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# Rodent islet amyloid polypeptide (IAPP) selectively enhances GABA<sub>A</sub> receptor-mediated neuronal inhibition in mouse ventral but not dorsal hippocampal dentate gyrus granule cells

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Islet amyloid polypeptide (IAPP, amylin) is a peptide hormone that plays an important role in glucose homeostasis but has been implicated in the pathophysiology of type 2 diabetes and Alzheimer's disease. However, its effect on neurotransmission in the hippocampus remains poorly understood. Here, we investigated the impact of non-amyloidogenic rodent IAPP (rIAPP) on GABA<sub>A</sub> receptor-mediated neuronal inhibition in mouse dorsal and ventral hippocampal dentate gyrus (DG) granule cells. Using whole-cell patch-clamp recordings, we showed that rIAPP selectively enhanced both GABA-activated spontaneous and miniature inhibitory postsynaptic currents (sIPSCs and mIPSCs) in ventral, but not dorsal, hippocampal DG granule cells. The effect of rIAPP on sIPSCs was completely abolished in the presence of the amylin receptor antagonist IAPP<sub>8–37</sub>. Interestingly, GABA<sub>A</sub> receptor-mediated tonic current density remained unchanged in either dorsal or ventral hippocampal DG granule cells during rIAPP application. This region-specific and inhibition type-specific effect of rIAPP is likely associated with differential modulation of presynaptic GABA release as well as postsynaptic GABA<sub>A</sub> receptors in the ventral as compared to the dorsal hippocampus. Our results suggest that rodent IAPP acts as a neuromodulator in hippocampal subregions by altering the strength of GABA<sub>A</sub> receptor-mediated inhibitory signaling.

## KEYWORDS

amylin, GABA<sub>A</sub> receptor, hippocampus, islet amyloid polypeptide, neuronal inhibition, synaptic transmission, GABA

## Introduction

Metabolic hormones, including insulin, leptin, and glucagon-like peptide-1 (GLP-1), regulate glucose homeostasis and body metabolism. Additionally, mounting evidence suggests that these hormones and their analogs exert neuromodulatory effects in the central nervous system (Wang et al., 2024; Ferrari et al., 2022; Irving and Harvey, 2021;

Hammoud et al., 2021; Jin et al., 2011b; Lathe, 2001). Islet amyloid polypeptide (IAPP), also known as amylin, is a peptide hormone co-released with insulin from pancreatic  $\beta$  cells. In addition to its peripheral effect on glucose regulation and energy homeostasis (Boyle et al., 2022), IAPP also exerts substantial effects on the central nervous system (Foll and Lutz, 2020). The plasma IAPP level is typically measured in the picomolar range, although it indeed varies depending on factors such as fasting state, meal consumption and diseases (Hartter et al., 1991; Phillips et al., 2001; Paulsson et al., 2014). IAPP efficiently crosses the blood-brain barrier (BBB) (Banks et al., 1995), and interacts with amylin receptors distributed throughout various brain regions, including the hindbrain, hypothalamus, and hippocampus (Becskei et al., 2004; Kimura et al., 2012). Amylin receptors (AMY1-3) are heterodimers composed of the calcitonin receptor (CTR) and one of the three receptor activity-modifying proteins (RAMP1-3), triggering intracellular signaling cascades that involve the Erk1/2 and Akt pathways (Fu et al., 2017a). It has been clearly demonstrated that IAPP signaling in the brain is associated with food intake, stress response, rewarding behavior and cognitive function (Geisler et al., 2024; Laugero et al., 2022; Foll and Lutz, 2020; Boccia et al., 2020). Notably, IAPP has been shown to contribute to the pathophysiology of Alzheimer's disease (AD) (Corrigan et al., 2022; Zhang and Song, 2017; Oskarsson et al., 2015).

The hippocampus is an elongated curved structure in the medial temporal lobe, composed of several subregions, including cornu ammonis (CA) fields and the dentate gyrus (DG). DG acts as a gate or filter, regulating the flow of information from the entorhinal cortex to the CA3 regions. These subregions have distinct anatomical organization, electrophysiological properties, connectivity patterns and functional roles, which vary along hippocampal longitudinal axis (dorsal-ventral in rodents and posterior-anterior in primates) (Papatheodoropoulos, 2018; Strange et al., 2014; Risold and Swanson, 1996). The optimal hippocampal function depends on a fine-tuned balance between excitatory and inhibitory neurotransmission. Gamma-aminobutyric acid (GABA) plays a crucial role in maintaining inhibitory tone, which is manifested through both synaptic and extrasynaptic mechanisms (Farrant and Nusser, 2005). The activation of synaptic and extrasynaptic GABA<sub>A</sub> receptors mediates inhibitory postsynaptic currents (IPSCs) and extrasynaptic currents, respectively (Sallard et al., 2021; Jin et al., 2011a; Birnir et al., 1994). Various molecules, including metabolic hormones such as insulin and GLP-1, can modulate these currents through direct and indirect mechanisms (Hammoud et al., 2021; Korol et al., 2015; Jin et al., 2011b; Wan et al., 1997). To date, the ability of IAPP to regulate GABA-activated inhibitory currents in hippocampal neurons remains unexplored.

