IBRO Neuroscience Reports 18 (2025) 644–656

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Hippocampal dorsal CA1: Functional connectivity and role in HCN channelopathies in affective diseases and epilepsy

Tsz Wei So [a,1], Hoi Yi Choi [a,1], Haoyu Xu [a], Jinwei Zhu [b], Lei Shi [c], Jacque Pak Kan Ip [a,d,*]

[a] School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China
[b] Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University, Shanghai 200240, China
[c] JNU-HKUST Joint Laboratory for Neuroscience and Innovative Drug Research, State Key Laboratory of Bioactive Molecules and Druggability Assessment, College of Pharmacy, Jinan University, Guangzhou, Guangdong 510632, China
[d] Gerald Choa Neuroscience Institute, The Chinese University of Hong Kong, Hong Kong, China

ARTICLE INFO

Keywords:
Hippocampus
CA1 Region
Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels
Channelopathies
Post-Traumatic Stress Disorder
Depressive Disorder
Epilepsy

ABSTRACT

The hippocampus is a complex structure consisting of the dentate gyrus (DG), cornu ammonis (CA) and the subiculum. CA1 is further subdivided into the ventral (vCA1) and dorsal (dCA1) compartments, with dCA1 believed to be crucial in spatial learning and memory as well as cognitive processing. Although dCA1 was traditionally thought to be not likely relevant to affective diseases, recent studies suggest otherwise. In fact, it has been found that diseases including certain types of post-traumatic stress disorder (PTSD), depression and epilepsy may be attributed to channelopathies in dCA1, particularly that of hyperpolarization-activated cyclic nucleotide gated (HCN) channels. However, it remains unclear how disruptions of HCN transcription, post-transcriptional modification and activation kinetics are related to changes of downstream structures along neural circuits. Their effect on behavioural changes and disease development, as well as the corresponding potential therapeutic strategies implicated in the findings have not been extensively studied as well. With the existing research gap and the significant clinical implications of dCA1 HCN channelopathies, the mechanisms of how defects of these channels result in brain disorders including PTSD, depression and temporal lobe epilepsy are worthy of further investigation. Therefore, in this review, we summarize the recent findings on the involvement of dCA1 HCN channelopathies in brain disorders after providing an outline on the neuroanatomy and functional connectivity of dCA1, and the features of HCN channels in that region. We also propose future directions of molecular and systems neuroscience studies, as well as the translational research on potential therapeutics that address the brain disorders related to dCA1 HCN channelopathies.

1. Introduction

Following several decades of lesion and behavioural studies, dCA1 has long been thought to be mainly involved in spatial cognition and is less related to emotions when compared to vCA1 (Fanselow & Dong, 2010). However, recent preclinical studies have identified dCA1 as a region that is important in the development of affective diseases including depression and post-traumatic stress disorder (Kim et al., 2018; Kim et al., 2022), challenging the traditional belief that dCA1 is not likely related to emotions. In addition, the advancement of genetic engineering, staining and imaging techniques has allowed researchers to better understand epileptogenesis in different brain regions (Xiao et al., 2024). Recently, more studies that investigate dCA1 have revealed how the molecular changes in the region may possibly contribute to the occurrence of seizures (Arnold et al., 2019; McClelland et al., 2011). Our understanding of the clinical implications of dCA1 is therefore no longer confined to spatial cognition and its impairment, but is gradually extending to affective diseases and epilepsy.

As mentioned, multiple studies show that dCA1 may be implicated in the development of epilepsy, depression and post-traumatic stress disorder (PTSD). One of the molecular changes in dCA1 that leads to the development of these diseases is attributed to channelopathies of hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, in which defects of these channels are caused by genetic or acquired factors (Kim et al., 2018; Kim et al., 2022). However, since the dysregulation of HCN channels is related to the deviation from the normal dorso-ventral

* Corresponding author at: School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China.
E-mail address: jacqueip@cuhk.edu.hk (J.P.K. Ip).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ibneur.2025.03.008
Received 14 September 2024; Received in revised form 31 January 2025; Accepted 25 March 2025
Available online 4 April 2025

Table 1
A summary table showing the type and function of direct neuronal inputs from non-hippocampal origins to dCA1.

Pathway	Type of input	Function of the neuronal connection
Lateral entorhinal cortex (LEC) → dCA1	GABAergic input (Basu et al., 2016)	Increasing the precision of contextual and object memory encoding by inducing heterosynaptic plasticity (Basu et al., 2016)
	Excitatory input that is not GABAergic (Li et al., 2017)	Recollecting olfactory association information during early stage of learning (Igarashi et al., 2014; Li et al., 2017)
Medial entorhinal cortex (MEC) → dCA1	Excitatory input (Grienberger & Magee, 2022)	Inducing the formation of new place fields by providing instructive signals based on the salience of environmental cues (Grienberger & Magee, 2022)
		Allowing the generation of long-range extended replays during quiet awake state by providing spatial information of events (Yamamoto & Tonegawa, 2017)
Prefrontal cortex (PFC) → dCA1	GABAergic input (Malik et al., 2022)	Enhancing the encoding of spatial information for objects and driving object exploration (Malik et al., 2022)
Ventral tegmental area (VTA) → dCA1	Dopaminergic input (weak) (Kempadoo et al., 2016; Tsetsenis et al., 2021)	Uncertain
Substantia nigra pars compacta → dCA1	Dopaminergic input (weak) (Kempadoo et al., 2016; Tsetsenis et al., 2021)	Uncertain
Locus coeruleus (LC) → dCA1	Dopaminergic and noradrenergic input (Takeuchi et al., 2016)	Modulating the association between contextual cue and experience (Kaufman et al., 2020; Tsetsenis et al., 2021)
		Participating in the consolidation process of memory (Mello-Carpes & Izquierdo, 2013; Takeuchi et al., 2016)
Raphe nucleus → dCA1	Serotonergic input (Chowdhury et al., 2022; McKenna & Vertes, 2001; Varga et al., 2009)	Controlling reward delivery and locomotion (Luchetti et al., 2020)
Medial septum → dCA1	Cholinergic and GABAergic input (Wang et al., 2022)	Controlling the theta rhythm of hippocampal neurons (Wang et al., 2022)
Striatum → dCA1 Thalamus → dCA1 Hypothalamus → dCA1	Input of uncertain type (Tao et al., 2021)	Uncertain
Perirhinal cortex (PRH) → dCA1	Input with excitatory synapse (Li et al., 2019; Shi & Cassell, 1999)	Controversial, may be involved in object recognition (Bussey et al., 2005; Deshmukh et al., 2012; Mumby & Pinel, 1994; Norman & Eacott, 2004), non-spatial memory (Deshmukh et al., 2012; Wan et al., 1999) and contextual processing (Bucci et al., 2000; Burwell et al., 2004; Eacott et al., 2001; Ennaceur et al., 1996; Murray et al., 2007)

Table 2
A summary table showing the type and function of direct neuronal outputs from dCA1 to non-hippocampal destinations.

Pathway	Type of output	Function of the neuronal connection
dCA1 → Medial entorhinal cortex (MEC)	Uncertain (Qiu et al., 2024)	Uncertain
dCA1 → Lateral entorhinal cortex (LEC)	Uncertain (Qiu et al., 2024)	Transmitting spatiotemporal information at the moment being triggered by the occurrence of an event (Soma et al., 2023)
dCA1 → Nucleus accumbens (NAc)	Glutamatergic output (Trouche et al., 2019)	Retrieving spatial appetitive memory for modulating the reinforcement of reward-seeking locomotory behaviours (Trouche et al., 2019)
dCA1 → Medial prefrontal cortex (mPFC)	Uncertain (Barker et al., 2017)	Encoding the temporal component of episodic memory (Barker et al., 2017)
dCA1 → Retrosplenial cortex (RC)	Uncertain (Lee et al., 2023)	Consolidating remote contextual memory (Lee et al., 2023)
dCA1 → Lateral septum (LS)	Glutamatergic output (Zhang et al., 2022)	Transmitting spatial information to downstream brain regions for the control of motor functions (van der Veldt et al., 2021; Zhang et al., 2022)
dCA1 → Medial septum (MS)	Glutamatergic and GABAergic output (Qiu et al., 2024; Takács et al., 2008)	Uncertain

differences along CA1 (Arnold et al., 2019), vCA1 should not be overlooked when the role of dCA1 in HCN channelopathies is investigated. Moreover, since dCA1 is connected to various brain regions, channelopathies in dCA1 may lead to functional changes of other downstream structures along the neural circuits, which may in turn impact the manifestation of certain symptoms. By having a better understanding of the changes in molecular systems related to dCA1, we can develop a clearer and more complete picture of the related diseases.

Due to an increasingly large body of literature investigating HCN channelopathies in dCA1, and due to the significant clinical implications of this abnormal molecular change which are related to depression, post-traumatic stress disorder and epilepsy, a summary of the recent relevant research is provided in this review for a clearer overview. In addition, due to the lack of studies investigating the relationship between dCA1 molecular changes and HCN channelopathies as well as their impact on neural circuitry and disease development, directions on future studies that may address this research gap are also suggested after outlining the neuroanatomy and functional connectivity of dCA1. By summarizing the recent findings and proposing directions for future basic and translational studies, this review aims at shedding light onto research on HCN channelopathies in dCA1 while triggering researchers to rethink the role of dCA1 as well as its clinical implications.

2. Structure & function of dCA1

The hippocampus is a complex structure embedded in the temporal lobe of the cerebral cortex. Consisting of the dentate gyrus (DG), cornu ammonis (CA) and the subiculum, hippocampus is a functionally diverse region that contributes to a vast array of cognitive functions including learning, memory, emotional processing, and spatial navigation (Anand & Dhikav, 2012). CA1 is further subdivided into ventral (vCA1) and dorsal (dCA1) compartments that perform distinct functions. Studies have reported that vCA1 serves as a processor of emotions, stress, and socially relevant information, while dCA1 contributes to cognitive

Table 3
A summary table summarizing the set-up, results and conclusion of studies that investigate the involvement of HCN channels in depressive behaviours.

