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Nociceptin and the nociceptin receptor in learning and memory

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Summary

There are many processes in which the neuropeptide nociceptin/orphanin FQ (N/OFQ or nociceptin) is involved in the brain. The role of nociceptin in learning and memory holds promise in modulating these processes in health and disease in the human brain. This review summarizes the body of research focused on N/OFQ and its specific receptor, the nociceptin receptor (NOP receptor), in learning and memory, and its potential mechanisms of action, in which acetylcholine, NMDA receptor and noradrenaline may be critical. Finally, the association between NOP receptor and Posttraumatic stress disorder (PTSD), a psychiatric disorder with altered fear learning, is examined as one of the potential outcomes resulting from pathological consequences of dysregulation of N/OFQ-NOP receptor in the brain.

Keywords

Orl1; Oprl1; NOP receptor; nociceptin; N/OFQ; learning; memory; fear; amygdala; hippocampus; PTSD

1. Introduction

Nociceptin receptor (NOP receptor) (Mollereau et al., 1994), encoded by the gene Opioid receptor-like 1 (*Oprl1*), is a G protein-coupled receptor, and the last discovered member of the opioid family. Its specific endogenous agonist was named Nociceptin/Orphanin FQ (N/OFQ). The term nociceptin comes from one of the first physiological actions shown for this peptide which was pronociceptive (Meunier et al., 1995). Civellís group also reported that the same peptide, which they called Orphanin FQ, was a heptadecapeptide (FGGFTGARKSARKLANQ) that activated the NOP receptor (Reinscheid et al., 1995). Similar to other opioid peptides, N/OFQ is synthesized from a precursor protein,

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Conflicts of interest

None declared.

PreproN/OFQ (encoded by the Prepronociceptin gene, *Pnoc*) (Saito et al., 1995). N/OFQ is homologous with the opioid peptides, but it does not bind to the opioid receptors (Meunier, 1997). At a genetic level, NOP receptor belongs to the opioid family for its similarity. However, opioid ligands do not bind with high affinity to NOP receptor and this is why it was called the “orphan” opioid receptor.

N/OFQ-NOP receptors are abundantly expressed in the central nervous system and peripheral organs, having different roles in several functions such as stress, immunology, depression, cardiovascular responses, drug abuse and anxiety (Bodnar, 2013; Gavioli and Calo, 2013; Mallimo and Kusnecov, 2013). In recent years the association between N/OFQ-NOP receptor and memory functions has gained considerable interest. The discovery of the molecular mechanisms of learning and memory are helping to elucidate how brain processes store and recall information normally and in pathological states, although little is still known. The N/OFQ-NOP receptor pathway may have an important advantage as a mediator of memory regulation, in contrast to other opioids, which makes it an attractive potential therapeutic tool. For example, NOP receptor activation does not induce rewarding effects, per se, in monkeys and rats (Devine et al., 1996; Ko et al., 2009). In brief, it is well known that N/OFQ and NOP receptor agonism impairs memory whereas NOP receptor antagonists have been shown to block this effect (see Table 1). Surprisingly, there are very few studies examining the role of N/OFQ-NOP receptor antagonism enhancing learning and memory, which could have relevant implications for treating several human disorders (see Table 2).

2. Nociceptin and the Nociceptin receptor in learning and memory

Memories arise from interactions between a number of structures that compose a neural circuit. However, this review will only focus on the hippocampus and amygdala because they are the brain areas that have been studied for the role of N/OFQ-NOP receptor in learning and memory.

It is widely accepted that synaptic plasticity is necessary for the formation of memories. Synaptic plasticity is the process by which connections between two neurons, or synapses, change in strength. These changes involve alterations of the synapses at a structural and functional level, which regulate long-term potentiation (LTP), as one model of synaptic plasticity. Sigurdsson and colleagues defined LTP as a “... long-lasting enhancement in the efficiency of synaptic communication between neurons” (Sigurdsson et al., 2007).

The hippocampus is crucial for emotional, spatial and declarative memory. This information is processed in the hippocampus, from the entorhinal cortex, to the dentate gyrus, CA3 and then to CA1, the main hippocampal output. The hippocampus has a critical role in time-limited consolidation of new short-term memory into more stable long-term memory. These memories are gradually stored in the cortex at the completion of this hippocampus-dependent consolidation (Zola-Morgan and Squire, 1990).

