The role of adiponectin receptors in the regulation of synaptic transmission in the hippocampus

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Abstract

In the last two decades adiponectin, member of the adipokines family, gained attention because of its unique antidiabetic effects. However, the presence in the brain of adiponectin receptors and adiponectin itself raised interest because of the possible association with neuropsychiatric diseases. Indeed, clinical studies found altered concentration of adiponectin both in plasma and cerebrospinal fluid in several pathologies including depression, multiple sclerosis, Alzheimer’s disease and stroke. Moreover, recent preclinical studies also suggest its involvement in different physiological functions. Despite this evidence very few studies attempted to elucidate the functional role of adiponectin at the synapse. To address this question, here we investigated the effect of Adiporon, an agonist of both adiponectin receptors on synaptic transmission and LTP at Schaffer-collateral CA1 pathway. Surprisingly, increasing concentration of Adiporon correlated with lower CA1-LTP levels and paired-pulse ratio, whereas basal transmission was always preserved. Collectively, our data show that the adiponectin system, beyond its involvement in metabolic diseases, plays also a critical role in synaptic activity thereby representing a putative target for the treatment of synaptic pathologies.

Key words: Adiponectin, synaptic plasticity, hippocampus, Long Term Potentiation, electrophysiology, Adiporon

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INTRODUCTION

Adiponectin, a member of the Adipokine family, has sparked new enthusiasm in the field of metabolic diseases and paved the way for a new generation of drugs affecting metabolism (Okada-Iwabu et al., 2015). In fact, a key role of adiponectin in several metabolic and inflammatory disorders has recently emerged. Accordingly, plasma adiponectin levels were found decreased in obesity, insulin resistance, and type 2 diabetes (Kadowaki et al., 2006). Moreover, adiponectin exerts a protective role in several pathologies, such as cardiovascular diseases, cancer, and appears also to promote longevity (Yamauchi and Kadowaki, 2013). However, after the discovery of adiponectin in human cerebrospinal fluid (Kos et al., 2007), the adiponectin system gained attention and several clinical studies suggested a role in neuropsychiatric diseases, such as depression (Leo et al., 2006; Narita et al., 2006), cognitive impairment associated with diabetes (Masaki et al., 2012; Gorska-Ciebiada et al., 2015), Alzheimer’s disease (Teixeira et al., 2013), stroke (Sasaki et al., 2007), multiple sclerosis (Musabak et al., 2010) and attention deficit hyperactivity disorder (Mavroconstanti et al., 2014). In particular, those studies have all reported lower circulating levels of adiponectin. Preclinical studies further confirmed the involvement of adiponectin in several brain disorders including depression (Yau et al., 2014), Alzheimer’s disease (Chan et al., 2012; Ali et al., 2015), stroke (Song et al., 2013), fear learning (Zhang et al., 2016b) and epilepsy (Lee et al., 2011). These pathologies share, to different degrees, a disruption in synaptic plasticity (Ganguly and Poo, 2013). Adiponectin also pays a role in several physiological conditions such as hormonal release (Wen et al., 2008; Hoyda et al., 2009; Hoyda and Ferguson, 2010; Mimee et al., 2013), feeding behavior (Qi et al., 2004) and neurogenesis (Yau et al., 2014). Adiponectin is an adipocyte-derived polypeptide released into the circulation in the configuration of full-length trimers, hexamers, high molecular weight (HMW) multimers and a globular fraction called globular adiponectin (gAD), generated by proteolytic cleavage of the full-length protein (Waki et al., 2005). Surprisingly this protein is one of the most abundant, representing 0.05% of total plasma proteins (Scherer et al., 1995). Adiponectin exerts its effects by binding three receptors. Two of them, adipor1 and adipor2, are integral membrane proteins with seven transmembrane domains (7TM). However, these receptors possess an intracellular amino terminus and an extracellular carboxyl-terminus which renders them a novel structural class (Tanabe et al., 2015). The third receptor is T-cadherin which is also an LDL receptor. The transduction pathways of adipor1 and 2 culminate in the activation of AMPK and PPARα while T-cadherin acts in an unknown way (Wang and Scherer, 2016). Adiponectin is released in a unique fashion since it is the only protein that increases with weight loss (Wang and Scherer, 2016). However, it has been suggested that adiponectin plasmatic level could increase also with chronic and acute physical activity (Vuolteenaho et al., 2014). Once adiponectin reaches the circulation, it could pass, at least in the trimeric form, the blood-brain barrier (Kusminski et al., 2007; Yau et al., 2014). On other hand adiponectin mRNA has been repeatedly detected in central nervous system (Rodriguez-Pacheco et al., 2007; Iannitti et al., 2015). Thus, central nervous system could have the competence to locally produce and release adiponectin, although it is not clear whether this protein acts locally or rather its effect might influence larger numbers of cells and cerebrospinal fluid content. However, it is well recognized that both adiponectin receptors are highly expressed in different brain areas; in particular the hypothalamus, thalamus, neocortex and hippocampus (Repunte-canonigo et al., 2011; Yau et al., 2014). In the latter area, Adipor1 and 2 have been localized both in the CA3 and CA1 sub-regions (Liu et al., 2012). Subcellular localization performed in hippocampal and cortical cell cultures showed a mixed pattern of expression ranging from soma and dendrites to axon terminals (Qiu et al., 2011; Thundyl et al., 2010).