Study	Animal model	Experimental group		Control group	Results of behavioural tests, which are conducted on both experimental and control groups	Conclusion for the effect of the intervention
		Intervention (Timing of intervention)	Molecular effect of the intervention			
(Lyman et al., 2021)	Mice after experiencing chronic social defeat	Acute elevation of cAMP in bilateral dorsal hippocampi that is mediated by: a. Bilateral dorsal hippocampal injection of AAV-rM3D(Gs)-DREADD [1] (Pre-protocol), *AND* b. Intraperitoneal injection of CNO [3] (Post-protocol, acute administration)	HCN channel opening probability increases (Porro et al., 2019).	Animal model subject to a. Bilateral dorsal hippocampal injection of AAV-rM3D(Gs)-DREADD (Pre-protocol), *AND* b. Intraperitoneal injection of saline (Post-protocol)	Experimental group, when compared to control group, has: 1. Increased immobility time in tail suspension test 2. Increased immobility time in forced swim test. 3. Deteriorated performance in object-location memory task.	Depressive effect is produced as behavioural despair is increased and spatial memory is impaired.
(Lyman et al., 2021)	Naive Mice without experiencing any paradigm	Chronic elevation of cAMP in bilateral dCA1 that is mediated by: a. Bilateral dCA1 injection of AAV-rM3D(Gs)- DREADD (Pre-protocol), *AND* b. Consumption of drinking water containing CNO (Post-protocol, chronic administration lasting 3 weeks).	HCN surface expression is reduced due to conformational change in HCN that disrupts TRIP8b-HCN interaction and upsets the effect of physiological TRIP8b in promoting HCN surface expression (DeBerg et al., 2015; Han et al., 2011).	(1) Naïve mice subject to bilateral dCA1 injection of AAV-rM3D (Gs)-DREADD and 3-week consumption of drinking water containing saline (2) Naïve mice subject to bilateral dCA1 injection of AAV-GFP [2] and 3-week consumption of drinking water containing CNO (3) Naïve mice subject to bilateral dCA1 injection of AAV-GFP and 3-week consumption of drinking water containing saline (4) Naïve mice subject to bilateral dCA1 injection of AAV-rM3D (Gs)-DREADD and 24-hour consumption of drinking water containing CNO	Experimental group, when compared to control group (1)-(4), has: 1. Decreased immobility time in tail-suspension test. 2. Decreased immobility time in forced swim test. Experimental group, when compared to control group (1), has: 1. Improved performance in object-location memory task.	Antidepressive effect is produced as behavioural despair is reduced and spatial memory is enhanced.
(Lyman et al., 2021)	Mice which are susceptible by demonstrate less social interaction after experiencing chronic social defeat	Chronic elevation of cAMP in bilateral dCA1 that is mediated by: a. Bilateral dCA1 injection of AAV-rM3D(Gs)- DREADD (Pre-protocol), *AND* b. Consumption of drinking water containing CNO (Post-protocol, chronic administration lasting 3 weeks).	HCN surface expression is reduced due to conformational change in HCN that disrupts TRIP8b-HCN interaction and upsets the effect of TRIP8b in promoting HCN surface expression (DeBerg et al., 2015; Han et al., 2011).	Animal model subject to a. Bilateral dCA1 injection of AVV-rM3D(Gs)-DREADD (Pre-protocol), *AND* b. Consumption of drinking water containing saline (Post-protocol, chronic administration lasting 3 weeks)	Experimental group, when compared to control group, has: 1. Decreased immobility time in forced swim test. 2. Improved performance in object-location memory task.	Antidepressive effect is produced as behavioural despair and impairment in spatial memory is rescued.
(Kim & Johnston, 2020)	Rats exposed to chronic unpredictable stress	Intraperitoneal injection of (S)-ketamine (Pre-protocol)	HCN channels are blocked, with a specifically high blocking potency of HCN1-containing channels that is even higher than racemic ketamine (Chen et al., 2009).	1. Animal model subject to intraperitoneal injection of saline (Pre-protocol) 2. Naive rats subject to intraperitoneal injection of saline 3. Naive rats subject to intraperitoneal injection of (S)-ketamine	Experimental group, when compared to control group, has: 1. Increased sucrose preference in sucrose preference test. 2. Increased number of entries into centre square and increased total travelling in open field test. 3. Decreased passive activity time in forced swim test.	Antidepressive effect is produced as resiliency is enhanced.

[1] AAV-rM3D(Gs)-DREADD: AAV (adeno-associated virus) that mediates the expression of rM3D(Gs), which is the DREADD (designer receptor exclusively activated by designer drugs).
[2] AAV-GFP: Control AAV (adeno-associated virus) that mediates the expression of GFP (green fluorescent protein)
[3] CNO: Clozapine-N-oxide, the designer drug that activates the DREADD and induces cAMP production in cell.

Table 4
A summary table summarizing the set-up, results and conclusion of studies that investigate the involvement of HCN channels in post-traumatic stress disorder (PTSD)-like behaviours.

Study	Animal model	Experimental group		Control group	Results of behavioural tests, which are conducted on both experimental and control groups	Conclusion for the effect of the intervention
		Intervention (Timing of intervention)	Molecular effect of the intervention			
(Ni et al., 2020)	Rats which demonstrate PTSD-like behaviours including hyperarousal, avoidance, behavioural despair and impaired spatial learning after experiencing single prolonged stress and electric foot shock	Intracerebroventricular injection of ZD7288 (Post-protocol)	HCN channels are blocked (Gasparini & DiFrancesco, 1997)	Animal model subject to no pre- or post-protocol intervention	Experimental group, when compared to control group, has: 1. Decreased escape latency time in water maze test. 2. Decreased passive activity time in forced swim test.	Behavioural despair and impaired spatial learing, as PTSD-like behaviours, improve.
		Intracerebroventricular injection of 8-Br-cAMP (Post-protocol)	HCN channel opening probability increases (L. Chen et al., 2015).	Animal model subject to no pre- or post-protocol intervention	Experimental group, when compared to control group, has: 1. Increased escape latency time in water maze test. 2. Decreased number of entries to open arms in elevated plus maze test. 3. Decreased travelling distance in centre square and total travelling distance in open field test.	Behavioural despair, impaired spatial learning, avoidance and hyperarousal, as PTSD-like behaviours, persist.
(Zhang et al., 2021)	Mice after experiencing single prolonged stress	Intraperitoneal injection of ketamine (Post-protocol)	HCN channels are blocked, with channels containing HCN1 subunit being more susceptible (Chen et al., 2009).	Animal model subject to post-protocol intraperitoneal saline injection	Experimental group, when compared to control group, has: 1. Increased number of crossings to central square, increased time in central square, increased number of upright positions in open field test. 2. Increased time spent in open arms in elevated plus maze test. 3. Increased sucrose intake in sucrose preference test. 4. Decreased immobility time in forced swim test.	Behavioural despair and anhedonia, avoidance and hyperarousal, as PTSD-like behaviours, are fewer.

processing, as well as spatial learning and memory (Fanselow & Dong, 2010). Table 1

2.1. The Classical Corticohippocampal Circuit

According to (Basu & Siegelbaum, 2015), the classical corticohippocampal circuit is comprised of projections from the superficial layers of the entorhinal cortex (EC), a region located in the medial temporal lobe, to dCA1 pyramidal neurons via the monosynaptic and trisynaptic paths. The monosynaptic perforant pathway involves direct neuronal projections from EC superficial layer III to dCA1, transmitting both glutamatergic excitatory and GABAergic inhibitory signals which are important in modulating hippocampal output. Meanwhile, the trisynaptic hippocampal circuit involves neuronal projections from EC superficial layer II to the granule cells of DG, which in turn project mossy fibers to CA3 pyramidal neurons that subsequently synapse with CA1 neurons via the Schaffer collaterals. The CA1 neurons then project back to the lateral ventricles of EC, forming a complete loop (EC → DG → CA3 → CA1 → EC). In recent decades, the understanding of the trisynaptic hippocampal circuit has been greatly extended, and different reviews have comprehensively summarized these findings (Amaral, 1993; Amaral & Witter, 1989; Geiller et al., 2017; Stepan et al., 2015). Table 2

2.2. Direct neuronal inputs to dCA1 from extrahippocampal structures

While the classical corticohippocampal circuit is well established, other anatomical connections associated with dCA1 as well as their functions remain unclear, largely due to technological limitations. Yet, with the use of new tracing techniques such as retrobeads and viral tracing and whole-brain mapping, the neuronal input and output between dCA1 and other brain regions can be revealed in greater detail. Table 3

Projections from entorhinal cortex (EC) to dCA1 have been extensively studied. Fundamental studies investigated the functional difference between projections from lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC), in which LEC-hippocampus circuit is more involved in non-spatial aspects, while MEC-hippocampus circuit is more spatially involved (Hargreaves et al., 2005). In recent studies, it has been shown that both excitatory and inhibitory inputs are present in projecting from LEC to dCA1. The excitatory input is responsible for recalling olfactory association at the early stage of learning (Igarashi et al., 2014; Li et al., 2017), while the GABAergic inhibitory input induces heterosynaptic plasticity in dCA1 to increase the specificity of contextual and object memory encoding (Basu et al., 2016). In contrast to the LEC-dCA1 projections, which are less spatially related, MEC-dCA1 circuit is more involved in spatial cognition as it induces the formation of new place fields by providing instructive signals that are related to salient environmental cue (Grienberger & Magee, 2022). During quiet awake state, this pathway relays spatial information of events and enables long-range extended replays to be generated in memory formation (Yamamoto & Tonegawa, 2017). Table 4

Other studies have shown that dCA1 directly receives heavy dopaminergic and noradrenergic input from the locus coeruleus (LC) (Takeuchi et al., 2016). The LC-dCA1 circuit is involved in learning through modulating the association between contextual cue and experience (Kaufman et al., 2020; Tsetsenis et al., 2021), as well as memory through contributing to its consolidation process (Mello-Carpes & Izquierdo, 2013; Takeuchi et al., 2016). Input from prefrontal cortex (PFC) to dCA1, which is GABAergic, enhances spatial information of objects and drives object exploration (Malik et al., 2022). dCA1 receives weak dopaminergic input from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) (Kempadoo et al., 2016; Tsetsenis et al., 2021). Apart from dopaminergic and noradrenergic signals, dCA1 receives strong serotonergic input from the ralph nucleus (RN) (Chowdhury et al., 2022; McKenna & Vertes, 2001; Varga et al., 2009), and this projection is suggested to be involved in the control of reward delivery and locomotion (Luchetti et al., 2020). The medial septum (MS) projects cholinergic and GABAergic signals to dCA1 to control hippocampal theta rhythm (Wang et al., 2022). Other brain structures that provide weak neuronal input to dCA1 include the striatum (STR), thalamus (TH) and hypothalamus (HY) (Tao et al., 2021).

Multiple studies have also suggested anatomical and functional connections between perirhinal cortex (PRH) and dCA1. Direct projections from PRH to dCA1 have been documented in past investigations (Li et al., 2019; Shi & Cassell, 1999). However, the role of PRH in this pathway remains unclear and controversial, with some studies indicating that it is involved in object recognition (Bussey et al., 2005; Deshmukh et al., 2012; Mumby & Pinel, 1994; Norman & Eacott, 2004), non-spatial memory (Deshmukh et al., 2012; Wan et al., 1999), and contextual processing (Bucci et al., 2000; Burwell et al., 2004; Eacott et al., 2001; Ennaceur et al., 1996; Murray et al., 2007). Meanwhile, some argued that the function of the projection is more confined to object recognition (Norman & Eacott, 2005). Thus, PRH is a region of interest that requires further investigation and more solid evidence regarding its anatomical and functional connections with dCA1.

2.3. Direct neuronal output from dCA1 to extrahippocampal structures

dCA1 output pathways that are more comprehensively studied include those to the lateral entorhinal cortex (LEC), nucleus accumbens (NAc), medial prefrontal cortex (mPFC), retrosplenial cortex (RC) and lateral septum (LS). Output from dCA1 to LEC as a part of the entorhinal-hippocampal circuit is triggered to send spatiotemporal information when certain event occurs (Soma et al., 2023). dCA1-NAc circuit is activated during the retrieval of spatial appetitive memory, allowing it to modulate the reinforcement of reward seeking locomotory behaviours through glutamatergic output (Trouche et al., 2019). dCA1-mPFC direct connection is responsible for encoding the temporal component of episodic memory (Barker et al., 2017; Qiu et al., 2024). Meanwhile, the pathway from dCA1 to retrosplenial cortex (RC), which further extends to mPFC, serves in the consolidation of remote contextual memory (Lee et al., 2023). The projection of dCA1 to LS is involved in the control of motor functions by transmitting spatial information to downstream brain regions (van der Veldt et al., 2021; Zhang et al., 2022)

Other output pathways of dCA1 are less clear in terms of their functions. It has been recently shown that dCA1 projects to medial entorhinal cortex (MEC), with dCA1-MEC fibres significantly denser than vCA1-MEC fibres (Qiu et al., 2024). Moreover, projections from dCA1 to medial septum (MS) exist (Takács et al., 2008), and these neuronal output can be either glutamatergic or GABAergic (Qiu et al., 2024). However, the roles of these pathways are currently understudied and remain unclear.

3. HCN channelopathies in DCA1

3.1. Features of dCA1 HCN channels

HCN channels are expressed in the heart and in most regions of the brain, including the hippocampus (Combe & Gasparini, 2021). In the brain, HCN channels demonstrate differential expression characteristics, with different densities and different subunits at different structures of the brain. This special feature of HCN channels has received attention from researchers, and disruptions to it can result in the manifestation of diseases (Kase & Imoto, 2012).

