Author/s:
Bleakley, LE;Keenan, RJ;Graven, RD;Metha, JA;Ma, S;Daykin, H;Cornthwaite-Duncan, L;Hoyer, D;Reid, CA;Jacobson, LH

Title:
Altered EEG power spectrum, but not sleep-wake architecture, in HCN1 knockout mice

Date:
2023-02-02

Citation:
Bleakley, L. E., Keenan, R. J., Graven, R. D., Metha, J. A., Ma, S., Daykin, H., Cornthwaite-Duncan, L., Hoyer, D., Reid, C. A. & Jacobson, L. H. (2023). Altered EEG power spectrum, but not sleep-wake architecture, in HCN1 knockout mice. Behavioural Brain Research, 437, https://doi.org/10.1016/j.bbr.2022.114105.

Abstract:

Sleep is a complex biological state characterized by large populations of neurons firing in a rhythmic or synchronized manner. HCN channels play a critical role in generating and sustaining synchronized neuronal firing and are involved in the actions of anaesthetics. However, the role of these channels in sleep-wakefulness *per se* has yet to be studied. We conducted polysomnographic recordings of *Hcn1* constitutive knockout (*Hcn1* KO) and wild-type (WT) mice in order to investigate the potential role of HCN1 channels in sleep/wake regulation. EEG and EMG data were analysed using the Somnivore™ machine learning algorithm. Time spent in each vigilance state, bout number and duration, and EEG power spectral activity were compared between genotypes. There were no significant differences in the time spent in wake, rapid eye movement (REM) or non-REM (NREM) sleep between *Hcn1* KO and WT mice. Wake bout duration during the inactive phase was significantly shorter in *Hcn1* KO mice whilst no other bout parameters were affected by genotype. *Hcn1* KO mice showed a reduction in overall EEG power which was particularly prominent in the theta (5-9 Hz) and alpha (9-15 Hz) frequency bands and most evident during NREM sleep. Together these data suggest that HCN1 channels do not play a major role in sleep architecture or modulation of vigilance states. However, loss of these channels significantly alters underlying neuronal activity within these states which may have functional consequences.

Key words: HCN1, sleep, wakefulness, EEG power spectrum

Abbreviations: EEG (electroencephalography); EMG (electromyography); HCN channels (hyperpolarization-activated cyclic nucleotide-gated channels); KO (knockout); NREM (non-rapid eye movement); PPI (prepulse inhibition); REM (rapid eye movement); SEM (standard error of the mean); WT (wild-type).

Sleep is a complex biological state characterized neuronally by large populations of cells firing in a rhythmic or synchronized manner [1, 2]. Assessment of the differences in dominant rhythmic firing frequencies (typically measured using electroencephalography (EEG)), combined with measures of muscle tone (by electromyography (EMG)) are primary components of polysomnography, an analysis which informs on an individual's vigilance states and sleep architecture. Non-Rapid Eye Movement (NREM) sleep is characterized by an EEG dominated by high-amplitude, low-frequency delta oscillations at frequencies of 0.5-4 Hz; Rapid Eye Movement (REM) sleep EEG has greater activity in the faster theta band (5-9 Hz), accompanied by complete postural muscle atonia; while wake is a heterogeneous state where both dominant EEG oscillations and muscle activity vary [3]. Despite its essential function, the molecular and cellular mechanisms underlying sleep are yet to be fully elucidated.

Hyperpolarization-activated Cyclic Nucleotide-gated channels (HCN channels) are non-selective cation channels that are widely expressed throughout the brain [4], pass K+ ions with greater efficiency than Na+ ions [5], and play critical roles in synchronous neuronal firing [5]. These channels pass an inward cationic current, I_h, that is activated by membrane hyperpolarization and is stopped by channel closure upon depolarization, conferring an intrinsic negative feedback mechanism that acts to return a cell towards its resting membrane potential. These unique properties enable groups of neurons to depolarize and repolarize synchronously [5].