Despite mounting evidence of adiponectin involvement in many neuropsychiatric diseases which show a synaptic pathology (Ganguly and Poo, 2013), their physiological role in the synapse remains elusive. One
experimental difficulty could be represented by the fact that, for the majority of relevant functions, both principal receptors must be activated simultaneously (Yamauchi et al., 2007). On the other hand, adipoR1 and 2 show divergent $K_d$ values for different adiponectin forms (Yamauchi and Kadowaki, 2013). As the receptors are highly expressed in hippocampus (Repunte-canigo et al., 2011; Thundyil et al., 2010) we employed a selective agonist for adipoR1 and 2 (Adiporon, ADPO) with similar $K_d$ values for both subtypes (Okada-Iwabu et al., 2013). In this way, we were able to investigate their functional role in synaptic transmission and neuroplasticity at CA1 hippocampal synapses.

**MATERIALS AND METHODS**

**Animals**

Experiments were carried out in accordance with the guidelines established by the European Communities Council (Directive 2010/63/EU of 22 September 2010) and accepted by the Italian Ministry of Health (D.Lgs. 26/2014) and approved by the Ethical Committee on animal experiments of Santa Lucia Foundation (Rome, Italy). Two- to four-week-old male C57BL/6J mice (Young group) and five-to eight-week-old male C57BL/6J mice (Adult group) were used for all experiments.

**Electrophysiology**

Preparation of mouse brain slices was performed as previously described (Nisticò et al., 2013). Parasagittal hippocampal slices (thickness, 250–350 μm) were cut using a Vibratome (Leica VT1000 S) and incubated for 1 h in a holding chamber and then transferred to a recording chamber, completely submerged in artificial cerebrospinal fluid (ACSF, 30–31°C) of the following composition (in mM): NaCl (124), KCl (3), MgCl$_2$ (1), CaCl$_2$ (2), Na$_2$HPO$_4$ (1.25), NaHCO$_3$ (26), glucose (10); saturated with 95% O$_2$, 5% CO$_2$. For extracellular recordings, bipolar stimulating electrode was placed in the stratum radiatum to activate the Schaffer collateral commissural fibers. Recordings of field excitatory post-synaptic potentials (fEPSPs) were made in the middle of the stratum radiatum by using microelectrodes filled with ACSF (resistance 3–5 MΩ). For slices in which the presynaptic fiber volley was distinguishable, input-output curves were examined by plotting the initial slope of the fEPSP against the amplitude of the presynaptic fiber volley. Long-term potentiation (LTP) was induced by high-frequency stimulation (HFS; 100 Hz, duration 1 s).

For patch-clamp experiments, CA1 pyramidal neurons were recorded in whole-cell configuration using 1.5 mm borosilicate glass electrodes (4-7 MΩ) filled with a solution containing the following (in mM): CsCH$_2$SO$_3$ (115), CsCl (135), KCl (10), CaCl$_2$ (0.05), EGTA (0.1), Hepes (10), Na$_3$GTP (0.3), Mg-GTP (4), pH adjusted to 7.3 with CsOH. The AMPA/NMDA ratio was obtained from EPSCs elicited at 0.033 Hz with a glass pipette filled with ACSF, close to the dendritic region of the recorded neuron. The AMPA component was evaluated by the peak amplitude of the EPSC recorded at -80 mV holding potential, while the NMDA component in a 2 ms window at 60 ms delay from the stimulation artefact, while holding the cell at +40 mV.

**Drug Treatments**

Adiporon (ADPO; Sigma) was dissolved in dimethyl sulfoxide (DMSO), prepared as stock solutions and diluted to the final concentration immediately before use. Final concentrations were as follows: ADPO (1.5, 3, 30 µM). DMSO was used both in treated and in vehicle groups and the final concentration of DMSO was less than 0.5% in all experiments. Incubation of hippocampal slices with drugs was performed in an
incubation chamber. The pre-incubated treated and vehicle slices were held in ACSF with or without several concentration of ADPO for 1.5-2 hours before recordings.