Each HCN channel is a tetramer, comprising of four subunits (HCN1–4) in a homomeric or heteromeric manner (He et al., 2014). In CA1 pyramidal neurons, HCN1 homomeric channels constitute the majority of HCN channels, followed by HCN1-HCN2 heteromeric and HCN2 heteromeric channels (Notomi & Shigemoto, 2004). The voltage range of activation for HCN1 homotetramers is more depolarized than that of HCN2 homotetramers, with HCN1/HCN2 heterotetrameric channels in between (Chen et al., 2001). Each subunit consists of a

transmembrane domain and a cytoplasmic domain, with the cyclic nucleotide binding domain (CNBD) existing near the C-terminal of the cytoplasmic domain, and the C-linker bridging the transmembrane domain and CNBD. The binding of cAMP to CNBD induces C-linker and thus the transmembrane domain to experience miniature structural changes, promoting the channel pore to widen and increasing the channel's tendency to open (Porro et al., 2019). Triggered by hyperpolarization, HCN channels open and produce a hyperpolarization-activated current (I_h) (Cowgill et al., 2019).

HCN channels show unique properties as they open during hyperpolarization and produce a hyperpolarization-activated current (Ih) (Cowgill et al., 2019). I_h stabilizes membrane potential by producing excitatory and inhibitory effects to a neuron. Regarding its excitatory effect, HCN channels are activated in hyperpolarized membrane potentials, providing an excitatory current. Regarding its inhibitory effect, when a neuron becomes depolarized as it experiences a train of excitatory postsynaptic potentials (EPSP) in temporal summation, HCN channels are deactivated. The reduction in I_h counters the depolarizing effect of temporal summation (Magee, 1999). Moreover, as a neuron is at rest, some HCN channels can be activated to produce I_h that limit repolarization. Without sufficient repolarization, this causes more voltage-gated calcium channels to stay at their inactivated state and fail to be re-activated, suppressing calcium spike initiation (Tsay et al., 2007). Regarding the detailed mechanisms that explain the effect of HCN channels, reviews taking a neurophysiological perspective elucidated them comprehensively (He et al., 2014; Mishra & Narayanan, 2025).

In CA1, the expression profile of HCN channels varies along the somatodendritic axis of pyramidal neurons and along the dorsoventral axis of CA1, and this can associate with the differences of I_h within the region. Along the somatodendritic axis of pyramidal neurons, the expression of HCN channels increases from soma to dendrites, with I_h increasing in parallel (Magee, 1998, 1999). As a result, the effect of I_h in limiting temporal summation and calcium spike initiation becomes more pronounced, causing distal inputs to be more dampened and the synaptic-driving neuronal excitability in the region to be lower (He et al., 2014). Along the dorsoventral axis of CA1, HCN1-to-HCN2 ratio increases along the somatodendritic axis of pyramidal neurons in vCA1 while essentially remains constant in dCA1 (Dougherty et al., 2013). Given that HCN1-containing channels exhibit more depolarized voltage ranges of activation (Chen et al., 2001), such expression pattern featuring a lower proportion of HCN1 in dCA1 alters the membrane propeties of dCA1 neurons, as I_h is activated to depolarize the membrane and suppress temporal summation in a more hyperpolarized membrane potential. This correlates with the finding of a more hyperpolarized resting membrane potential and a lower input resistance in dCA1, which contribute to a lower intrinsic excitability in dCA1 (Arnold et al., 2019; Marcelin et al., 2012).

3.2. Depressive behaviours can be linked to the overexpression of perisomatic HCN channels in dCA1, with resilience promoted by (S)-ketamine, improvement produced by chronic cAMP elevation while induction produced by acute cAMP administration

Patients of major depressive disorder typically present with diminised interest or pleasure in activities, and/or complain of psychological symptom of depressed mood. Other manifestations include cognitive deficits; physical signs such as significant weight changes, insomnia or hypersomia, psychomotor agitation or retardation, fatigue or loss of energy; as well as psychological manifestations such as feelings of worthlessness and recurrent suicidal ideation (American Psychiatric Association, 2022). Animal models which have been widely adopted to replicate major depressive disorder, for example, chronic unpredictable stress and chronic social defeat stress, are unable to test for psychological manifestations, but can test for observable presentations which can be elicited as depressive-like behaviours in animals. For example, diminished interest or pleasure in activities as observed in human patients can be resembled by anhedonic-like behaviours in animals, and are commonly tested by sucrose preference test. Other depressive-like behaviours such as behavioural despair and altered locomotor activity, which are commonly tested by forced swim test and tail suspension test, can resemble patients' symptoms of fatigue or loss of energy (Becker et al., 2021; Czéh et al., 2016).

In animal models, HCN1 perisomatic expression in dCA1 is increased as rats are exposed to chronic unpredictable stress to become triggered to exhibit depressive behaviours, including anhedonia and behavioural despair. (Kim et al., 2018). As a result, I_h is upregulated, and its membrane stabilizing effect becomes larger in dCA1 pyramidal neurons. The reduction in the excitability of these neurons and the activity of dorsal hippocampus is hypothesized to associate with the development of depressive behaviours (Kim & Johnston, 2018).

The tendency for depressive behaviours to develop following stress can be increased or decreased by modulators of HCN channels, including cAMP and (S)-ketamine, by affecting the trafficking and opening probability of dCA1 HCN channels. In the study by Lyman et al. (2021), acute administration of cAMP in dCA1 following chronic social defeat stress is linked to the development of depressive behaviours, while chronic elevation of cAMP level following the stress produces antidepressant effect by disrupting TRIP8b-HCN interaction and limiting HCN surface expression. For (S)-ketamine, which is a potent HCN1 blocker (Chen et al., 2009), the study by Kim and Johnston (2020) shows that administrating it before chronic unpredictable stress produces resilience to the development of depressive behaviours.

cAMP's effect on dCA1 HCN channels of whether being depressant or antidepressant is dependent on the duration of administration. Acutely elevating cAMP level in mice dCA1 yields an immediate effect of an increased HCN channel opening probability. This promotes I_h of dCA1 and contributes to the development of depressive behaviours of the mice. In contrast, chronically increasing cAMP level in mice dCA1 downregulates dCA1 I_h and produces antidepressant effect (Lyman et al., 2021). The latter phenomenon, which was unexpected since the duration of cAMP administration was generally believed to be positively correlated to cAMP's effect in modulating HCN channels, is related to Tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b) (Zagotta et al., 2003). TRIP8b, a protein auxiliary subunit for HCN channels, exists in multiple isoforms through alternative splicing. Different TRIP8b isoforms alter surface expression in a cell type-specific manner by producing distinct trafficking effects (Lewis et al., 2009). In physiological conditions of CA1, due to the high abundance of two specific TRIP8b isoforms in the pyramidal neurons, the general effect of TRIP8b is to mediate the trafficking of HCN and promote HCN channel surface expression (DeBerg et al., 2015). However, TRIP8b-HCN interaction can be disrupted by a chronically elevated cAMP level, and chronic cAMP treatment in dCA1 can upset the effect of TRIP8b in promoting HCN channel surface expression (Han et al., 2011). Nonetheless, when dCA1 experiences a chronically elevated level of cAMP, TRIP8b-HCN interaction is disrupted and the surface expression-promoting effect of TRIP8b is hampered. The reduced surface density of HCN channels overrides the effect of cAMP in potentiating their opening probability, limiting the generation of Ih in dCA1. Eventually, the reduced I_h in dCA1, which is produced by chronic cAMP treatment, contributes to the production of the antidepressant effect in the rat model.

Regarding (S)-ketamine, which is a blocker of HCN1-containing channels that is even more potent than racemic ketamine (Chen et al., 2009), administrating it produces antidepressant effects. Administering (S)-ketamine before rats are subject to chronic unpredictable stress produces resilience to the development of depressive behaviours (Kim & Johnston, 2020). Given that (S)-ketamine selectively inhibits HCN1-containing channels, while the expression of somatic HCN1 increases in dCA1 following chronic unpredictable stress (Kim et al., 2018), it can be hypothesized that (S)-ketamine inhibits the upregulated

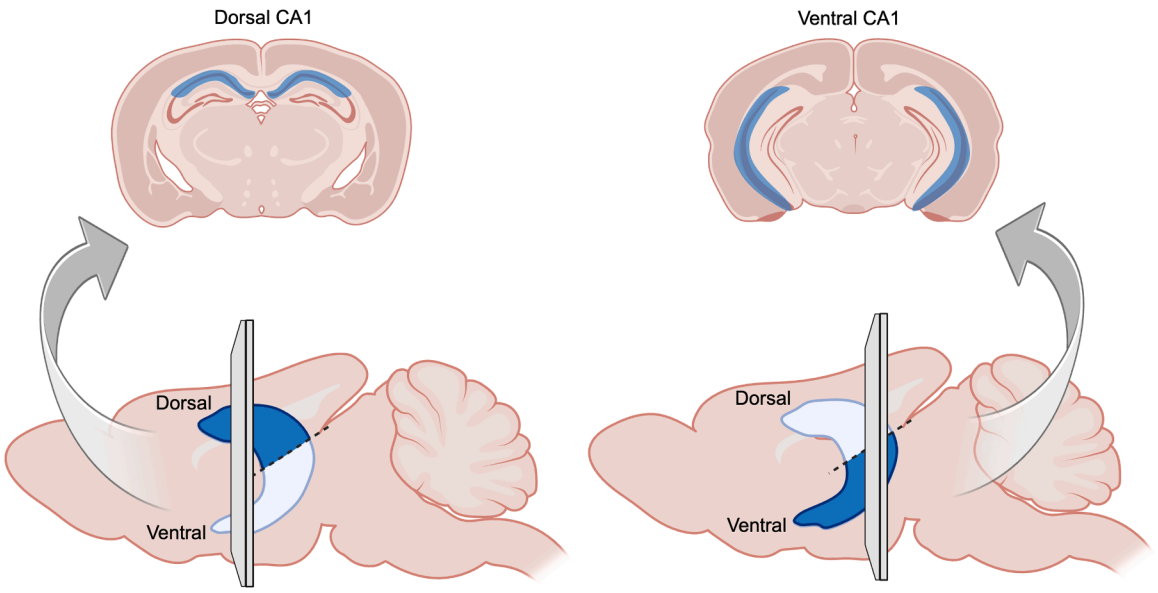

Fig. 1. Location of dorsal CA1 and ventral CA1 shown in longitudinal and transverse sections of mouse brain.

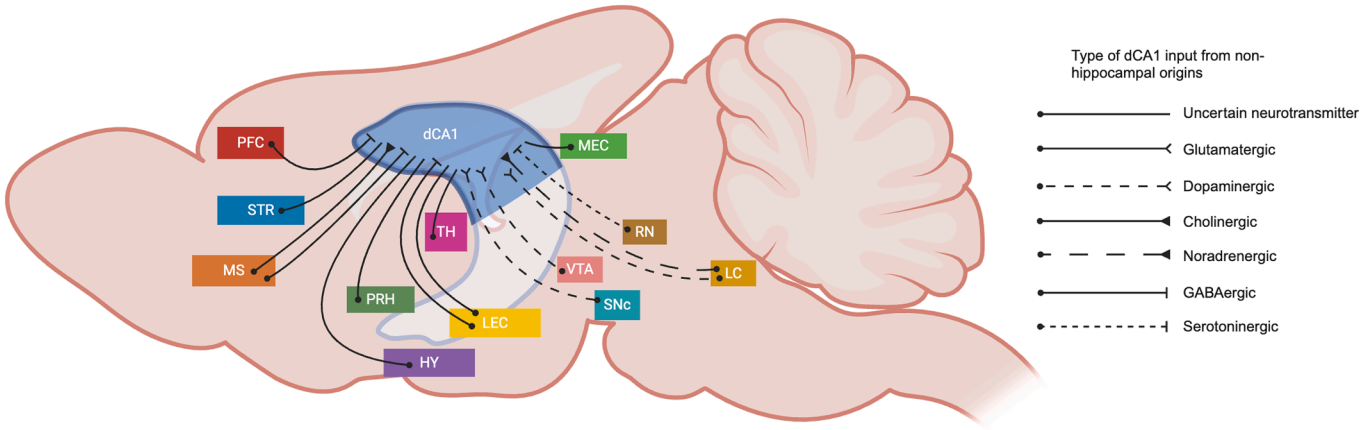

Fig. 2. Structures that provide direct neuronal inputs to dCA1 of hippocampus shown in a mouse brain. Lateral entorhinal cortex (LEC) provides GABAergic and excitatory inputs (Basu et al., 2016; Li et al., 2017). Medial entorhinal cortex (MEC) provides an excitatory input (Grienberger & Magee, 2022). Prefrontal cortex (PFC) provides a GABAergic input (Malik et al., 2022). Ventral tegmental area (VTA) provides a dopaminergic input (Kempadoo et al., 2016; Tsetsenis et al., 2021). Substantia nigra pars compacta (SNc) provides a dopaminergic input (Kempadoo et al., 2016; Tsetsenis et al., 2021). Locus coeruleus (LC) provides dopaminergic and nonadrenergic inputs (Takeuchi et al., 2016). Raph nucleus (RN) provides a serotonergic input (Chowdhury et al., 2022; McKenna & Vertes, 2001; Varga et al., 2009). Medial septum provides cholinergic and GABAergic inputs (Wang et al., 2022). Striatum (STR), Thalamus (TH), Hypothalamus (HY) each provides an input of uncertain neurotransmitter (Tao et al., 2021). Perirhinal cortex (PRH) makes an excitatory synapse of uncertain neurotransmitter with dCA1(Li et al., 2019; Shi & Cassell, 1999;.

somatic HCN1 in dCA1, reduces I_h of the region and leads to antidepressant effects.