Human IAPP was initially discovered in amyloid isolated from pancreatic tumors and islets from patients with type 2 diabetes (Cooper et al., 1987; Westermark et al., 1986), indicating its amyloidogenic nature. In contrast, the mouse and rat IAPP is non-amyloidogenic and differ from human IAPP in six positions. Especially, the proline residues at positions 25, 28, and 29 protect rodent IAPP against the formation of cytotoxic amyloid (Fortin and Benoit-Biancamano, 2015; Hay et al., 2015). In this study, we sought to examine whether the application of rodent IAPP at a physiologically relevant concentration (in the picomolar

range) could modulate GABA<sub>A</sub> receptor-mediated synaptic and extrasynaptic tonic currents in DG granule cells of mouse dorsal and ventral hippocampus, and if so, are such effects reversed by amylin/IAPP receptor antagonist.

## Materials and methods

### Animals

Male mice (C57BL/6J) between 8 and 10 weeks of age were used in this study. All experimental procedures were conducted following local ethical guidelines and protocols, approved by Uppsala Animal Ethical Committee, Swedish law and regulations based on Directive 2010/63/EU, C129/14.

### Hippocampal slice preparation

The preparation of hippocampal slices followed the previously described protocols (Jin et al., 2011a; Netsyk et al., 2020; Ting et al., 2014). In brief, the brain was swiftly removed and immersed in an ice-cold N-methyl D-glucamine (NMDG)-based cutting solution, which comprised of (in mM): 93 NMDG, 2.5 KCl, 1.2 NaH<sub>2</sub>PO<sub>4</sub>, 30 NaHCO<sub>3</sub>, 20 HEPES, 25 D-glucose, 10 MgSO<sub>4</sub>, 0.5 CaCl<sub>2</sub>, 5 sodium ascorbate, 2 thiourea, and 3 sodium pyruvate, pH 7.3–7.4 when saturated with 95% O<sub>2</sub> and 5% CO<sub>2</sub> and with an osmolality of 300–305 mOsm. Brain slices (350  $\mu$ m) were obtained using Leica VT 1200S microtome (Leica Microsystems AB, Germany). Dorsal and ventral hippocampal slices prepared as previously described (Hammoud et al., 2021; Netsyk et al., 2020) were initially placed in NMDG-based solution for 12–15 min at 32°C, followed by transferring to a HEPES-based holding solution containing (in mM): 92 NaCl, 2.5 KCl, 1.2 NaH<sub>2</sub>PO<sub>4</sub>, 30 NaHCO<sub>3</sub>, 20 HEPES, 25 D-glucose, 2 MgSO<sub>4</sub>, 2 CaCl<sub>2</sub>, 5 sodium ascorbate, 2 thiourea, and 3 sodium pyruvate, pH 7.3–7.4 and osmolality 300–305 mOsm. All slices were maintained in this holding solution at room temperature (20–22°C) for a minimum of 1 h before recording.

### Electrophysiology

Whole-cell patch-clamp recordings were conducted on DG granule cells from both dorsal and ventral hippocampal slices. All experiments were performed at room temperature. Slices were transferred to a recording chamber and perfused with artificial cerebrospinal fluid (ACSF) containing (in mM): 119 NaCl, 2.5 KCl, 1.3 MgSO<sub>4</sub>, 1 NaH<sub>2</sub>PO<sub>4</sub>, 26.2 NaHCO<sub>3</sub>, 2.5 CaCl<sub>2</sub>, 11 D-glucose, and 3 kynurenic acid (to block glutamatergic synaptic transmission), pH 7.3–7.4 and osmolality 300–305 mOsm, equilibrated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The resistance of glass patch pipettes was 3.4–4 M $\Omega$  when filled with an intracellular solution comprising (in mM): 140 CsCl, 8 NaCl, 2 EGTA, 0.2 MgCl<sub>2</sub>, 10 HEPES, 2 MgATP, 0.3 Na<sub>3</sub>GTP, and 5 QX314-Br, pH 7.2 and osmolality 285–290 mOsm. Voltage-clamp recordings were conducted at the holding potential of –60 mV with a sampling rate of 10 kHz and filtered at 2 kHz using a Multipatch 700B amplifier, and digitized with an Axon Digidata board

1550A, which were controlled by pCLAMP 10.5 software (Axon Instruments, Molecular Devices). GABA-activated spontaneous inhibitory postsynaptic currents (sIPSCs) were recorded for a minimum of 5 min after baseline stabilization, and miniature IPSCs (mIPSCs) recordings were performed in the presence of tetrodotoxin (TTX, 1  $\mu$ M). GABA<sub>A</sub>R antagonist picrotoxin (100  $\mu$ M) was applied at the end of each recording to reveal the extrasynaptic GABA<sub>A</sub>R-mediated extrasynaptic tonic currents.