Within the circuitry of fear formation, the amygdala is key, since it is considered to be the main site of plasticity for fear learning. During fear conditioning, the amygdala receives information associating the conditioned stimulus (CS) and unconditioned stimulus (US) in the lateral nucleus of the amygdala. The lateral nucleus of the amygdala is interconnected

with the central nucleus of the amygdala (CeA). Outputs from the CeA, via the basolateral amygdala (BLA), elicit specific fear-related behaviors called conditioned fear responses (Maren and Quirk, 2004).

After the initial surprise and excitement of the role of N/OFQ-NOP receptor on memory and their postulated molecular mechanisms (Goda and Mutneja, 1998), there have been some updates in recent years that will be reviewed here. Different groups have reported that deletion of the NOP receptor in transgenic mice enhances NMDA receptor-dependent LTP in the CA1 and improves performance in memory tests that are highly dependent on hippocampal functioning, such as the water maze (Mamiya et al., 1998; Manabe et al., 1998; Taverna et al., 2005). Of note, rats with constitutive *Oprl1* deletion present unaltered levels in μ , δ and κ opioid receptors (Homberg et al., 2009). Concordantly, *Pnoc* knockout (ko) mice present similar improvements to the above *Oprl1* ko animals in hippocampal functioning in spatial memory (Higgins et al., 2002; Kuzmin et al., 2009). Of note, however, two studies found discrepancies with these findings, showing that *Pnoc* ko mice exhibit normal LTP (Higgins et al., 2002) and no significant differences in memory consolidation in the water maze when compared to wild-type mice (Koster et al., 1999). The differences in electrophysiological and behavioral data in these studies may be caused by procedural differences, or they may be due to biological effects such as differences in the mechanisms of synaptic plasticity with the loss of the receptor compared to the loss of the peptide. Moreover, it needs to be highlighted that the *Pnoc* gene encodes other peptides besides N/OFQ. Thus, other peptides are also knocked out in these transgenic mice. This factor could also be influencing the conflicting results from experiments involving *Pnoc* ko and *Oprl1* ko mice. Clearly, more studies are needed for a better understanding of this issue (see Table 3).

Based on the above data, the generation of mice with constitutive manipulations of a gene has provided helpful information in the study of the functions of the N/OFQ-NOP receptor in the brain. However, it would be quite helpful for the field to generate new transgenic mice that allow temporal and spatial specificity allowing conditional manipulation of the mouse genome (Spangler et al., 2012), for example, using the Cre-lox technology or the tetracycline transactivator (tTA). Additionally, the use of techniques such as optogenetics and Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) that allow precise control of specific N/OFQ-NOP receptor neuronal populations in learning and memory would provide important new approaches.

These new technologies would allow the study of the functions of the N/OFQ and the NOP receptor in specific areas of the brain in memory functions. For example, it has recently been reported that the CA2 area of the hippocampus is a critical hub of sociocognitive memory processing (Hitti and Siegelbaum, 2014). Thus, it could be relevant to study the specific role of N/OFQ and the NOP receptor in the CA2 area related to social memory.

2.1. Nociceptin and nociceptin receptor agonists/antagonists in learning and memory

The pharmacological studies of N/OFQ-NOP receptor in animals may help us to find drugs that could be given to humans to impair or enhance memory functions in health and disease. Since N/OFQ does not cross the blood brain barrier, molecules have been synthesized to mimic its actions and activate the NOP receptor in the brain when systemically injected.

Overall, the pharmacological studies are in line with the reports in transgenic *Prn⁰/Opr¹* ko mice, together suggesting that decreased activation of the NOP receptor is associated with enhanced memory, whereas its activation impairs memory. Initial studies suggested a dose-dependent biphasic effect of an intrahippocampal infusion of N/OFQ, in which low doses (0.33 to 1nmol) enhanced memory in the water maze and high doses (>5nmol) resulted in an impairment (Redrobe et al., 2000; Sandin et al., 1997; Sandin et al., 2004). Interestingly, this effect is rescued by NOP receptor antagonists (Hiramatsu et al., 2008; Redrobe et al., 2000; Sandin et al., 2004). The impairment of learning and memory by a single dose of N/OFQ or NOP receptor agonists has been consistently reported in different tasks that are highly dependent on hippocampal and amygdala functioning, when N/OFQ or NOP receptor agonists are administered through different routes (See Table 1 for detailed information). Concordantly, N/OFQ decreases LTP in the CA1 in rats (Yu et al., 1997). However, the enhanced spatial memory functions elicited by low doses of N/OFQ have not been replicated in a study in mice, suggesting differences between species (Kuzmin et al., 2009). More studies would be needed to further understand the potential role of N/OFQ agonism enhancing learning and memory.