In conclusion, post-stress overexpression of perisomatic HCN1 in dCA1 is associated with the development of depressive behaviours. In dCA1, chronic administration of cAMP following stress disrupts HCN trafficking, which reduces the tendency for depressive behaviours to develop, while acute administration of cAMP following stress increases HCN channel opening probability, thus increases the tendency for depressive behaviours to develop. (S)-ketamine administration prior to stress blocks HCN channels, and is hypothesized to act on overexpressed HCN channels in dCA1 to produce resilience to depressive behaviours.

3.3. PTSD-like behaviours can be linked to the overexpression of perisomatic HCN channels in dCA1, being improved by ZD7288 and ketamine while persisting under 8-Br-cAMP

PTSD can occur in humans who have been exposed to certain traumatic events, with manifestations of intrusion symptoms and persistent avoidance of the event, negative alterations in cognitions and mood, as well as marked alterations in arousal and reactivitiy associated with it (American Psychiatric Association, 2022). In translational studies, researchers have made much attempt in eliciting PTSD-like behaviours in animals and design paradigms that may model PTSD. To date, although it remains inconclusive to determine an 'ideal' paradigm, behavioural tests such as single-prolonged stress, foot shock and social defeat stress have been widely adopted and have been assessed regarding their ability to induce PTSD-like behaviours (Borghans & Homberg, 2015; Verbitsky et al., 2020; Whitaker et al., 2014). When PTSD-like behaviours are

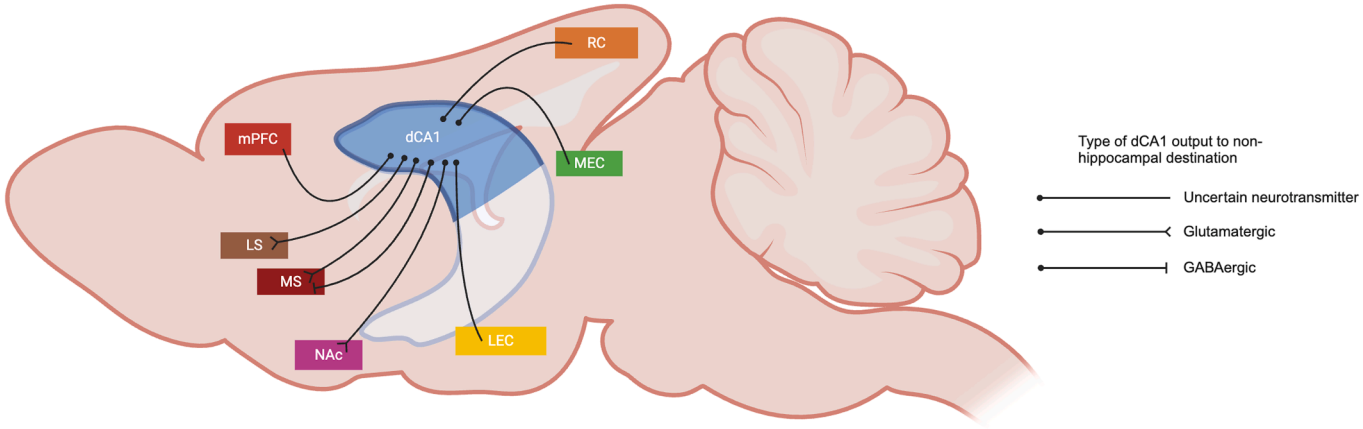

Fig. 3. Structures that receive direct neuronal inputs from dCA1 shown in a mouse brain. dCA1 provides output of uncertain neurotransmitter to medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC) (Qiu et al., 2024). dCA1 provides glutamatergic output to nucleus accumbens (NAc) (Trouche et al., 2019). dCA1 provides output of uncertain neurotransmitter to medial prefrontal cortex (mPFC) (Barker et al., 2017). dCA1 provides output of uncertain neurotransmitter to retrosplenial cortex (RC) (Lee et al., 2023). dCA1 provides glutamatergic output to lateral septum (LS) (Zhang et al., 2022). dCA1 provides glutamatergic and GABAergic output to medial septum (MS) (Qiu et al., 2024; Takács et al., 2008).

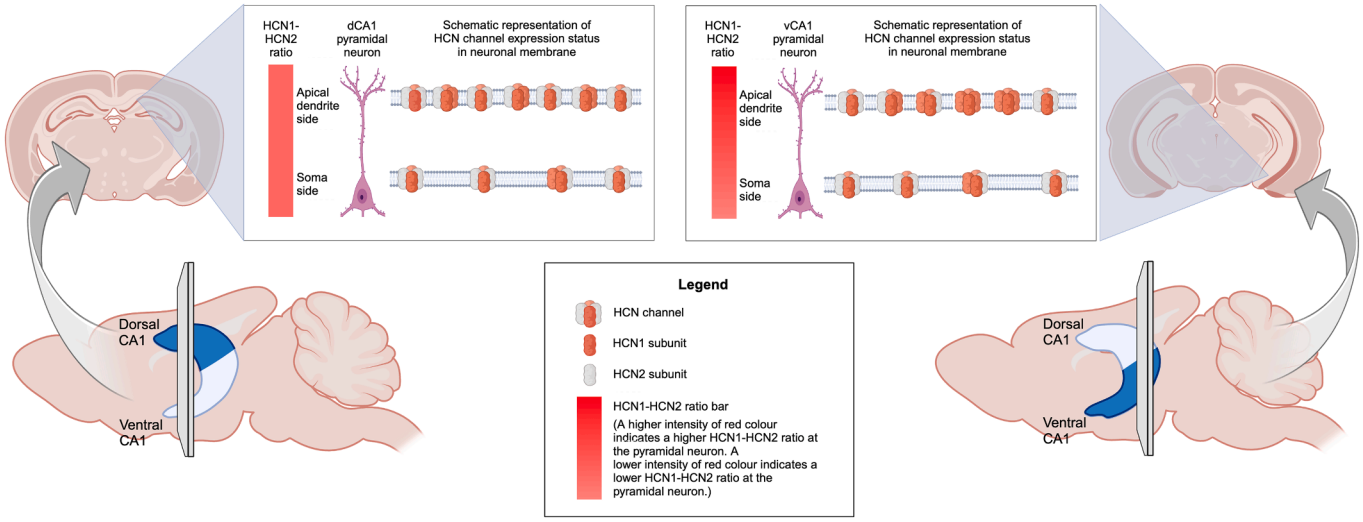

Fig. 4. Expression profile of HCN channels along the somatodendritic axis of CA1 pyramidal neurons and the ventrodorsal axis of CA1. In dorsal CA1 (dCA1) and ventral CA1 (vCA1), density of HCN channels increases along the somatodendritic axis of pyramidal neurons (Magee, 1998, 1999). This is illustrated in the figure by different densities of membrane HCN channel along the somatodendritic axis, increasing from the apical dendrite to the soma side of the pyramidal neuron, in both dCA1 and vCA1. Meanwhile, the structure of HCN channels changes across the ventrodorsal axis of CA1, with the HCN1-to-HCN2 ratio increasing along the somatodendritic axis in vCA1 but not in dCA1 (Dougherty et al., 2013). This is illustrated in the figure as the proportion of HCN1 subunit increases from the soma side to the apical dendrite side of the pyramidal neuron, in vCA1 but not in dCA1. Moreover, at the bar showing the HCN1-HCN2 ratio bar at the left of both panels, vCA1 shows an increasing trend along the somatodendritic axis, while that of dCA1 remains constant.

assessed in animals exposed to these stressors, open-field and startle response tests are used in evaluating avoidance and hyperarousal respectively. For other PTSD-like behaviours, they may overlap with behaviours that can be elicited in animal model of depression, including anhedonia, behavioural despair and altered cognitive functions. Sucrose preference test, forced swim test and water maze test have been widely adopted to test these behaviours respectively, with their validity and use evaluated in the literature (Török et al., 2019).

The development of PTSD-like behaviours in animals can be linked to the overexpression of perisomatic HCN1 at dCA1. In an experiment aiming to elicit PTSD-like behaviours through exposing mice to chronic social defeat stress, mice which acutely and persistently developed social avoidance were examined across those which did not despite being exposed to the same stressor. These mice experienced an increase in the expression of perisomatic HCN1 in dCA1 pyramidal neurons, and an elevation of I_h in dCA1 (Kim et al., 2022). It has been demonstrated that the development of PTSD-like behaviours, which are associated with the upregulation of HCN1 in CA1, is mediated by a reduced level of BDNF and mTOR signaling (Ni et al., 2020; Zhang et al., 2021). This finding is consistent with lines of evidence in previous studies that focus on the relationship between hippocampal BDNF and PTSD-like behaviours. For example, a reduced BDNF mRNA levels in CA1 correlates with PTSD-like behaviours such as hyperarousal in rats (Chang et al., 2021; Kozlovsky et al., 2007).

Using modulators of HCN channels including ZD7288, 8-Br-cAMP and ketamine, evidence from other studies conducted at the hippocampus is in line with this finding as well. After rats experience single prolonged stress and electric foot shock, they exhibit PTSD-like behaviours including hyperarousal, avoidance, negative mood and impaired spatial learning, which do not manifest in the control group. However, as ZD7288, a blocker of HCN channels in CA1 pyramidal neurons (Gasparini & DiFrancesco, 1997), is administered, negative mood and

impaired spatial learning as some aspects of PTSD-like manifestations improve. In contrast, upon the administration of 8-Br-cAMP, which is a cAMP analogue that binds to CNBD of HCN channels and increases their opening probability (L. Chen et al., 2015), PTSD-like behaviours including negative mood, impairment in spatial learning, avoidance and hyperarousal persist (Ni et al., 2020). In another study, mice under single prolonged stress are found to associate with an increased HCN1 expression in CA1. Comparing with those infused with saline, mice that are administered with ketamine exhibit fewer PTSD-like behaviours including negative mood, avoidance and hyperarousal (Zhang et al., 2021). Given that ketamine demonstrates a specifically high blocking potency among HCN1 homomeric channels (Chen et al., 2009), ketamine is hypothesized to block hippocampal HCN1 homomeric channels, which have been upregulated in dCA1 pyramidal neurons following the single prolonged stress in this model.

Given that the increase in perisomatic HCN1 at dCA1 pyramidal neurons is linked to PTSD-like behaviours, as demonstrated as acute and persistent social avoidance, are linked to an increase in perisomatic HCN1 at dCA1 pyramidal neurons in the study of Kim et al. (2022), it can be hypothesized that modulators including ketamine, which has a high blocking potency on HCN1 homomeric channels (Chen et al., 2009), act on the overexpressed HCN channels at dCA1 and lead to the improvement of PTSD-like behaviours. In humans, evidence of using ketamine to treat PTSD is emerging as multiple trials showed that infusion of certain dosage of ketamine can reduce PTSD symptoms in patients (Almeida et al., 2024; Feder et al., 2020). With further investigation on the action of ketamine in dCA1 HCN channels, the mechanism for ketamine in reducing PTSD symptoms can become better elucidated.