All chemicals and drugs were obtained from Sigma-Aldrich (Steinheim, Germany), except for rodent IAPP (amylin, Cat. No. 4030201) and amylin receptor antagonist amylin (8–37) (mouse, rat, Cat. No. 4030346) from BACHEM Ltd (Bubendorf, Switzerland), and TTX from Alomone Labs Ltd (Jerusalem, Israel).

## Data analysis

Recordings were rejected for analysis if the serial resistance varied by more than 20%. Analysis of sIPSCs and mIPSCs was conducted using MiniAnalysis software 6.0 (Synaptosoft, USA). IPSCs were identified as events based on a threshold of 5 $\times$  the root-mean-square (RMS) of baseline noise, followed by visual inspection to eliminate false-positives. Only single-peak IPSC events were included in amplitude and kinetics analysis (Hammoud et al., 2021; Netsyik et al., 2020). Extrasynaptic tonic current amplitude was measured as a baseline shift in holding current after applying a GABA<sub>A</sub>R inhibitor picrotoxin (PTX). The IPSC charge transfer Q (fC) was measured from integral area that is determined by amplitude, rise and decay time in MiniAnalysis. The total IPSC current was calculated as frequency ( $s^{-1}$ )  $\times$  Q (fC). Synaptic and extrasynaptic current densities were calculated by normalizing total currents to cell membrane capacitance (Cm) (Netsyik et al., 2020).

## Statistical analysis

All data were analyzed with GraphPad Prism 10 (GraphPad Software, La Jolla, USA). Each group data was tested for normality with Shapiro–Wilk test. Paired Student *t*-test or Wilcoxon matched-pairs signed rank test was performed based on the data distribution. Statistical significance was defined as  $P < 0.05$ .

## Results

### Rodent IAPP potentiates GABA-activated spontaneous IPSCs (sIPSCs) in DG granule cells in ventral but not dorsal mouse hippocampus

To examine whether rIAPP affects GABA-activated inhibitory currents along the hippocampal longitudinal axis, we recorded sIPSCs in DG granule cells from dorsal and ventral hippocampal slices and acutely applied rIAPP (10 pM) for minimal 15 min. Representative sIPSC recordings in dorsal and ventral hippocampus are shown in Figures 1A, B and Supplementary Figures 1A, B, respectively. The mean frequency,

median amplitude, total synaptic current, and current density of sIPSCs were significantly increased after rIAPP application in DG granule cells from ventral hippocampus (Figures 1C–F), whereas rise time (10–90%), decay time (63%), and median charge transfer remained unchanged (Supplementary Table 1). In contrast, in dorsal hippocampus rIAPP did not alter any sIPSC parameters in recorded DG granule cells (Figures 1C–F and Supplementary Table 1). These results show that rIAPP selectively enhances GABA-activated synaptic currents in hippocampal subregions.