**Statistical Analysis**

For statistical analysis we used unpaired t test after LTP induction (on the average of the last 10 min of recording). The overall depolarization during HFS has been quantified using a slightly modified method (Kuenzi et al., 2000) by measuring the area under the curve (AUC) during the 100 Hz train stimulus using as y value the baseline and normalising each obtained AUC to the first fEPSP in each train. All data are presented as mean ± SEM, statistical differences were evaluated using Student t-test paired or unpaired, and “n” indicates the number of slices or neurons. P < 0.05 was considered significant.

**RESULTS**

**Adiporon affects paired pulse ratio but does not influence basal synaptic transmission**

After 20 min of stable baseline recordings, consecutive application of increasing concentrations of ADPO (1.5, 3, 30 μM) for 15 minutes did not modify basal synaptic transmission (data not shown). In a subset of experiments, we delivered a tetanic stimulation to Schaffer collaterals (100 Hz, 1 sec) following perfusion of ADPO. Although some increase in LTP magnitude was present, it did not reach statistical significance (data not shown). Since adiponectin receptors display a slow activation rate upon agonist exposure on a time scale of minutes to hours (Qiu et al., 2011; Song et al., 2013; Shah et al., 2014), we then evaluated ADPO effects after pre-incubating slices for 2 hours with increasing concentrations (1.5, 3, 30 µM). ADPO effect was always evaluated in hippocampal slices from young (two- to four-week-old) and adult (five- to eight-week-old) male C57BL/6J mice, since the mechanisms underlying synaptic transmission differ at the two age stages (Lohmann and Kessels, 2014). We then performed a paired pulse ratio (PPR) protocol to assess the paired pulse facilitation, which represents a form of short-term plasticity that occurs through presynaptic mechanisms and mirrors presynaptic release probability (Zucker and Regehr, 2002). A decrease in the PPR was present when slices were pre-incubated with ADPO at the concentration of 30 μM (p < 0.05 at all intervals; fig.1A,C) suggesting an increase in the release probability in both experimental groups. However, at the concentration of 1.5 and 3 μM, ADPO did not significantly modify the PPR (p > 0.05; fig.1A,C). Next, we performed an input-output curve analysis to investigate whether the decrease in PPR was accompanied by some changes in basal excitatory transmission. Surprisingly, none of tested concentrations of ADPO (1.5, 3, 30 μM), either pre-incubated or perfused, significantly affected the input-output curve at both ages groups (p > 0.05; fig.1B,D). The latter data suggest that, despite a change in PPR at the highest ADPO tested concentration (30 μM), the amplitude of fEPSPs was always preserved.

**Dose-dependent effect of Adiporon on CA1-LTP**

Following the investigation on the effects of ADPO on PPR and baseline transmission, we next evaluated LTP, a widely recognized model that underlies the synaptic basis of memory (Bliss and Collingridge, 1993). In a subset of experiments hippocampal slices were pre-incubated for 2 hours with different concentrations of ADPO (1.5, 3, 30 μM) and after obtaining a stable baseline, we delivered HFS protocol to Schaffer collaterals. Both age groups showed a marked reduction of LTP at the highest tested concentration of ADPO (30 μM) (fig.2A,B). However, the young age-group seemed less prone to ADPO’s dampening effect on LTP compared to the adult group. Indeed, in the Young group, meanwhile we still found a strong effect of ADPO on the PPR, the ADPO’s capability to inhibit LTP was low at the highest tested concentration (30 μM)
Adiporon affects field excitatory post-synaptic potential during tetanic stimulation

Although basal synaptic transmission was never affected by increasing concentrations of ADPO in both age-groups, we noticed an interesting alteration of fEPSP during tetanus in adult hippocampal slices pre-incubated with increasing concentrations of ADPO. Notably, fEPSPs amplitude elicited by a high frequency tetanic stimulation decreased earlier in slices treated with several ADPO concentrations (1.5, 3, 30 µM) compared to control (fig.2C). Thus, we decided to further investigate the ability of ADPO to modulate fEPSP during the high frequency tetanic stimulation, which is known to induce in neurons a strong level of depolarization which depends on calcium influx (Herron et al., 1986). To this aim, we utilized a modified method of analysis which measures the AUC (area under the curve) normalised to the first fEPSP in each train (Kuenzi et al., 2000). This method allows quantifying the level of depolarization of the post-synaptic cell during the HFS train which is correlated to the extent of LTP amplitude (Bliss and Collingridge, 1993). Unlike paired pulse facilitation, the attenuation of depolarization during HFS was concentration-dependent and correlated to the degree of LTP attenuation (p < 0.05 at all tested concentrations vs. vehicle; fig.2C).