As a higher expression level of HCN1 in dCA1 pyramidal neurons can be examined in animal models of both PTSD and depression, what accounts for the difference in the behaviours elicited? Rats in an animal model of PTSD are exposed to single-prolonged stress and foot shock. As rats demonstrate PTSD-like behaviours including hyperarousal, avoidance, behavioural despair and impaired spatial learning, they are found to have higher HCN1 not only in hippocampus, but also in prefrontal cortex (Ni et al., 2020). For depression, rats are exposed to chronic unpredictable stress, a stressor aiming to elicit depressive-like behaviours. As they are induced with behavioural despair and anhedonia, there is only evidence showing the association between these depressive-like behaviours and a higher expression level of HCN1 in hippocampus but not in prefrontal cortex (Kim et al., 2018). The involvement of prefrontal cortex might be one of the factors accounting for the difference in the behavioural manifestations between these two animal models. Meanwhile, the common part of the pathophysiology of PTSD and depression, which is an upregulated HCN1 level in dorsal CA1, might be related to the overlapping presentation of behavioural despair in the animal model of the two diseases.

3.4. dCA1 HCN channelopathies in temporal lobe epilepsy

Changes in the region-specific expression of HCN channels can be linked to the recurrence of seizures. In post-status epilepticus rat models with temporal lobe epilepsy, HCN1 located in the distal dendrites of dCA1 pyramidal neurons are expressed at a lower level. Such change is associated with the recurrence of seizures (Arnold et al., 2019). With the reduction of I_h and the upregulated synaptic-driving excitability in distal dendrites, dCA1 pyramidal neurons experience increased action potential firing rates, with such change preceding the initiation of spontaneous seizures (Fujita et al., 2014). These findings suggest that seizures can be predisposed when HCN channels become under-expressed at the distal dendrites of dCA1 pyramidal neurons, which increases the excitability of dCA1. Moreover, findings in human studies are in line with animal studies. In hippocampal biopsies from patients with chronic medial temporal lobe epilepsy, there is a downregulation of HCN channel transcription and expression levels in CA1 (Lin et al., 2020). Although the study did not examine the change specific to different position along the dorsoventral axis of CA1, it can provide evidence on the association between epilepsy and a downregulation of CA1 HCN channels.

The predisposition of seizures caused by epilepsy-inducing insults, including status epilepticus, can be mediated by an increased expression of neuron-restrictive silencer factor (NRSF), which is also known as Repressor Element-1 Silencing Transcription factor (REST), that represses HCN expression. In rat temporal lobe epilepsy model, the level of REST/NRSF is shown to be higher in dCA1 after kainic-acid induced status epilepticus (McClelland et al., 2011). It is hypothesized that hippocampal REST/NRSF may be upregulated after epilepsy-inducing seizures, being more likely to bind to *hcn1* gene to repress its expression (McClelland et al., 2014). The result is a suppression in HCN1 expression and I_h in dCA1 pyramidal neurons, and thus an increased excitability in the region. As dCA1 and vCA1 excitabilities become more similar, seizures become more likely to be predisposed. This hypothesis may also explain the clinical phenomenon that among drug-resistant mesial temporal lobe epilepsy patients, hippocampal REST/NRSF level is proportional to seizure frequency, where epilepsy-inducing insults may precipitate seizures as REST/NRSF, at a higher level, represses *hcn1* to a larger extent (Navarrete-Modesto et al., 2019).

While transcriptional factors regulate the amount of HCN channels, post-translational modification modulators regulate key processes including proper membrane expression of HCN channels. In the distal dendrites of dCA1 pyramidal neurons, TRIP8b, when phosphorylated, has a higher affinity to the cyclic nucleotide binding domain (CNBD) of HCN channels, and can better promote the trafficking of HCN channels and their enrichment at the site (Han et al., 2017). In a rat model with temporal lobe epilepsy, phosphorylation of TRIP8b, which is thought to be mediated by Ca2 + /calmodulin-dependent protein kinase II (CaMKIIα) and protein kinase A (PKA), is reduced after status epilepticus (Foote et al., 2019). A reduced phosphorylation of TRIP8b at the distal dendrites of dCA1 pyramidal neurons is hypothesized to be involved in limiting the trafficking and proper membrane expression of HCN channels. Subsequently, the downregulation of I_h may predispose post-status epilepticus seizures in temporal lobe epilepsy.

Overall, in temporal lobe epilepsy, transcriptional and post-translational modification factors of HCN channels in dCA1 experience changes following epilepsy-inducing insults, including status epilepticus. The upregulated level of REST/NRSF represses *hcn1* gene to a larger extent and may reduce neuronal HCN1 level in dCA1. The downregulated phosphorylation of TRIP8b in distal dendrites possibly contributes to the disruption of the trafficking and localization of HCN. These postictal changes manifest as a reduction in the enrichment of HCN channels in the distal dendrites of dCA1 pyramidal neurons. As a result, the gradient of HCN channel density along the somatodendritic axis of dCA1 pyramidal neurons is lost, and that along the dorsoventral axis of CA1 is disrupted as well. Eventually, with lower I_h but higher excitability in dCA1, seizures become predisposed in the region.

4. Future directions

dCA1 HCN channelopathies remain largely unknown as it is unclear how disruptions of HCN transcription, post-translational modification and activation kinetics are linked to disease phenotypic changes. However, different HCN channelopathy studies related to PTSD, depression and epilepsy may provide insights to one another, and can help researchers identify the possible focus of future investigations. On the other hand, treatments that tackle this class of disease are not extensively studied, while evidence converged from different research may hint on some future investigation directions. Some possible research directions regarding dCA1 HCN channelopathies are elaborated in this section.

4.1. Future directions on research regarding dCA1 HCN channelopathies in PTSD and depression

In rat models, post-stress overexpression of perisomatic HCN channels in dCA1 pyramidal neurons can be linked to the development of PTSD-like and depressive behaviours. However, the detailed molecular mechanisms underlying this post-stress change remain unknown. Factors that affect the transcription, post-translational modification such as protein trafficking and localization, and channel functioning are possible to be involved in these processes, and may even provide directions to the development of novel therapeutics.

HCN transcriptional changes in dCA1 may be a factor mediating the development of PTSD and depression. As discussed in the findings regarding the association between the upregulation of REST/NRSF and downregulation of dendritic HCN, an elevated REST/NRSF level can cause *hcn1* gene to be less expressed, contributing to a reduced HCN1 expression (McClelland et al., 2014; McClelland et al., 2011; Navarrete-Modesto et al., 2019). Therefore, one may speculate whether the reverse applies – a downregulated REST/NRSF level leading to an upregulated HCN1 expression, which underlies the development of PTSD-like and depressive behaviours. It is noteworthy that existing evidence shows conflicting results that may not be in favour of this hypothesis. In a study, after young rodents experience chronic stress, which is modelled by isolation from mother, there is no REST/NRSF expression difference in their hippocampus (Uchida et al., 2010). However, in another study, after animal models experience chronic social defeat stress, increase in hippocampal REST/NRSF levels alongside with the development of depressive behaviours is shown (C. C. Chen et al., 2015). These results suggest that REST/NRSF alone may not be able to explain the post-stress upregulation of HCN1 expression in dCA1, and further studies are necessary to study how other mediators may be involved.

On the therapeutic level, basic biomedical studies on dCA1 HCN channelopathies and neural circuitry may provide directions on increasing the efficacy of deep brain stimulation (DBS). DBS, in which clinicians implant electrodes in specific brain structures, has been widely employed in treating Parkinson's disease since its clinical application in the 1990s (Lozano et al., 2019; Sironi, 2011). Nowadays, its use in treatment-resistant major depressive disorder is emerging. Some clinical studies show that deep brain stimulation of NAc (NAc-DBS) produce antidepressant effects among treatment-resistant depression patients (Bewernick et al., 2012; Grubert et al., 2011). However, the efficacy and mechanism of action of NAc-DBS are unclear, and this procedure remains an experimental one (Kisely et al., 2018). From connectivity studies, dCA1-NAc circuit is involved in reinforcing reward seeking locomotory behaviours (Trouche et al., 2019), and changes of this circuit may be linked to disruptions in reward-related behaviours that possibly contribute to the development of depression. Channelopathy studies reveal the association between the development of depression and an upregulated expression of dCA1 perisomatic HCN channels, which increases I_h and reduces the excitability of dCA1 pyramidal neurons (Kim et al., 2018). With these basic science research findings, it can be hypothesized that during the development of depression, as dCA1 perisomatic HCN channels increase following the exposure of chronic stress, firing in the dCA1-NAc circuit may be reduced as dCA1 witnesses a downregulated excitability. Therefore, it may also be hypothesized that upregulating dCA1 excitability by reducing I_h may rescue the activity of dCA1-NAc circuit. In a therapeutic perspective, since an inhibited dCA1-NAc projection lowers the antidepressant effect of DBS-NAcc (Zhou et al., 2022), interventions that reduce dCA1 I_h may upregulate dCA1-NAc circuit activity, and can theoretically promote the efficacy of DBS-NAcc. Further research that investigates the relationship between dCA1 channelopathy and neural circuitry changes in the context of depression and DBS-NAcc is necessary for testing this hypothesis.

4.2. Future directions on research regarding dCA1 HCN channelopathies in temporal lobe epilepsy

In rat models that experience epilepsy-inducing insults, including status epilepticus, the reduced expression of HCN channels in the distal dendrites of dCA1 pyramidal neurons causes a reduced I_h and increased excitability (Arnold et al., 2019). The increase in firing rates of pyramidal neurons leads to the initiation of spontaneous seizures (Fujita et al., 2014). However, other than REST/NRSF, which represses the transcription of *hcn1* gene, and phosphorylated TRIP8b, which mediates the trafficking and localization of HCN, one may question if there are factors that limit the expression and functioning of HCN channels in the distal dendrites of dCA1 pyramidal neurons.

One possible factor may be cAMP, as chronic administration of cAMP in dCA1 is reported to reduce HCN channel expression in studies investigating HCN channelopathy and depression (Lyman et al., 2021). It has been confirmed that a chronically increased cAMP level induces conformational change in HCN which disrupts the interaction between HCN and the surface expression-enhancing TRIP8b in dCA1 (Han et al., 2011; Zagotta et al., 2003), and causes a suppressed surface expression of HCN channels. Therefore, with fewer HCN channels expressed, it is possible that I_h is reduced and dCA1 neuronal excitability becomes upregulated, which lowers the threshold for seizures to occur in the hippocampal circuit and may explain the predisposition of seizures. To test this hypothesis, further research studies that investigate the effect of chronic cAMP treatment in dCA1 on epilepsy are required.

Investigating how different factors interact with HCN channels in dCA1 pyramidal neurons, one can develop a more comprehensive understanding that may provide key insights into the mechanism of the action of current antiepileptic drugs. These drugs may remain unclear on how they regulate I_h in dCA1 pyramidal neurons and contribute to the treatment of epilepsy. Examples include gabapentin and lamotrigine, which have been used to treat partial seizures (Marson et al., 2007; Yasam et al., 2016). Gabapentin and lamotrigine have been shown to increase I_h in CA1 pyramidal neurons when exerting its antiepileptic effect (Poolos et al., 2002; Surges et al., 2003). Counter to the expectation based on the understanding of HCN channelopathy in temporal lobe epilepsy, they both have no significant impact on the activation and kinetics of HCN1 and HCN2 (Merseburg et al., 2022; Tae et al., 2017). It is therefore speculated that they act on other targets that mediate HCN expression in CA1 pyramidal neurons, for example, transcription factors, molecules that affect the trafficking and surface expression of the channel, as well as factors that affect its functioning. Moreover, in future studies in which cellular targets of these antiepileptic drugs in dCA1 pyramidal neurons are unveiled, more information can be gathered to enable researchers to design novel drugs for epilepsy.