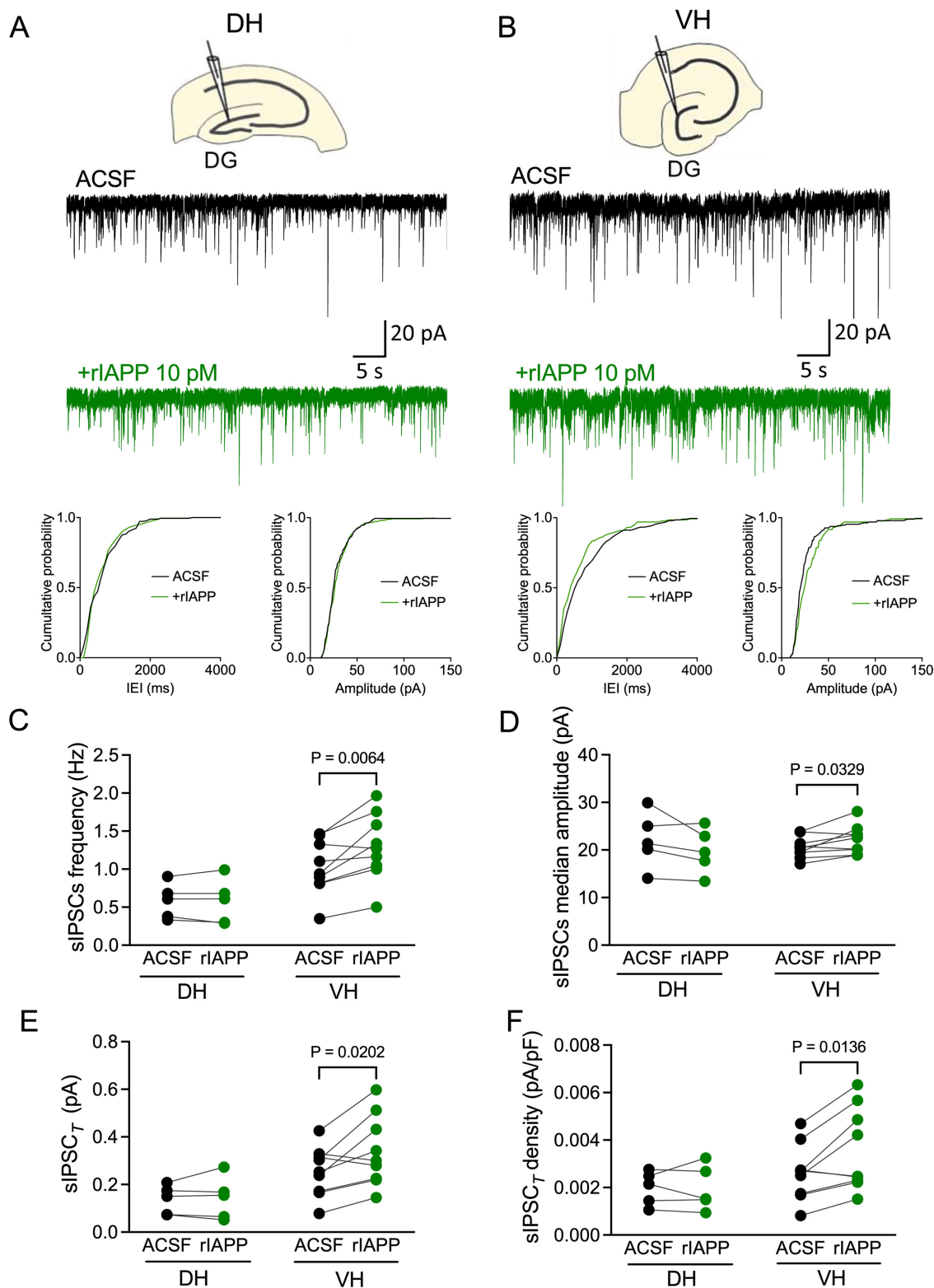
We further examine whether the sIPSC enhancement by rIAPP is via amylin receptors in the ventral hippocampus. An amylin receptor antagonist IAPP<sub>8–37</sub> (1  $\mu$ M), was initially perfused in the recording chamber, followed by co-perfusion of rIAPP and IAPP<sub>8–37</sub> (Supplementary Figure 2A). In ventral hippocampal DG granule cells in the presence of IAPP<sub>8–37</sub>, rIAPP no longer enhanced the sIPSC frequency and median amplitude (Supplementary Figures 2B, C). Thus, blocking the amylin receptor abolished the rIAPP-induced potentiation of the sIPSCs in ventral hippocampal DG granule cells.

### rIAPP increases GABA-activated miniature IPSCs (mIPSCs) total current density in ventral but not dorsal hippocampal DG granule cells

The augmentation of the sIPSCs by rIAPP can be associated with pre- or post-synaptic mechanisms. We thus examined the effect of rIAPP on mIPSCs in the presence of a voltage-gated sodium channel blocker TTX (1  $\mu$ M), which eliminates action potential-dependent GABA release. Representative current traces are shown for the dorsal (Figure 2A and Supplementary Figure 3A) and ventral (Figure 2B and Supplementary Figure 3B) hippocampal DG granule cells. rIAPP significantly increased mIPSC frequency (Figure 2C), median charge transfer (Supplementary Table 1), total synaptic current (Figure 2E), and total current density (Figure 2F) but not median amplitude (Figure 2D), rise time (10–90%) or decay time (63%) (Supplementary Table 1), in the DG granule cells of ventral hippocampus. In contrast, rIAPP had no effects on mIPSCs recorded in the dorsal hippocampal DG granule cells (Figures 2A, C–F and Supplementary Table 1), which was similar to the observations for the sIPSCs (Figures 1A, C–F). These data indicate that rIAPP affects pre-synaptic GABA release only in the ventral hippocampal DG granule cells.