NOP receptor agonism with N/OFQ or the NOP receptor agonist Ro64-6198 has consistently been shown to impair memory consolidation in contextual fear and passive avoidance paradigms (Fornari et al., 2008; Goeldner et al., 2009; Higgins et al., 2002; Hiramatsu and Inoue, 1999; Mamiya et al., 2003; Roozendaal et al., 2007), tasks highly dependent on hippocampal functioning. However, results in cued-fear conditioning, where the association of the CS+US is dependent primarily on the amygdala, appear to be drug and dose dependent. Experiments in mice show that neither Ro64-6198 injected subcutaneously nor N/OFQ infused at low doses i.c.v. (0.1 to 1nmol) did not affect cued-fear memory consolidation (Goeldner et al., 2009; Mamiya et al., 2003). In contrast, higher doses of N/OFQ i.c.v. (2.5 to 5nmol) and the recently discovered NOP receptor agonist SR-8993, given i.p. and intra-CeA after fear acquisition, impairs cued-fear memory consolidation (Andero et al., 2013; Fornari et al., 2008). It is not possible to draw conclusions about these experiments because different drugs were administered through different routes. Therefore, more experiments about contextual and cue-dependent fear are needed to further understand the role of N/OFQ-NOP receptor in learning and memory.

Two studies show differences in the effect of the central amygdala (CeA) NOP receptor activation in memory consolidation. It was reported that infusion of N/OFQ (1pmol) in the CeA following inhibitory avoidance training in rats had no effect on memory consolidation, whereas the same dose in the BLA caused an impairment (Roozendaal et al., 2007). Another more recent study in mice showed that an intra-CeA infusion of SR-8993 (100ng) given immediately after cued-fear acquisition impaired memory consolidation (Andero et al., 2013). Thus, these differences may be task-dependent or due to the fact that these two studies performed experiments in different species.

It is known that stress can alter N/OFQ-NOP receptor memory functions (Mallimo and Kusnecov, 2013). Thus, it is interesting that SR-8993 showed efficacy in preventing cued-fear memory consolidation in mice that had a previous traumatic stress exposure to immobilization to a wooden board (IMO) 6 days before being tested for cued-fear learning

(Andero et al., 2013). Of note, SR-8993 given systemically before cued-fear conditioning did not elicit changes in pain sensitivity evaluated with shock reactivity.

At a translational level, the use of radiolabeled molecules that bind the NOP receptor in the brain (Hostetler et al., 2013; Kimura et al., 2011; Linz et al., 2014; Lohith et al., 2014; Lohith et al., 2012; Pedregal et al., 2012; Pike et al., 2011; Thomsen et al., 2000) could provide insight into the association between N/OFQ-NOP receptor levels, human learning and memory, and brain disorders (e.g. Posttraumatic stress disorder, Alzheimer, Parkinson, etc.). However, more specific studies are needed.

3. Interactions of N/OFQ-NOP receptor with other systems in learning and memory

Upon binding of N/OFQ with the NOP receptor and activation of a G protein there is inhibition of the formation of cAMP, activation of phospholipase C (PLC) and stimulation of K⁺ conductance, inhibition of high voltage activated N-type Ca²⁺ channels, and activation of mitogen-activated protein-kinases (New and Wong, 2002). The regulation by N/OFQ of ion channel activity may cause this inhibition of neuronal excitability, LTP in the hippocampus and release of neurotransmitters, including substance P, dopamine, acetylcholine, noradrenaline, GABA and glutamate (Bongsebandhu-phubhakdi and Manabe, 2007; Hawes et al., 2000; Yu et al., 1997). Moreover, *in vitro* studies show that N/OFQ inhibits serotonin release in the cortex (Siniscalchi et al., 1999).