In conclusion, leveraging the findings on HCN channelopathies, future research may investigate novel agents that can target the dysregulated I_h and neuronal excitability of dCA1 in the development of therapeutics in PTSD, depression and epilepsy. Treatments may range from intervening HCN transcription, post-translational modifications related to protein trafficking, to channel opening and blocking. Some candidate intervention targets include 1) REST/NRSF level, which represses *hcn1* gene and its transcription in dCA1 (McClelland et al., 2014); 2) TRIP8b expression at dCA1 pyramidal neurons, which promotes the trafficking of HCN to neuronal surface and antagonizes the opening-potentiation effect of cAMP (Santoro et al., 2009); 3) TRIP8b phosphorylation at distal dendrites, which possibly contributes to the distal enrichment of HCN at the dendrites of dCA1 pyramidal neurons (Han et al., 2017); 4) cAMP level, which potentiates channel opening during acute administration but upsets TRIP8b's surface expression-enhancing effect during chronic administration (Han et al., 2011); 5) HCN channel blockers, such as ZD7288 (Gasparini & DiFrancesco, 1997) and ketamine (Chen et al., 2009).

5. Conclusion

HCN channelopathies of the dCA1 is an understudied yet significant cause of neurological and psychiatric disorders including PTSD, depression and temporal lobe epilepsy. While recent research has shed light on the role of HCN channels in altering neuronal excitability that leads to the mentioned disease states, the exact mechanisms of how HCN channels cause disease phenotypic changes and how their transcription, post-translational modifications as well as channel opening and blocking are regulated by other agents or factors are yet to be elucidated. At the same time, therapeutic strategies that are currently employed to treat such diseases should also be more extensively studied, so as to better understand their mechanism of action in regulating I_h in dCA1 pyramidal neurons, as well as to gain insights into methods that increase the efficacy of current treatments, and to develop novel treatments.

Funding

This work was supported by STI2030-Major Projects (2022ZD0214400; J.I., L.S., J.Z), Guangdong Basic and Applied Basic Research Foundation (2022B1515130007; J.I., L.S.), Research Grants Council (RGC) of Hong Kong SAR (24117220, J.I.), Lo Kwee-Seong Biomedical Research Fund (J.I.), and Faculty Innovation Awards (FIA2020/A/04) from the Faculty of Medicine, CUHK (J.I.).

CRediT authorship contribution statement

So Tsz Wei: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Choi Hoi Yi:** Writing – original draft, Visualization. **Xu Haoyu:** Writing – review & editing. **Zhu Jinwei:** Writing – review & editing. **Shi Lei:** Writing – review & editing. **Ip Jacque Pak Kan:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank Ip lab members for their helpful discussion.

Figures were created in BioRender. Fig. 1: Created in BioRender. So, T. (2025) https://BioRender.com/r72w073. Fig. 2: Created in BioRender. So, T. (2025) https://BioRender.com/q81u107. Fig. 3: Created in BioRender. So, T. (2025) https://BioRender.com/a13b220. Fig. 4: Created in BioRender. So, T. (2025) https://BioRender.com/o71i363.

References

Almeida, T.M., Lacerda da Silva, U.R., Pires, J.P., Borges, I.N., Martins, C.R.M., Cordeiro, Q., Uchida, R.R., 2024. Effectiveness of Ketamine for the Treatment of Post-Traumatic Stress Disorder - A Systematic Review and Meta-Analysis. Clin. Neuropsychiatry 21 (1), 22–31. https://doi.org/10.36131/cnfioritieditore20240102.

Amaral, D.G., 1993. Emerging principles of intrinsic hippocampal organization. Curr. Opin. Neurobiol. 3 (2), 225–229. https://doi.org/10.1016/0959-4388(93)90214-j.

Amaral, D.G., Witter, M.P., 1989. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31 (3), 571–591. https://doi.org/10.1016/0306-4522(89)90424-7.

American Psychiatric Association, 2022. Diagn. Stat. Man. Ment. Disord. https://doi.org/10.1176/appi.books.9780890425787 (5th ed., text rev. ed.).

Anand, K.S., Dhikav, V., 2012. Hippocampus in health and disease: An overview. Ann. Indian Acad. Neurol. 15 (4), 239–246. https://doi.org/10.4103/0972-2327.104323.

Arnold, E.C., McMurray, C., Gray, R., Johnston, D., 2019. Epilepsy-Induced Reduction in HCN Channel Expression Contributes to an Increased Excitability in Dorsal, But Not Ventral, Hippocampal CA1 Neurons. eNeuro 6 (2). https://doi.org/10.1523/eneuro.0036-19.2019.

Barker, G.R., Banks, P.J., Scott, H., Ralph, G.S., Mitrophanous, K.A., Wong, L.F., Bashir, Z.I., Uney, J.B., Warburton, E.C., 2017. Separate elements of episodic memory subserved by distinct hippocampal-prefrontal connections. Nat. Neurosci. 20 (2), 242–250. https://doi.org/10.1038/nn.4472.

Basu, J., Siegelbaum, S.A., 2015. The Corticohippocampal Circuit, Synaptic Plasticity, and Memory. Cold Spring Harb. Perspect. Biol. 7 (11). https://doi.org/10.1101/cshperspect.a021733.

Basu, J., Zaremba, J.D., Cheung, S.K., Hitti, F.L., Zemelman, B.V., Losonczy, A., Siegelbaum, S.A., 2016. Gating of hippocampal activity, plasticity, and memory by entorhinal cortex long-range inhibition. Science 351 (6269), aaa5694. https://doi.org/10.1126/science.aaa5694.

Becker, M., Pinhasov, A., Ornoy, A., 2021. Animal Models of Depression: What Can They Teach Us about the Human Disease? Diagn. (Basel) 11 (1). https://doi.org/10.3390/diagnostics11010123.

Bewernick, B.H., Kayser, S., Sturm, V., Schlaepfer, T.E., 2012. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. Neuropsychopharmacology 37 (9), 1975–1985. https://doi.org/10.1038/npp.2012.44.

Borghans, B., Homberg, J.R., 2015. Animal models for posttraumatic stress disorder: An overview of what is used in research. World J. Psychiatry 5 (4), 387–396. https://doi.org/10.5498/wjp.v5.i4.387.

Bucci, D.J., Phillips, R.G., Burwell, R.D., 2000. Contributions of postrhinal and perirhinal cortex to contextual information processing. Behav. Neurosci. 114 (5), 882–894. https://doi.org/10.1037//0735-7044.114.5.882.

Bussey, T.J., Saksida, L.M., Murray, E.A., 2005. The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. Q. J. Exp. Psychol. B 58 (3-4), 269–282. https://doi.org/10.1080/02724990544000004.

Burwell, R.D., Bucci, D.J., Sanborn, M.R., Jutras, M.J., 2004. Perirhinal and postrhinal contributions to remote memory for context. J. Neurosci. 24 (49), 11023–11028. https://doi.org/10.1523/jneurosci.3781-04.2004.

Chang, S.H., Yu, Y.H., He, A., Ou, C.Y., Shyu, B.C., Huang, A.C.W., 2021. BDNF Protein and BDNF mRNA Expression of the Medial Prefrontal Cortex, Amygdala, and Hippocampus during Situational Reminder in the PTSD Animal Model. Behav. Neurol. 2021, 6657716. https://doi.org/10.1155/2021/6657716.

Chen, C.C., Huang, C.C., Hsu, K.S., 2015. Chronic Social Stress Affects Synaptic Maturation of Newly Generated Neurons in the Adult Mouse Dentate Gyrus. Int J. Neuropsychopharmacol. 19 (3), pyv097. https://doi.org/10.1093/ijnp/pyv097.

Chen, L., Xu, R., Sun, F.J., Xue, Y., Hao, X.M., Liu, H.X., Wang, H., Chen, X.Y., Liu, Z.R., Deng, W.S., Han, X.H., Xie, J.X., Yung, W.H., 2015. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels regulate firing of globus pallidus neurons in vivo. Mol. Cell Neurosci. 68, 46–55. https://doi.org/10.1016/j.mcn.2015.04.001.

Chen, S., Wang, J., Siegelbaum, S.A., 2001. Properties of hyperpolarization-activated pacemaker current defined by coassembly of HCN1 and HCN2 subunits and basal modulation by cyclic nucleotide. J. Gen. Physiol. 117 (5), 491–504. https://doi.org/10.1085/jgp.117.5.491.

Chen, X., Shu, S., Bayliss, D.A., 2009. HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. J. Neurosci. 29 (3), 600–609. https://doi.org/10.1523/jneurosci.3481-08.2009.

Chowdhury, A., Luchetti, A., Fernandes, G., Filho, D.A., Kastellakis, G., Tzilivaki, A., Ramirez, E.M., Tran, M.Y., Poirazi, P., Silva, A.J., 2022. A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory linking. e3378 Neuron 110 (20), 3374–3388. https://doi.org/10.1016/j.neuron.2022.08.001.

Combe, C.L., Gasparini, S., 2021. I(h) from synapses to networks: HCN channel functions and modulation in neurons. Prog. Biophys. Mol. Biol. 166, 119–132. https://doi.org/10.1016/j.pbiomolbio.2021.06.002.

Cowgill, J., Klenchin, V.A., Alvarez-Baron, C., Tewari, D., Blair, A., Chanda, B., 2019. Bipolar switching by HCN voltage sensor underlies hyperpolarization activation. Proc. Natl. Acad. Sci. USA 116 (2), 670–678. https://doi.org/10.1073/pnas.1816724116.

Czéh, B., Fuchs, E., Wiborg, O., Simon, M., 2016. Animal models of major depression and their clinical implications. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 293–310. https://doi.org/10.1016/j.pnpbp.2015.04.004.

DeBerg, H.A., Bankston, J.R., Rosenbaum, J.C., Brzovic, P.S., Zagotta, W.N., Stoll, S., 2015. Structural mechanism for the regulation of HCN ion channels by the accessory protein TRIP8b. Structure 23 (4), 734–744. https://doi.org/10.1016/j.str.2015.02.007.

Deshmukh, S.S., Johnson, J.L., Knierim, J.J., 2012. Perirhinal cortex represents nonspatial, but not spatial, information in rats foraging in the presence of objects: comparison with lateral entorhinal cortex. Hippocampus 22 (10), 2045–2058. https://doi.org/10.1002/hipo.22046.

Dougherty, K.A., Nicholson, D.A., Diaz, L., Buss, E.W., Neuman, K.M., Chetkovich, D.M., Johnston, D., 2013. Differential expression of HCN subunits alters voltage-dependent gating of h-channels in CA1 pyramidal neurons from dorsal and ventral hippocampus. J. Neurophysiol. 109 (7), 1940–1953. https://doi.org/10.1152/jn.00010.2013.

Eacott, M.J., Machin, P.E., Gaffan, E.A., 2001. Elemental and configural visual discrimination learning following lesions to perirhinal cortex in the rat. Behav. Brain Res 124 (1), 55–70. https://doi.org/10.1016/s0166-4328(01)00234-0.

Ennaceur, A., Neave, N., Aggleton, J.P., 1996. Neurotoxic lesions of the perirhinal cortex do not mimic the behavioural effects of fornix transection in the rat. Behav. Brain Res 80 (1-2), 9–25. https://doi.org/10.1016/0166-4328(96)00006-x.

Fanselow, M.S., Dong, H.W., 2010. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65 (1), 7–19. https://doi.org/10.1016/j.neuron.2009.11.031.

Feder, A., Rutter, S.B., Schiller, D., Charney, D.S., 2020. The emergence of ketamine as a novel treatment for posttraumatic stress disorder. Adv. Pharm. 89, 261–286. https://doi.org/10.1016/bs.apha.2020.05.004.

Foote, K.M., Lyman, K.A., Han, Y., Michailidis, I.E., Heuermann, R.J., Mandikian, D., Trimmer, J.S., Swanson, G.T., Chetkovich, D.M., 2019. Phosphorylation of the HCN channel auxiliary subunit TRIP8b is altered in an animal model of temporal lobe epilepsy and modulates channel function. J. Biol. Chem. 294 (43), 15743–15758. https://doi.org/10.1074/jbc.RA119.010027.