### GABA<sub>A</sub>R-mediated extrasynaptic tonic current is not altered by rIAPP in mouse hippocampal DG granule cells

GABA-activated neuronal inhibition consists of not only synaptic but also extrasynaptic components, each with distinct properties and functional roles. Therefore, we further examined whether rIAPP changed the GABA<sub>A</sub>R-mediated extrasynaptic tonic currents in the absence or presence of TTX. The GABA tonic current was revealed as a shift of baseline current by applying the GABA<sub>A</sub>R antagonist PTX (Figures 3A, B). The extrasynaptic



**FIGURE 1**  
Rodent islet amyloid polypeptide (rIAPP) potentiated spontaneous synaptic GABA<sub>A</sub> receptor-mediated currents in the dentate gyrus granule cells in ventral, but not in dorsal mouse hippocampus. **(A, B)** Schematic illustrations and representative traces of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from DG granule cells in dorsal [DH, **(A)**] and ventral [VH, **(B)**] hippocampus under control conditions (ACSF, black trace) and bath rIAPP (10 pM) application (green trace). Cumulative probability plots of the inter-event interval (IEI) and median amplitude of sIPSCs from the above representative traces. Summary statistics of frequency **(C)**, total synaptic currents (sIPSC<sub>T</sub>) **(E)** and total current density [sIPSC<sub>T</sub> density, **(F)**] of sIPSC recorded from DG granule cells of DH (*n* = 5) and VH (*n* = 9) under control (ACSF, black color) and 10 pM rIAPP application (green color). Data are presented as scatter dot plots for individual values with connected lines, indicating data obtained from individual cells before (black) and during rIAPP application (green). The paired Student's *t*-test was used for statistical analysis. *V*<sub>hold</sub> = -60 mV.