NMDA

The interactions between N/OFQ-NOP receptor and other neurotransmitters in learning and memory are exemplified in studies in mice where activation of the NOP receptor impairs object recognition memory by interacting with N-methyl-D-aspartic acid (NMDA) receptor and its downstream signaling ERK-1/2 in the hippocampus (Goeldner et al., 2008). Also, NMDA receptor and N/OFQ-NOP receptor interactions may be critical for the consolidation of contextual fear memories (Goeldner et al., 2009). MK-801 (a non-competitive NMDA receptor antagonist) and Ro64-6198 given systemically in mice at sub-optimal doses separately do not elicit changes in fear memory consolidation. However, when these sub-optimal doses were given simultaneously, they reduced contextual freezing. One possible interpretation is that NOP receptor impairment of memory may be mediated through glutamatergic function at NMDA receptors. In fact, experiments in rat cortical neuronal slices suggest that NOP receptor activation inhibits K⁺ depolarization-evoked glutamate release (Nicol et al., 1996). However, it is also possible that there are no interactions of glutamate/NMDA and NOP receptors in fear memory and that these effects actually occur through parallel pathways. Thus, additional experiments addressing this issue would be very helpful to further understand potential interactions of N/OFQ-NOP with glutamate and the NMDA receptor in learning and memory.

Acetylcholine

A number of studies suggest N/OFQ-NOP receptor may interact with acetylcholine in learning and memory. However, divergent results are presented, making it difficult to

interpret them together. [Nphe1]nociceptin(1-13)NH₂(Nphe), an NOP receptor antagonist, has been shown to inhibit cholinergic transmission in the hippocampus (Cavallini et al., 2003). Moreover, N/OFQ given i.c.v reduces the acetylcholine release in the rat hippocampus (Hiramatsu et al., 2008). Finally, NOP receptor ko mice present enhanced basal hippocampal acetylcholine release (Uezu et al., 2005). Because acetylcholine is necessary for the formation of memories (Blake et al., 2014), specific experiments would be needed to determine if N/OFQ-NOP receptor modulates the consolidation of memory.

Noradrenaline

The β_1 -adrenoceptor antagonist, atenolol, within the BLA potentiates the effects of N/OFQ, thereby impairing the consolidation of inhibitory avoidance (Roosendaal et al., 2007). Moreover, the enhanced memory consolidation elicited by the NOP receptor antagonist [Nphe(1)]nociceptin(1-13)NH₂ is blocked by atenolol. Other data also suggest that the noradrenergic system may regulate the release of noradrenaline in the BLA. A systemic dose of the NOP receptor antagonist J-113397 was shown to increase the noradrenaline levels within the BLA and a local infusion of N/OFQ inhibits this release (Kawahara et al., 2004). Concordantly, infusions of N/OFQ into the BLA suppress noradrenaline levels (Kawahara et al., 2004). Thus, noradrenaline and N/OFQ-NOP receptor interactions could have an important impact on learning and memory functions.

4. Implications of N/OFQ-NOP receptor in human brain disorders of altered learning and memory and in animal models

Little is known about the role of N/OFQ-NOP receptor in brain disorders. Human studies show a relationship between OPRL1 and drug addiction, especially alcoholism, when evaluating single nucleotide polymorphisms (SNP) and DNA methylation in blood (Huang et al., 2008; Xuei et al., 2008; Zhang et al., 2013). This association seems more intense in subjects with a history of child abuse (Zhang et al., 2013), which is in line with studies on Posttraumatic stress disorder (PTSD). PTSD is a debilitating anxiety disorder with altered fear processing in which dysregulation of emotional memory consolidation is important. It has been shown that individuals with the G allele at the SNP rs6010719 of the OPRL1 gene present high rates of current and lifetime PTSD (Andero et al., 2013). Moreover, G carriers also have impaired discrimination between safety and danger cues in fear-potentiated startle and increased connectivity between the amygdala and the insula. Future research should address if the intronic SNP rs6010719 affects transcription, translation, expression or activity of the NOP receptor or if it is linked to another SNP modulating the function of other genes.