Fujita, S., Toyoda, I., Thamattoor, A.K., Buckmaster, P.S., 2014. Preictal activity of subicular, CA1, and dentate gyrus principal neurons in the dorsal hippocampus before spontaneous seizures in a rat model of temporal lobe epilepsy. J. Neurosci. 34 (50), 16671–16687. https://doi.org/10.1523/jneurosci.0584-14.2014.

Gasparini, S., DiFrancesco, D., 1997. Action of the hyperpolarization-activated current (Ih) blocker ZD 7288 in hippocampal CA1 neurons. Pflug. Arch. 435 (1), 99–106. https://doi.org/10.1007/s004240050488.

Geiller, T., Royer, S., Choi, J.S., 2017. Segregated Cell Populations Enable Distinct Parallel Encoding within the Radial Axis of the CA1 Pyramidal Layer. Exp. Neurobiol. 26 (1), 1–10. https://doi.org/10.5607/en.2017.26.1.1.

Grienberger, C., Magee, J.C., 2022. Entorhinal cortex directs learning-related changes in CA1 representations. Nature 611 (7936), 554–562. https://doi.org/10.1038/s41586-022-05378-6.

Grubert, C., Hurlemann, R., Bewernick, B.H., Kayser, S., Hadrysiewicz, B., Axmacher, N., Sturm, V., Schlaepfer, T.E., 2011. Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. World J. Biol. Psychiatry 12 (7), 516–527. https://doi.org/10.3109/15622975.2011.583940.

Han, Y., Heuermann, R.J., Lyman, K.A., Fisher, D., Ismail, Q.A., Chetkovich, D.M., 2017. HCN-channel dendritic targeting requires bipartite interaction with TRIP8b and regulates antidepressant-like behavioral effects. Mol. Psychiatry 22 (3), 458–465. https://doi.org/10.1038/mp.2016.99.

Han, Y., Noam, Y., Lewis, A.S., Gallagher, J.J., Wadman, W.J., Baram, T.Z., Chetkovich, D.M., 2011. Trafficking and gating of hyperpolarization-activated cyclic nucleotide-gated channels are regulated by interaction with tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b) and cyclic AMP at distinct sites. J. Biol. Chem. 286 (23), 20823–20834. https://doi.org/10.1074/jbc.M111.236125.

Hargreaves, E.L., Rao, G., Lee, I., Knierim, J.J., 2005. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. Science 308 (5729), 1792–1794. https://doi.org/10.1126/science.1110449.

He, C., Chen, F., Li, B., Hu, Z., 2014. Neurophysiology of HCN channels: from cellular functions to multiple regulations. Prog. Neurobiol. 112, 1–23. https://doi.org/10.1016/j.pneurobio.2013.10.001.

Igarashi, K.M., Lu, L., Colgin, L.L., Moser, M.B., Moser, E.I., 2014. Coordination of entorhinal-hippocampal ensemble activity during associative learning. Nature 510 (7503), 143–147. https://doi.org/10.1038/nature13162.

Kase, D., Imoto, K., 2012. The Role of HCN Channels on Membrane Excitability in the Nervous System. J. Signal Transduct. 2012, 619747. https://doi.org/10.1155/2012/619747.

Kaufman, A.M., Geiller, T., Losonczy, A., 2020. A Role for the Locus Coeruleus in Hippocampal CA1 Place Cell Reorganization during Spatial Reward Learning. e1014 Neuron 105 (6), 1018–1026. https://doi.org/10.1016/j.neuron.2019.12.029.

Kempadoo, K.A., Mosharov, E.V., Choi, S.J., Sulzer, D., Kandel, E.R., 2016. Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. Proc. Natl. Acad. Sci. USA 113 (51), 14835–14840. https://doi.org/10.1073/pnas.1616515114.

Kim, C.S., Brager, D.H., Johnston, D., 2018. Perisomatic changes in h-channels regulate depressive behaviors following chronic unpredictable stress. Mol. Psychiatry 23 (4), 892–903. https://doi.org/10.1038/mp.2017.28.

Kim, C.S., Johnston, D., 2018. A Possible Link Between HCN Channels and Depression. Chronic Stress (Thousand Oaks) 2. https://doi.org/10.1177/2470547018787781.

Kim, C.S., Johnston, D., 2020. Antidepressant Effects of (S)-Ketamine through a Reduction of Hyperpolarization-Activated Current I(h). iScience 23 (6), 101239. https://doi.org/10.1016/j.isci.2020.101239.

Kim, J., Lei, Y., Lu, X.Y., Kim, C.S., 2022. Glucocorticoid-glucocorticoid receptor-HCN1 channels reduce neuronal excitability in dorsal hippocampal CA1 neurons. Mol. Psychiatry 27 (10), 4035–4049. https://doi.org/10.1038/s41380-022-01682-9.

Kisely, S., Li, A., Warren, N., Siskind, D., 2018. A systematic review and meta-analysis of deep brain stimulation for depression. Depress Anxiety 35 (5), 468–480. https://doi.org/10.1002/da.22746.

Kozlovsky, N., Matar, M.A., Kaplan, Z., Kotler, M., Zohar, J., Cohen, H., 2007. Long-term down-regulation of BDNF mRNA in rat hippocampal CA1 subregion correlates with PTSD-like behavioural stress response. Int J. Neuropsychopharmacol. 10 (6), 741–758. https://doi.org/10.1017/s1461145707007560.

Lee, J.H., Kim, W.B., Park, E.H., Cho, J.H., 2023. Neocortical synaptic engrams for remote contextual memories. Nat. Neurosci. 26 (2), 259–273. https://doi.org/10.1038/s41593-022-01223-1.

Lewis, A.S., Schwartz, E., Chan, C.S., Noam, Y., Shin, M., Wadman, W.J., Surmeier, D.J., Baram, T.Z., Macdonald, R.L., Chetkovich, D.M., 2009. Alternatively spliced isoforms of TRIP8b differentially control h channel trafficking and function. J. Neurosci. 29 (19), 6250–6265. https://doi.org/10.1523/jneurosci.0856-09.2009.

Li, X., Li, Y., Zhang, J., Zhang, X., 2019. Selective Targeting of Perirhinal Cortex Projection to Hippocampal CA1 Interneurons. Neurosci. Bull. 35 (4), 763–765. https://doi.org/10.1007/s12264-019-00363-y.

Li, Y., Xu, J., Liu, Y., Zhu, J., Liu, N., Zeng, W., Huang, N., Rasch, M.J., Jiang, H., Gu, X., Li, X., Luo, M., Li, C., Teng, J., Chen, J., Zeng, S., Lin, L., Zhang, X., 2017. A distinct entorhinal cortex to hippocampal CA1 direct circuit for olfactory associative learning. Nat. Neurosci. 20 (4), 559–570. https://doi.org/10.1038/nn.4517.

Lin, W., Qin, J., Ni, G., Li, Y., Xie, H., Yu, J., Li, H., Sui, L., Guo, Q., Fang, Z., Zhou, L., 2020. Downregulation of hyperpolarization-activated cyclic nucleotide-gated channels (HCN) in the hippocampus of patients with medial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS). Hippocampus 30 (10), 1112–1126. https://doi.org/10.1002/hipo.23219.

Lozano, A.M., Lipsman, N., Bergman, H., Brown, P., Chabardes, S., Chang, J.W., Matthews, K., McIntyre, C.C., Schlaepfer, T.E., Schulder, M., Temel, Y., Volkmann, J., Krauss, J.K., 2019. Deep brain stimulation: current challenges and future directions. Nat. Rev. Neurol. 15 (3), 148–160. https://doi.org/10.1038/s41582-018-0128-2.

Luchetti, A., Bota, A., Weitemier, A., Mizuta, K., Sato, M., Islam, T., McHugh, T.J., Tashiro, A., Hayashi, Y., 2020. Two Functionally Distinct Serotonergic Projections into Hippocampus. J. Neurosci. 40 (25), 4936–4944. https://doi.org/10.1523/jneurosci.2724-19.2020.

Lyman, K.A., Han, Y., Zhou, C., Renteria, I., Besing, G.L., Kurz, J.E., Chetkovich, D.M., 2021. Hippocampal cAMP regulates HCN channel function on two time scales with differential effects on animal behavior. Sci. Transl. Med 13 (621), eabl4580. https://doi.org/10.1126/scitranslmed.abl4580.

Magee, J.C., 1998. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. J. Neurosci. 18 (19), 7613–7624. https://doi.org/10.1523/jneurosci.18-19-07613.1998.

Magee, J.C., 1999. Dendritic Ih normalizes temporal summation in hippocampal CA1 neurons. Nat. Neurosci. 2 (9), 848. https://doi.org/10.1038/12229.

Malik, R., Li, Y., Schamiloglu, S., Sohal, V.S., 2022. Top-down control of hippocampal signal-to-noise by prefrontal long-range inhibition. e1617 Cell 185 (9), 1602–1617. https://doi.org/10.1016/j.cell.2022.04.001.

Marcelin, B., Lugo, J.N., Brewster, A.L., Liu, Z., Lewis, A.S., McClelland, S., Chetkovich, D.M., Baram, T.Z., Anderson, A.E., Becker, A., Esclapez, M., Bernard, C., 2012. Differential dorso-ventral distributions of Kv4.2 and HCN proteins confer distinct integrative properties to hippocampal CA1 pyramidal cell distal dendrites. J. Biol. Chem. 287 (21), 17656–17661. https://doi.org/10.1074/jbc.C112.367110.

Marson, A.G., Al-Kharusi, A.M., Alwaidh, M., Appleton, R., Baker, G.A., Chadwick, D.W., Cramp, C., Cockerell, O.C., Cooper, P.N., Doughty, J., Eaton, B., Gamble, C., Goulding, P.J., Howell, S.J., Hughes, A., Jackson, M., Jacoby, A., Kellett, M., Lawson, G.R., Williamson, P.R., 2007. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 369 (9566), 1000–1015. https://doi.org/10.1016/s0140-6736(07)60460-7.

McClelland, S., Brennan, G.P., Dubé, C., Rajpara, S., Iyer, S., Richichi, C., Bernard, C., Baram, T.Z., 2014. The transcription factor NRSF contributes to epileptogenesis by selective repression of a subset of target genes. Elife 3, e01267. https://doi.org/10.7554/eLife.01267.

McClelland, S., Flynn, C., Dubé, C., Richichi, C., Zha, Q., Ghestem, A., Esclapez, M., Bernard, C., Baram, T.Z., 2011. Neuron-restrictive silencer factor-mediated hyperpolarization-activated cyclic nucleotide gated channelopathy in experimental temporal lobe epilepsy. Ann. Neurol. 70 (3), 454–464. https://doi.org/10.1002/ana.22479.

McKenna, J.T., Vertes, R.P., 2001. Collateral projections from the median raphe nucleus to the medial septum and hippocampus. Brain Res Bull. 54 (6), 619–630. https://doi.org/10.1016/s0361-9230(01)00465-8.

Mello-Carpes, P.B., Izquierdo, I., 2013. The Nucleus of the Solitary Tract → Nucleus Paragigantocellularis → Locus Coeruleus → CA1 region of dorsal hippocampus pathway is important for consolidation of object recognition memory. Neurobiol. Learn Mem. 100, 56–63. https://doi.org/10.1016/j.nlm.2012.12.002.

Merseburg, A., Kasemir, J., Buss, E.W., Leroy, F., Bock, T., Porro, A., Barnett, A., Tröder, S.E., Engeland, B., Stockebrand, M., Moroni, A., Siegelbaum, S.A., Isbrandt, D., Santoro, B., 2022. Seizures, behavioral deficits, and adverse drug responses in two new genetic mouse models of HCN1 epileptic encephalopathy. Elife 11. https://doi.org/10.7554/eLife.70826.

Mishra, P., Narayanan, R., 2025. The enigmatic HCN channels: A cellular neurophysiology perspective. Proteins 93 (1), 72–92. https://doi.org/10.1002/prot.26643.

Mumby, D.G., Pinel, J.P., 1994. Rhinal cortex lesions and object recognition in rats. Behav. Neurosci. 108 (1), 11–18. https://doi.org/10.1037//0735-7044.108.1.11.

Murray, E.A., Bussey, T.J., Saksida, L.M., 2007. Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. Annu Rev. Neurosci. 30, 99–122. https://doi.org/10.1146/annurev.neuro.29.051605.113046.