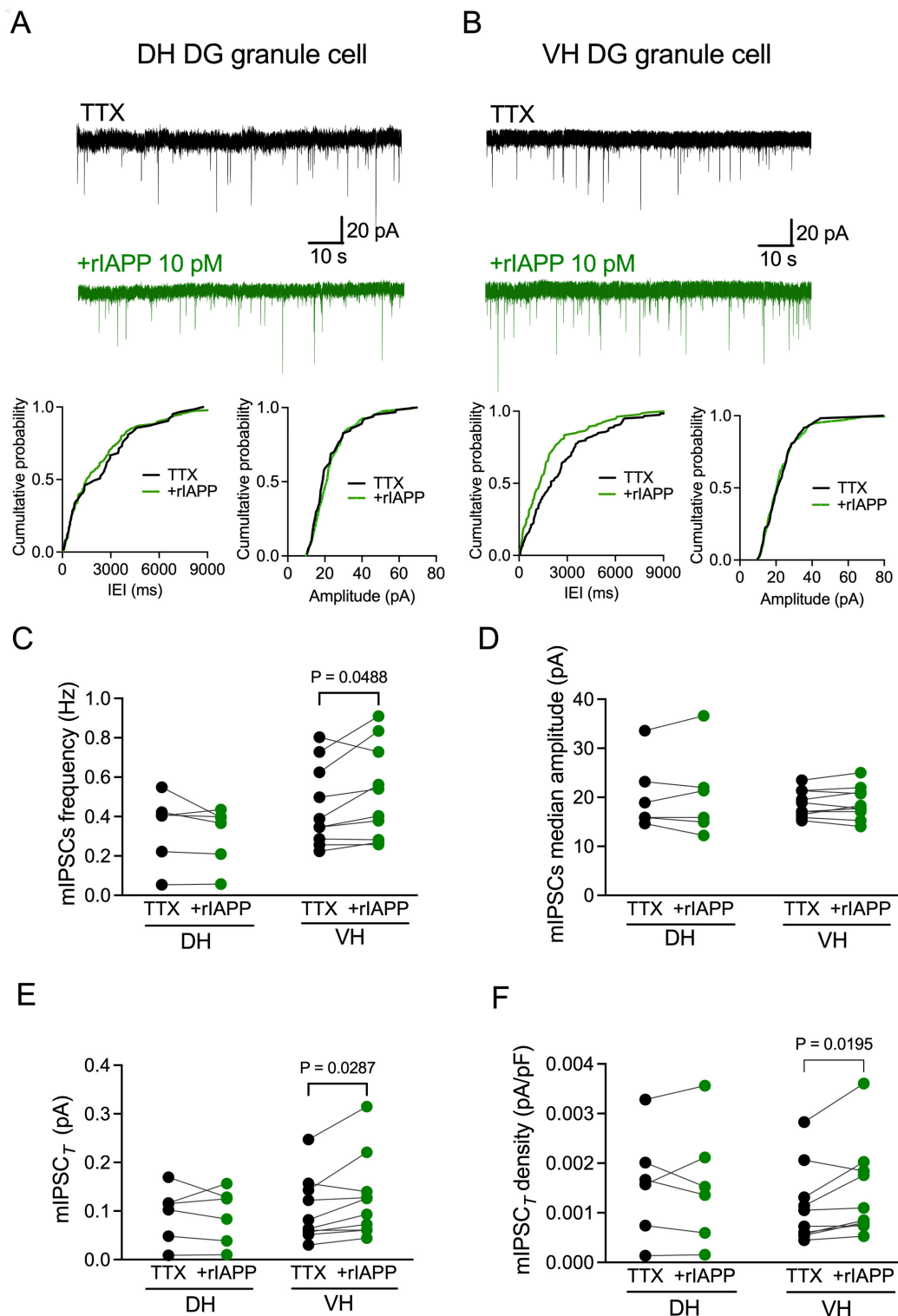


FIGURE 2

Rodent IAPP potentiated miniature GABA<sub>A</sub> receptor-mediated currents in the dentate gyrus granule cells in ventral mouse hippocampus. (A,B) Representative traces of miniature inhibitory postsynaptic currents (mIPSCs) recorded from DG granule cells in dorsal [DH, (A)] and ventral [VH, (B)] hippocampus before (black trace) and during rIAPP (10 pM) application (green trace) in the constant presence of tetrodotoxin (TTX, 1 μM). Cumulative probability plots of the inter-event interval (IEI) and median amplitude of mIPSCs from the above representative traces. (C–F) Summary statistics of frequency (C), median amplitude (D), total synaptic current [mIPSC<sub>T</sub>, (E)] and total current density [mIPSC<sub>T</sub> density, (F)] of mIPSCs recorded from DG granule cells of DH (*n* = 6 cells) and VH (*n* = 10 cells) under control (TTX, black color) and 10 pM rIAPP application (green color). Data are presented as scatter dot plot for individual values with connected lines, indicating data obtained from individual cells before (black) and during rIAPP application (green). The paired Student's *t*-test or Wilcoxon matched-pairs signed rank test was used for statistical analysis. *V*<sub>hold</sub> = −60 mV.

current density was not changed by rIAPP (10 pM) in DG granule cells in either dorsal (Figure 3A) or ventral (Figure 3B) hippocampus in the absence or presence of TTX. These results suggest rIAPP does not influence GABA-activated extrasynaptic tonic inhibition in mouse hippocampal DG granule cells.

## Discussion

A substantial body of research has provided evidence that the hippocampus is not homogenous and has distinct characteristics and functions, especially in the dorsal and ventral subregions (Netsyk et al., 2020; Papatheodoropoulos, 2018; Strange et al., 2014; Risold and Swanson, 1996). Our findings demonstrate that rIAPP affects GABA<sub>A</sub> receptor-mediated currents in the mouse hippocampus in both a region-specific and inhibition type-specific manner. Specifically, we have observed that rIAPP selectively potentiates synaptic GABAergic transmission in the ventral, but not the dorsal, hippocampal DG granule cells (Figure 4). Our results expand our understanding of how metabolic hormones influence GABAergic inhibition in the hippocampus (Hammoud et al., 2021; Korol et al., 2015; Jin et al., 2011b; Solovyova et al., 2009).