At a molecular level within the amygdala, gene regulation and protein synthesis are needed for the consolidation of fear memory formation. Interestingly, in the same study, authors found that mice with a previous exposure to IMO presented differences in the regulation of the NOP receptor when compared to mice with no previous stress exposure (Andero et al., 2013). Specifically it was found that the expression of NOP receptor mRNA levels in the amygdala of IMO mice exposed to cued-fear conditioning was significantly higher than that in mice that had not received IMO. This may suggest that under normal or pathological

conditions the regulation of N/OFQ-NOP receptor may present notable changes in the regulation of memory functions.

PTSD is often comorbid with chronic pain (Beckham et al., 1997; Seal et al., 2012) and N/OFQ-NOP receptors have been shown to have a role in pain modulation. Thus, another important point from PTSD-like animal models is their potential effects on hyperalgesia that could affect memory consolidation. A 2 hour exposure to IMO does not produce changes in the response to electric footshocks (Andero et al., 2011) but it cannot be ignored that other tests may reveal an effect on pain modulation. Interestingly, IMO in mice results in both impaired within-session extinction and extinction retention (Andero et al., 2013; Andero et al., 2011). Another PTSD-like model, Single Prolonged Stress (SPS) consists of a single exposure to 2 hours of restraint stress followed by 20 minutes of forced swimming and exposure to the anesthetic diethyl ether until loss of consciousness (Liberzon et al., 1997). SPS is mainly used in rats. SPS elicits a deficit in fear extinction retention (Knox et al., 2012), has been shown to present enhanced N/OFQ levels in the hippocampus, cerebrospinal fluid and changes in allodynia and hyperalgesia (Zhang et al., 2014).

5. Conclusions

It is clear that the N/OFQ-NOP receptor pathway is critical for learning and memory in animal studies and altered fear learning in PTSD. However, there is still much more work needed to understand the underlying mechanisms of this pathway. This may lead to new pharmacological tools that may help to boost human memory in the healthy individual and in the treatment of brain disorders with alterations in memory. Thus, it is necessary to perform more studies with old or new molecules that potently and specifically target the NOP receptor in humans. Preclinical studies can provide valuable information which may eventually enable human trials. However, special attention needs to be given when performing experiments studying the role of N/OFQ-NOP receptor in learning and memory because they are also important modulators of pain processing. Some experimental tasks such as fear conditioning have a component of pain. Thus, this pain component needs to be properly controlled to study mnemonic actions of N/OFQ-NOP receptor.

In short, the N/OFQ-NOP receptor pathway offers very exciting opportunities in the study of learning and memory that could eventually be translated to humans.

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Highlights

- Nociceptin receptor agonists impair memory whereas antagonists enhance it.
- Nociceptin receptor is associated with Posttraumatic stress disorder.
- Nociceptin interacts with NMDA, Noradrenaline and Acetylcholine in memory functions.

table 1

OFQ/N or NOP receptor agonists in learning and memory

Reference	Route	Molecule	Dose	Animal	Actions on consolidation
Fornari et al., 2008	i.c.v.	OFQ/N	2.5/5 nmol	Adult male Wistar rats	↓ Contextual and auditory fear conditioning
Andero et al., 2013	i.p. / intra-CeA	SR-8993	3mg/Kg / 100ng	Adult male C57 mice >	↓ Auditory fear conditioning
Reiss et al., 2012	ip.	Ro64-6198	0.3mg/Kg	8 week male C57 mice	↓ Object recognition
Goeldner et al., 2009	s.c.	Ro64-6198	1mg/Kg	8 week male C57 mice	↓ Contextual fear conditioning
Goeldner et al., 2009	s.c.	Ro64-6198	0.3/1mg/Kg	8 week male C57 mice	No effect in auditory fear conditioning
Higgins et al., 2002	systemic	Ro64-6198	0.3/1mg/Kg	22-28g male C57 mice	↓ Water Maze, contextual fear conditioning, passive avoidance and delayed (non) match to position.
Hiramatsu & Kaori Inoue, 1999	i.c.v.	OFQ/N	5 nmol	7 week old male ddY mice	↓ Passive avoidance learning
Kuzmin et al., 2009	i.c.v. / intra-CA3 / i.p.	OFQ/N / Ro64-6198	5-10 nmol / 1nmol / 0.3-1 mg/Kg	Adult male Phoc KO	↓ Water Maz
Kuzmin et al., 2009	i.c.v.	OFQ/N	10nmol	Adult male OFQ/N KO	No effect in Water Maze
Mamiya et al., 2003	i.c.v.	OFQ/N	0.1/1nmol	wild-type mice	↓ Contextual fear conditioning
Mamiya et al., 2003	i.c.v.	OFQ/N	0.1/1nmol	wild-type mice	No effect in auditory fear conditioning
Redrobe et al., 2000	intrahippocampal	OFQ/N	5nmol	Adult male Sprague-Dawley rats	↓ Water Maze
Sandin et al., 2004	intra-CA3	OFQ/N	3.3 nmol	Adult male Sprague-Dawley rats	↓ Water Maze
Sandin et al., 2004	intra-CA3	OFQ/N	0.33/1nmol	Adult male Sprague-Dawley rats	↑ Water Maze
Sandin et al., 1997	intra-CA3	OFQ/N	10nmol	Adult male Sprague-Dawley rats	↓ Water Maze
Rooszendaal et al., 2007	intra-BLA	OFQ/N	0.01-100 pmol	Adult male Sprague-Dawley rats	↓ Inhibitory avoidance
Rooszendaal et al., 2007	intra-CeA	OFQ/N	1pmol	Adult male Sprague-Dawley rats	No effect in Inhibitory avoidance