Navarrete-Modesto, V., Orozco-Suárez, S., Alonso-Vanegas, M., Feria-Romero, I.A., Rocha, L., 2019. REST/NRSF transcription factor is overexpressed in hippocampus of patients with drug-resistant mesial temporal lobe epilepsy. Epilepsy Behav. 94, 118–123. https://doi.org/10.1016/j.yebeh.2019.02.012.

Ni, L., Xu, Y., Dong, S., Kong, Y., Wang, H., Lu, G., Wang, Y., Li, Q., Li, C., Du, Z., Sun, H., Sun, L., 2020. The potential role of the HCN1 ion channel and BDNF-mTOR signaling pathways and synaptic transmission in the alleviation of PTSD. Transl. Psychiatry 10 (1), 101. https://doi.org/10.1038/s41398-020-0782-1.

Norman, G., Eacott, M.J., 2004. Impaired object recognition with increasing levels of feature ambiguity in rats with perirhinal cortex lesions. Behav. Brain Res 148 (1-2), 79–91. https://doi.org/10.1016/s0166-4328(03)00176-1.

Norman, G., Eacott, M.J., 2005. Dissociable effects of lesions to the perirhinal cortex and the postrhinal cortex on memory for context and objects in rats. Behav. Neurosci. 119 (2), 557–566. https://doi.org/10.1037/0735-7044.119.2.557.

Notomi, T., Shigemoto, R., 2004. Immunohistochemical localization of Ih channel subunits, HCN1-4, in the rat brain. J. Comp. Neurol. 471 (3), 241–276. https://doi.org/10.1002/cne.11039.

Poolos, N.P., Migliore, M., Johnston, D., 2002. Pharmacological upregulation of h-channels reduces the excitability of pyramidal neuron dendrites. Nat. Neurosci. 5 (8), 767–774. https://doi.org/10.1038/nn891.

Porro, A., Saponaro, A., Gasparri, F., Bauer, D., Gross, C., Pisoni, M., Abbandonato, G., Hamacher, K., Santoro, B., Thiel, G., Moroni, A., 2019. The HCN domain couples voltage gating and cAMP response in hyperpolarization-activated cyclic nucleotide-gated channels. Elife 8. https://doi.org/10.7554/eLife.49672.

Qiu, S., Hu, Y., Huang, Y., Gao, T., Wang, X., Wang, D., Ren, B., Shi, X., Chen, Y., Wang, X., Wang, D., Han, L., Liang, Y., Liu, D., Liu, Q., Deng, L., Chen, Z., Zhan, L., Chen, T., Xu, C., 2024. Whole-brain spatial organization of hippocampal single-neuron projectomes. Science 383 (6682), eadj9198. https://doi.org/10.1126/science.adj9198.

Santoro, B., Piskorowski, R.A., Pian, P., Hu, L., Liu, H., Siegelbaum, S.A., 2009. TRIP8b splice variants form a family of auxiliary subunits that regulate gating and trafficking of HCN channels in the brain. Neuron 62 (6), 802–813. https://doi.org/10.1016/j.neuron.2009.05.009.

Shi, C.J., Cassell, M.D., 1999. Perirhinal cortex projections to the amygdaloid complex and hippocampal formation in the rat. J. Comp. Neurol. 406 (3), 299–328. https://doi.org/10.1002/(sici)1096-9861(19990412)406:3< 299::aid-cne2> 3.0.co;2-9.

Sironi, V.A., 2011. Origin and evolution of deep brain stimulation. Front Integr. Neurosci. 5, 42. https://doi.org/10.3389/fnint.2011.00042.

Soma, S., Ohara, S., Nonomura, S., Suematsu, N., Yoshida, J., Pastalkova, E., Sakai, Y., Tsutsui, K.I., Isomura, Y., 2023. Rat hippocampal CA1 region represents learning-related action and reward events with shorter latency than the lateral entorhinal cortex. Commun. Biol. 6 (1), 584. https://doi.org/10.1038/s42003-023-04958-0.

Stepan, J., Dine, J., Eder, M., 2015. Functional optical probing of the hippocampal trisynaptic circuit in vitro: network dynamics, filter properties, and polysynaptic induction of CA1 LTP. Front Neurosci. 9, 160. https://doi.org/10.3389/fnins.2015.00160.

Surges, R., Freiman, T.M., Feuerstein, T.J., 2003. Gabapentin increases the hyperpolarization-activated cation current Ih in rat CA1 pyramidal cells. Epilepsia 44 (2), 150–156. https://doi.org/10.1046/j.1528-1157.2003.36802.x.

Tae, H.S., Smith, K.M., Phillips, A.M., Boyle, K.A., Li, M., Forster, I.C., Hatch, R.J., Richardson, R., Hughes, D.I., Graham, B.A., Petrou, S., Reid, C.A., 2017. Gabapentin Modulates HCN4 Channel Voltage-Dependence. Front Pharm. 8, 554. https://doi.org/10.3389/fphar.2017.00554.

Takács, V.T., Freund, T.F., Gulyás, A.I., 2008. Types and synaptic connections of hippocampal inhibitory neurons reciprocally connected with the medial septum. Eur. J. Neurosci. 28 (1), 148–164. https://doi.org/10.1111/j.1460-9568.2008.06319.x.

Takeuchi, T., Duszkiewicz, A.J., Sonneborn, A., Spooner, P.A., Yamasaki, M., Watanabe, M., Smith, C.C., Fernández, G., Deisseroth, K., Greene, R.W., Morris, R.G., 2016. Locus coeruleus and dopaminergic consolidation of everyday memory. Nature 537 (7620), 357–362. https://doi.org/10.1038/nature19325.

Tao, S., Wang, Y., Peng, J., Zhao, Y., He, X., Yu, X., Liu, Q., Jin, S., Xu, F., 2021. Whole-Brain Mapping the Direct Inputs of Dorsal and Ventral CA1 Projection Neurons. Front Neural Circuits 15, 643230. https://doi.org/10.3389/fncir.2021.643230.

Török, B., Sipos, E., Pivac, N., Zelena, D., 2019. Modelling posttraumatic stress disorders in animals. Prog. Neuropsychopharmacol. Biol. Psychiatry 90, 117–133. https://doi.org/10.1016/j.pnpbp.2018.11.013.

Trouche, S., Koren, V., Doig, N.M., Ellender, T.J., El-Gaby, M., Lopes-Dos-Santos, V., Reeve, H.M., Perestenko, P.V., Garas, F.N., Magill, P.J., Sharott, A., Dupret, D., 2019. A Hippocampus-Accumbens Tripartite Neuronal Motif Guides Appetitive Memory in Space. e1316 Cell 176 (6), 1393–1406. https://doi.org/10.1016/j.cell.2018.12.037.

Tsay, D., Dudman, J.T., Siegelbaum, S.A., 2007. HCN1 channels constrain synaptically evoked Ca2+ spikes in distal dendrites of CA1 pyramidal neurons. Neuron 56 (6), 1076–1089. https://doi.org/10.1016/j.neuron.2007.11.015.

Tsetsenis, T., Badyna, J.K., Wilson, J.A., Zhang, X., Krizman, E.N., Subramaniyan, M., Yang, K., Thomas, S.A., Dani, J.A., 2021. Midbrain dopaminergic innervation of the hippocampus is sufficient to modulate formation of aversive memories. Proc. Natl. Acad. Sci. USA 118 (40). https://doi.org/10.1073/pnas.2111069118.

Uchida, S., Hara, K., Kobayashi, A., Funato, H., Hobara, T., Otsuki, K., Yamagata, H., McEwen, B.S., Watanabe, Y., 2010. Early life stress enhances behavioral vulnerability to stress through the activation of REST4-mediated gene transcription in the medial prefrontal cortex of rodents. J. Neurosci. 30 (45), 15007–15018. https://doi.org/10.1523/jneurosci.1436-10.2010.

van der Veldt, S., Etter, G., Mosser, C.A., Manseau, F., Williams, S., 2021. Conjunctive spatial and self-motion codes are topographically organized in the GABAergic cells of the lateral septum. PLoS Biol. 19 (8), e3001383. https://doi.org/10.1371/journal.pbio.3001383.

Varga, V., Losonczy, A., Zemelman, B.V., Borhegyi, Z., Nyiri, G., Domonkos, A., Hangya, B., Holderith, N., Magee, J.C., Freund, T.F., 2009. Fast synaptic subcortical control of hippocampal circuits. Science 326 (5951), 449–453. https://doi.org/10.1126/science.1178307.

Verbitsky, A., Dopfel, D., Zhang, N., 2020. Rodent models of post-traumatic stress disorder: behavioral assessment. Transl. Psychiatry 10 (1), 132. https://doi.org/10.1038/s41398-020-0806-x.

Wan, H., Aggleton, J.P., Brown, M.W., 1999. Different contributions of the hippocampus and perirhinal cortex to recognition memory. J. Neurosci. 19 (3), 1142–1148. https://doi.org/10.1523/jneurosci.19-03-01142.1999.

Wang, X., Xu, Y., Zhang, S., Qu, Y., Wang, D., An, X., Zeng, L., Xu, W., Wu, Y., Chen, H., 2022. MicroRNA-195 rescues the impaired MS-dCA1 neural circuit and spatial memory in rats with chronic cerebral hypoperfusion. Adv. Neurol. 1, 116.

Whitaker, A.M., Gilpin, N.W., Edwards, S., 2014. Animal models of post-traumatic stress disorder and recent neurobiological insights. Behav. Pharm. 25 (5-6), 398–409. https://doi.org/10.1097/fbp.0000000000000069.

Xiao, W., Li, P., Kong, F., Kong, J., Pan, A., Long, L., Yan, X., Xiao, B., Gong, J., Wan, L., 2024. Unraveling the Neural Circuits: Techniques, Opportunities and Challenges in Epilepsy Research. Cell Mol. Neurobiol. 44 (1), 27. https://doi.org/10.1007/s10571-024-01458-5.

Yamamoto, J., Tonegawa, S., 2017. Direct Medial Entorhinal Cortex Input to Hippocampal CA1 Is Crucial for Extended Quiet Awake Replay. e214 Neuron 96 (1), 217–227. https://doi.org/10.1016/j.neuron.2017.09.017.

Yasam, V.R., Jakki, S.L., Senthil, V., Eswaramoorthy, M., Shanmuganathan, S., Arjunan, K., Nanjan, M.J., 2016. A pharmacological overview of lamotrigine for the treatment of epilepsy. Expert Rev. Clin. Pharm. 9 (12), 1533–1546. https://doi.org/10.1080/17512433.2016.1254041.

Zagotta, W.N., Olivier, N.B., Black, K.D., Young, E.C., Olson, R., Gouaux, E., 2003. Structural basis for modulation and agonist specificity of HCN pacemaker channels. Nature 425 (6954), 200–205. https://doi.org/10.1038/nature01922.

Zhang, J., Navarrete, M., Wu, Y., Zhou, Y., 2022. 14-3-3 Dysfunction in Dorsal Hippocampus CA1 (dCA1) Induces Psychomotor Behavior via a dCA1-Lateral Septum-Ventral Tegmental Area Pathway. Front Mol. Neurosci. 15, 817227. https://doi.org/10.3389/fnmol.2022.817227.

Zhang, X., Zhao, Y., Du, Y., Sun, H., Zhang, W., Wang, A., Li, Q., Li, C., Wang, Y., Du, Z., Sun, H., Sun, L., 2021. Effect of ketamine on mood dysfunction and spatial cognition deficits in PTSD mouse models via HCN1-BDNF signaling. J. Affect Disord. 286, 248–258. https://doi.org/10.1016/j.jad.2021.02.058.

Zhou, H., Zhu, J., Jia, J., Xiang, W., Peng, H., Zhang, Y., Liu, B., Mu, Y., Lu, Y., 2022. The antidepressant effect of nucleus accumbens deep brain stimulation is mediated by parvalbumin-positive interneurons in the dorsal dentate gyrus. Neurobiol. Stress 21, 100492. https://doi.org/10.1016/j.ynstr.2022.100492.