.001 2. P < 0.001	Ghrelin plus saline	Morphine/Lidocaine	[16]
Zahiri	2019	Guilan	200–250	64	1. STL 2. TDC	1. P < 0.001 2. P < 0.001	PTZ + Ghrelin	Saline	[17]

Abbreviations: MVM: Morris water maze; GH: Ghrelin; PTZ: Pentylentetrazol; AMPK: Adenosine Monophosphate Kinase; PAL: Passive avoidance learning; STL: Step-through latency; TDC: Time spent in the dark compartment; NST: Step-through into the dark compartment; GHRP: Growth hormone-releasing peptide

In an animal model, ghrelin has a significant role to improve memory ability and learning. But the most effective stimulating (intraventricular injection of ghrelin or systemic) is still imprecise. The results of this review have shown that the effect of ghrelin improves acquisition, consolidation, and retrieval of passive avoidance memory and could reduce the time of escape latency, decrease the frequency of cross-platform.

Author Contributions

All authors contributed equally to this manuscript and approved the final version of the manuscripts.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Ethical declarations

Not applicable.

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