Reference	Route	Molecule	Dose	Animal	Actions on consolidation
Goeldner et al., 2008	i.c.v. / intra-Hippocampus	OFQ/N	1nmol / 3nmol	8 week male C57 mice	↓ Object recognition
Hiramatsu & Kaori Inoue, 1999	i.c.v.	OFQ/N	1-1000fmol	7 week old male ddY mice	↑ Y-Maze and passive avoidance (rescues the deficit in memory elicited by scopolamine)
Sandin et al., 1999	intra-CA3	OFQ/N(1-13)	10nmol	Adult male Sprague-Dawley rats	No effect in Water Maze
Mamiya et al., 1999	i.c.v.	OFQ/N	1-10pmol	Adult male C57 mice	No effect in Y Maze
Mamiya et al., 1999	i.c.v.	OFQ/N	1-10pmol	Adult male C57 mice	↓ Passive avoidance learning
Yu et al., 1997	CA1	OFQ/N	1μM	24-40 days male Sprague-Dawley rats	↓ Long-term potentiation
Hiramatsu et al., 2008	i.c.v.	OFQ/N	500pmol	Adult male Sprague-Dawley rats	↓ Passive avoidance learning

table 2

NOP receptor antagonists in learning and memory

Reference	Route	Molecule	Dose	Animal	Actions on consolidation
Redrobe et al., 2000	intrahippocampal	[Nphe1]-Nociceptin	50nmol	Adult male Sprague-Dawley rats	Rescues the deficit elicited by OFQ/N in Water Maze
Sandin et al., 2004	intra-CA3	NC-NH ₂	10nmol	Adult male Sprague-Dawley rats	Rescues the deficit elicited by OFQ/N in Water Maze.
Roosendaal et al., 2007	intra-BLA	[Nphe(1)]nociceptin(1-13)NH(2)	1-100 pmol	Adult male Sprague-Dawley rats	↑ Inhibitory avoidance
Hiramatsu et al., 2008	i.c.v.	[Nphe(1)]nociceptin(1-13)NH(2)	1nmol	Adult male Sprague-Dawley rats	Rescues the deficit elicited by OFQ/N in Passive avoidance

table 3

Pnoc/Oprl1 transgenic mice in learning and memory

Reference	Animal	Actions on consolidation
Manabe et al., 1998	Adult male Oprl1 KO	↑ Water Maze, passive avoidance and LTP (CA1)
Mamiya et al., 1998	Adult male Oprl1 KO	↑ Water-finding test
Higgins et al., 2002	Adult male Pnoc KO	↑ Water Maze, passive avoidance, cued-fear conditioning, no effect in LTP (CA1)
Taverna et al., 2005	Adult male Oprl1 KO	↑ LTP and EPSP (CA1)
Kuzmin et al., 2009	Adult male Pnoc KO	↑ Water Maze
Koster et al. 1999	Adult male Pnoc KO	No effect in Water Maze