The concentration-dependent effect of ADPO on AUC reduction matched the inhibitory effect on LTP and strongly suggests that ADPO might exert an effect also through a post-synaptic mechanism. Taken together, these data suggest that ADPO influenced PPR and LTP through different synaptic mechanisms.

Adiporon affects AMPA/NMDA ratio

We further investigated the synaptic mechanisms affected by ADPO by measuring the relative contribution of AMPA and NMDA receptors to EPSCs. AMPA/NMDA ratio was recorded following incubation of slices with ADPO (30µM) for two hours, the same condition which induces the maximal inhibition of LTP. We found a reduction of the AMPA/NMDA ratio in slices pre-incubated with ADPO compared to vehicle (vehicle 3,33±0,63 vs ADPO 1,85±0,29  p<0.05; fig 2D). These data show a change in function of AMPA and NMDA receptors that further suggest that the dampening effect of ADPO on LTP might rely also on post-synaptic mechanisms.

DISCUSSION

In this study we provide the first compelling evidence that ADPO, a selective agonist for adipor1 and 2 is able to influence synaptic plasticity in CA1 hippocampal region. Importantly, the dose-dependent dampening effect on LTP was mirrored by a reduction of responses during high frequency stimulation despite a preserved basal synaptic transmission. We assume that the inhibitory effect on LTP relies, mostly, on a post-synaptic mechanism. Indeed, we found a strong decrease of fEPSP during the high frequency
stimulation protocol that closely mirrors the concentration-dependent reduction of LTP. The induction of LTP depends critically on the depolarization of the pyramidal cells, that is a function of both excitatory synaptic connections and local GABAergic inhibitory connections (Bliss and Collingridge, 1993). The failure to induce LTP does not seem due to lack of excitatory drive as revealed by the input-output curve. The alteration in PPR could also suggest a presynaptic mechanism but, as aforementioned, ADPO effect on paired pulse facilitation was present only at the highest tested concentration (30 µM). During HFS protocol cells are heavily depolarized, therefore the more attractive candidate, which might be influenced by adiponectin receptor activation, is the NMDA receptor because of its voltage-dependency. The AMPA/NMDA ratio analysis suggests that ADPO mainly influences AMPA receptor function. However, a role for NMDA receptors cannot be ruled out, also considering the involvement of adiponectin in the response rate to ketamine in depressed patients (Machado-Vieira et al., 2016). It is conceivable that the lower depolarization during high frequency stimulation in the presence of ADPO depends on a reduction of AMPA receptor-mediated responses, which might not allow a sufficient local depolarization thereby restraining induction of LTP. On a similar note, pioneering studies using AMPA receptor antagonists showed that LTP could be completely blocked if approximately 50% of receptors were antagonized (Rammes et al., 1994), thus suggesting that even small changes in AMPA receptor function could strongly influence LTP. The fact that, at least at the highest tested ADPO concentration, the reduction of AMPA receptor function is somehow balanced by the increased glutamate release, as observed by the PPR reduction, suggests that some compensatory mechanism might occur which might also underlie the preserved input-output curve.

Of note, a previous study has shown sustained outward potassium current elicited by adiponectin in hypothalamic neurons. This TEA-sensitive current was able to broaden the action potential (Hoyda and Ferguson, 2010), which in turn may dramatically increase the probability of neurotransmitter release due to the enhancement of calcium influx in presynaptic terminal (Bean, 2007). The effect of ADPO at the presynaptic site might also involve other ion channels or specialized calcium sensors, such as synaptotagmin 7, which has been recently linked to synaptic facilitation (Jackman et al., 2016). It is possible to hypothesize that during the HFS protocol massive presynaptic stimulation strongly activates pre-synaptic voltage-gated channels which might be modulated by ADPO thus resulting in changes of AUC.