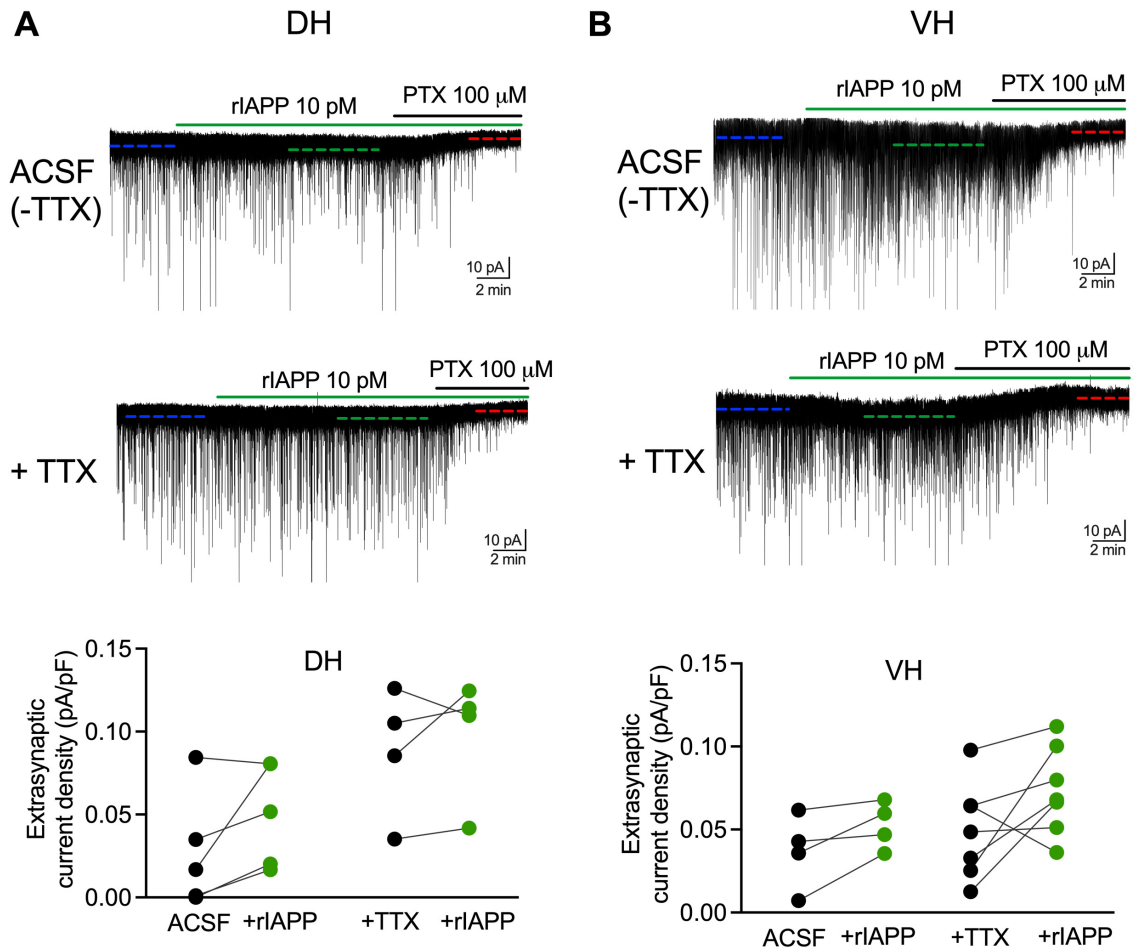
Hippocampal DG granule cells exhibit distinctively low levels of excitability, which is mainly attributed to the extensive GABAergic inhibition present in DG (Coulter and Carlson, 2007). Notably, a diverse array of synaptic and extrasynaptic GABA<sub>A</sub> receptors are expressed in DG granule cells, mediating IPSCs and tonic inhibitory currents when activated by GABA (Birnir et al., 1994). Our results reveal that rIAPP enhances sIPSCs exclusively in ventral hippocampal DG granule cells, whereas insulin (1 nM), as shown in our previous study, potentiates sIPSCs in both dorsal and ventral regions (Hammoud et al., 2021). rIAPP potentiates sIPSCs in ventral hippocampal DG granule cells, as evidenced by increased frequency and amplitude, suggesting both pre- and post-synaptic mechanisms. In contrast, insulin selectively increases the frequency, but not the amplitude of sIPSCs in these cells from 8 to 10 weeks old wild-type mice. However, this insulin effect is absent in 5–6 months old wild-type or AD tg-APP<sup>Sw</sup> mice, indicating an age- and disease-dependent modulation (Hammoud et al., 2021). The increased frequency indicates a potential enhancement of pre-synaptic GABA release probability from GABAergic interneurons, while the increased amplitude might reflect both pre- and post-synaptic changes, such as increased GABA concentration per vesicle released (Yamashita et al., 2018; Takamori, 2016) or increased GABA<sub>A</sub> receptor density or conductance (Netsyk et al., 2020). In the presence of TTX, rIAPP-induced increase in mIPSC frequency and total current density, without changes in amplitude, suggests that rIAPP mainly affects pre-synaptic GABA release only in ventral hippocampal DG granule cells. The potentiated pre-synaptic GABA release may involve increased GABA concentration per vesicle released, increased probability of GABA vesicle release, increased size or mobility of the readily releasable pool of GABA vesicles, interactions with pre-synaptic auto-receptors or GABA transporters. Similarly, insulin also enhances mIPSC only in ventral DG granule cells, primarily via a presynaptic mechanism (Hammoud et al., 2021). In contrast, rIAPP did not change extrasynaptic GABA<sub>A</sub> receptor-mediated tonic currents in hippocampal DG granule cells. This finding suggests that rIAPP

does not alter interstitial GABA concentration or extrasynaptic GABA<sub>A</sub>R. In summary, our findings reveal that rIAPP exerts selective modulation on various modes of GABAergic transmission in DG granule neurons.

The amylin receptor antagonist IAPP<sub>8–37</sub> completely abolishes the rIAPP-induced potentiation of sIPSCs in ventral DG granule cells, confirming that this effect is mediated specifically through amylin receptors. The combination of CTR with different RAMPs (RAMP1, 2, 3), resulting in three amylin receptor subtypes (AMY1, AMY2 and AMY3) that bind IAPP/amylin with various affinities (Poyner et al., 2002). In heterozygous CRT knockout mice, the uptake of the amylin receptor antagonist cyclic AC253 is markedly reduced in the hippocampus (Soudy et al., 2017). Additionally, amylin-induced c-fos (a marker for neuronal activation) activity in the dentate gyrus is significantly decreased in RAMP1/3 knockout mice (Skovbjerg et al., 2021). These findings indicate the presence of functional AMY1 and AMY3 receptors in the hippocampal neurons. Interestingly, AMY3 is expressed not only in neurons but also in microglia and mediates Aβ-induced brain inflammation in a transgenic mouse model of AD (Fu et al., 2017b). However, the difference in distribution, cell type specificity and expression levels of AMY1 and AMY3 between the dorsal and ventral hippocampus have not yet been thoroughly investigated. Activation of amylin receptors increases intracellular cAMP levels, stimulating protein kinase A (PKA) and downstream signaling pathways (Fu et al., 2017a), which potentially alter pre-synaptic GABA release (Trudeau et al., 1996; Stephens, 2009). A recent study has demonstrated that activation of amylin receptors expressed on pre-synaptic GABAergic neurons in the ventral tegmental area enhances local GABA release, which subsequently inhibits the activity of projecting dopamine neurons (Geisler et al., 2024). Similarly, our findings clearly demonstrate an association between IAPP signaling and GABAergic transmission in the ventral hippocampus.