At the single neuron level, adiponectin receptors activation can either have an excitatory, inhibitory effect or neither of the two (Hoyda et al., 2009; Hoyda and Ferguson, 2010; Repunte-canonigo et al., 2011). A recent report showed that intracerebroventricular injection of adiponectin increases synapse number and dendritic complexity in the hippocampus (Zhang et al., 2016a) suggesting that adiponectin receptor mediates also changes in structural plasticity. Interestingly, osmotin, a plant homologue of mammalian adiponectin, induced neuroprotection by preserving synaptic integrity that relies on AMPA receptor trafficking (Shah et al., 2014; Ali et al., 2015). Moreover osmotin seems to have an important protective role against memory impairment in an Alzheimer’s model mice (Ali et al., 2015). This effect is consistent with the protective role of adiponectin in cells which overexpressed amyloid-beta (Chan et al., 2012). Indeed, despite their wide range of electrophysiological effects, adiponectin receptors mediate a protective role in several in vitro (Qiu et al., 2011; Shah et al., 2014) and in vivo (Nishimura et al., 2008; Jeon et al., 2009; Lee et al., 2011; Song et al., 2013) disease paradigms. Indeed, adiponectin decreased seizure severity in mice model of epilepsy (Lee et al., 2011).

In summary, our main finding is a strong reduction of LTP with the highest tested concentration of ADPO, albeit the potential mechanisms underlying this effect remains to be investigated. Certainly, data here presented suggest for the first time that the adiponectin system, beyond its implication in metabolic and inflammatory diseases, plays also a central modulating role at the synapse thereby representing a novel...
target for the treatment of brain diseases. Importantly, in all aforementioned pathologies, patients showed a reduction of serum levels of adiponectin. On the other hand, preclinical evidence strongly suggests that increased glutamatergic transmission is a key feature of the above diseases models (Gleichmann et al., 2012; Popoli et al., 2012; Casillas-Espinosa et al., 2012; Chao and Li, 2014; Mandolesi et al., 2015). Although further experiments are needed to investigate possible detrimental effects of adiporon, our data suggest that targeting the adiponectin system could have a beneficial effect in brain disorders.

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Author Contributions

FW, SP and DM performed experiments. FW, RTN, NM, FN and RN designed research. FW and DM analyzed data. FW and RN wrote the paper.
REFERENCES


Figure 1. Effects of different concentrations of Adiporon (ADPO; 1.5, 3, 30 μM) on PPR and input-output relationship

A, C, PPR induced by pairs of stimulation delivered at several interstimulus intervals (20, 50, 100, 200, 300, 500 ms). Data are presented as mean ± SEM. Young group (A), n=8–9 for each ADPO concentration from six mice; and adult group (C), n=6–7 for each ADPO concentration from six mice. Sample traces (above) show superimposed fEPSPs during PPF (interstimulus interval, 50 ms) in the vehicle vs. ADPO (30 μM) group. *p <0.05 vs. the vehicle group.

B, D, Input-output relationship of fEPSPs as a function of presynaptic fiber volley size at the Schaffer collateral/CA1 pyramidal cell synapses. Young group (B), n=5–6 separate recordings for each concentration from five mice; and adult group (D), n= 5–6 for each concentration from six mice. No significant difference was observed between ADPO and vehicle-treated slices.

Figure 2. Effects of different concentrations of Adiporon (ADPO; 1.5, 3, 30 μM) on CA1-LTP and on fEPSPs during tetanus

A, B, LTP induced by high frequency stimulation (HFS; 100Hz, 1 sec) delivered at Schaffer collaterals. Sample traces (above) and summary graph (below) of the averaged time course of LTP. Data are presented as mean ± SEM. Young group (A), n=5–7 for each ADPO concentration from nine mice; adult group (B), n=7–9 for each ADPO concentration from nine mice. *p <0.05 vs. the vehicle group; **p<0.01 vs. the vehicle group.

C, fEPSP during tetanus in the adult group. Sample traces (above) show fEPSP during tetanus in the vehicle group (left) vs. pre-incubated slice (ADPO, 30 μM) (right). Bar graph (below) representing the overall depolarization during tetanus as AUC normalized to the first fEPSP in each train at increasing ADPO concentrations. n=7-9 for each concentration from nine mice. *p <0.05 vs. the vehicle group; **p<0.01 vs. the vehicle group. ***p<0.001 vs. the vehicle group.

D, AMPA/NMDA ratio in the adult group. Sample traces (above) show AMPA/NMDA ratio in vehicle (left) and pre-incubated (ADPO, 30 μM) neuron (right). Bar graph represents mean ± SEM for vehicle group n=9 and ADPO group n=10. *p<0.05 vs. the vehicle group.
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Utilizing fEPSP recording in hippocampal slices the authors showed that adiponectin receptors activation led to a dose-dependent dampening of LTP. Adiporon (ADPO) had no effect on basal evoked synaptic transmission but it decreased the paired pulse facilitation and the responses during High frequency Stimulation (HFS). A reduction of AMPA receptor-mediated current is probably involved in the latter effect.