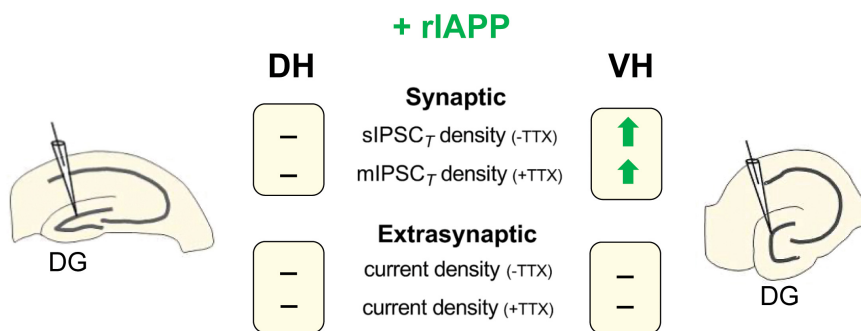
The regional specificity of rIAPP's effects, confined to the ventral hippocampus, is particularly intriguing. This specificity may reflect regional differences between the dorsal and ventral hippocampus in the expression and distribution of amylin receptors, GABA<sub>A</sub> receptors, and their downstream signaling pathways (Hammoud et al., 2021; Netsyk et al., 2020; Papatheodoropoulos, 2018; Strange et al., 2014). Given that the ventral hippocampus is more involved in emotion, stress response and metabolic control due to its distinct connectivity with various brain regions including the amygdala (Strange et al., 2014; Lathe, 2001; Risold and Swanson, 1996; Fanselow and Dong, 2010; Boccia et al., 2020), our findings suggest that rIAPP might modulate these functions through its region-specific enhancement of GABAergic inhibition. Future studies should investigate several important questions, including the potential differences in amylin receptor expression patterns between the dorsal and ventral hippocampus, as well as examine how human IAPP and its non-amyloidogenic analogs, such as pramlintide, modulate GABAergic inhibition in these distinct hippocampal regions.

In conclusion, our results reveal a neuromodulatory role for rIAPP in the hippocampus, specifically enhancing GABAergic synaptic inhibition in the ventral region mainly through pre-synaptic mechanism. These findings provide new insights into the complex functions of IAPP/amylin in the brain and highlight



**FIGURE 3**  
 Rodent IAPP did not affect GABA<sub>A</sub>R-mediated extrasynaptic current in DG granule cells along hippocampal dorsal-ventral axis. Representative GABA<sub>A</sub>R-mediated current traces and summary statistics of extrasynaptic current density in dentate granule cells of DH (A) and VH (B) recorded in ACSF without TTX or constant presence of tetrodotoxin (+TTX, 1 μM) with rIAPP (10 pM) application (green horizontal line). The extrasynaptic current was revealed by the application of GABA<sub>A</sub>R antagonist picrotoxin (PTX, 100 μM, black horizontal line) and its current amplitude was calculated by the shift of the baseline current (dashed line) under different conditions. Data are presented as scatter dot plots for individual values with connected lines, indicating data obtained from individual cells before (black) and during rIAPP application (green). *n* = 4–7 cells. The paired Student's *t*-test was used for statistical analysis. *V*<sub>hold</sub> = –60 mV.

DG granule cells



**FIGURE 4**  
 Schematic summary of rIAPP effects on GABA<sub>A</sub>R-mediated synaptic and extrasynaptic current density in dentate gyrus (DG) granule cells of mouse dorsal (DH) and ventral (VH) hippocampus. -TTX, in the absence of TTX; +TTX, in the presence of TTX; –, no change; ↑, current density increased by rIAPP (10 pM).

the importance of considering regional heterogeneity in the hippocampus when studying its effects on neuronal function.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The animal study was approved by the Uppsala Animal Ethical Committee, Swedish law and regulations based on Directive 2010/63/EU. The study was conducted in accordance with the local legislation and institutional requirements.

## Author contributions

ON: Writing – review and editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization. SVK: Formal analysis, Supervision, Visualization, Writing – review and editing. GTW: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review and editing, Project administration. BB: Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Visualization, Writing – review and editing. ZJ: Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review and editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fncel.2025.1531790/full#supplementary-material>



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