Numerous previous studies have linked neuronal HCN channels to the generation of whole-brain rhythms, including those observed during sleep. In particular, HCN2 channels are highly expressed in thalamocortical and reticular thalamic neurons [4, 6], brain regions which play essential roles in the genesis of slow rhythmicity seen in deeper sleep stages (reviewed in [7] and see [8]). Computational modelling has also suggested that I_h is critical for generating the spontaneous bursting in thalamocortical neurons which underpins the synchronised slow-wave activity seen in the thalamocortical network during sleep [9]. The HCN1 channel subtype has also been shown to play unique and key roles in neuronal oscillatory activity. In particular, due to their rapid kinetics of activation, HCN1 channels play a key role in resonance: the ability of some neurons to respond preferentially to inputs at specific frequencies, which is critical to the propagation of synchronized neuronal firing under some circumstances [10]. Furthermore, several sedative and anaesthetic drugs, which induce rhythmic neuronal activity [11] and lead to states of reduced or lost consciousness that share similarities with sleep [12], act at HCN1 channels as part of their mechanism of action [13-15]. The importance of HCN1 channels in rhythmicity is also evidenced by the link between HCN1 channel dysfunction and epilepsy, with *Hcn1* constitutive knockout (*Hcn1* KO) mice showing increased proconvulsant susceptibility and enhanced epileptogenesis [16], whilst a number of pathogenic variants in *HCN1* have been identified in human patients with epilepsy [17, 18].

However, despite the key roles of HCN1 channels in neuronal rhythmicity and the presence of disordered rhythmicity such as epileptiform neuronal activity when these channels are dysfunctional, surprisingly the role of HCN1 channels in sleep is yet to be closely investigated. In this study, we conducted polysomnographic (EEG/EMG) recordings on *Hcn1* KO mice in order to investigate whether *HCN1* plays a role in vigilance state and sleep-wake architecture.

Hcn1 KO mice were acquired from the Jackson Laboratory (stock #016566, [19]) and maintained on a pure inbred 129SVEV genetic background. Wild-type (WT) 129SVEV mice were maintained the same way in a separate colony. This breeding strategy was applied in accordance with the Jackson Laboratory's advice to minimise genetic drift, including refreshment of breeders every 5-8 generations. Animals were single- or group-housed in standard, transparent open-top cages (29.5 x 16 x 13 cm) with sawdust and tissue paper nesting material. Standard rodent food and water were available ad libitum. Mice were initially housed on a 12 h light/dark cycle (lights on at 0700 h) before being moved into a new housing area with their respective experimental light cycle (lights on at 2130 h) ten days before EEG/EMG surgery. N = 8 *Hcn1* KO (2.3 months ± 0.3) and N = 8 WT (3.3 months ± 0.6) mice formed the experimental cohort. Ages reported as means ± standard deviation. All animals were male.

All experimentation was performed in accordance with the Prevention of Cruelty to Animals Act (2004), under the guidelines of the National Health and Medical Research Council Code of Practice for the Care and Use of Animals for Experimental Purposes in Australia (2013). Experiments were approved by the Animal Ethics Committee at the Florey Institute of Neuroscience and Mental Health prior to commencement. Mice were monitored in accordance with protocols approved by this committee. All experiments comply with the ARRIVE guidelines.

EEG/EMG preformed head mounts (Catalogue number: #8201-SS, Pinnacle Technology Inc.) were surgically implanted as previously described (see [20], supplementary material Fig. S1, Table S1). Following surgery and recovery, mice were individually housed in transparent, cylindrical sleep recording chambers (29 cm diameter x 30 cm height) for one week of acclimatisation prior to the commencement of recordings.

The experimental protocol involved three consecutive 23 h polysomnographic recordings commencing at the start of the active phase (Zeitgeber time 12 (ZT12)). Head mounts were plugged into the pre-amplifier 24 h before recordings began. Three 23 h recordings were then performed over three consecutive days using Sirenia Acquisition software (version 1.8.0, Pinnacle Technology Inc.) for EEG/EMG acquisition. Three channels were recorded: EEG1, EEG2 and EMG. The sampling rate was 200 Hz. 100 Hz EEG and EMG low pass filters were applied. Recordings began at 0930 h (ZT12) and finished at 0830 h (ZT11). Following EEG/EMG recordings all mice were returned to their original cages.

Sirenia recording files were imported into Somnivore™ [21] in 4 s epochs for vigilance state and sleep/wake architecture analyses. Each recording was scored by first training the Somnivore machine learning algorithm with 101 epochs of wake, NREM and REM. The entire hypnogram was then populated using Somnivore's auto-score function (see Fig. S2 for examples). Contextual scoring rules included a minimum bout length setting of 8 s (two contiguous epochs) for both wake and NREM, and 12 s (three contiguous epochs) for REM. A further 50 epochs of each state were then trained, and the auto-score function was run again. The entire recording was then manually checked and corrected as required. All sleep scoring was performed by an experienced researcher blinded to genotype. Vigilance state-specific (wake, NREM or REM) and overall normalized power spectral data were obtained using Somnivore's built in power spectral analysis capabilities [21] (Fig. S2). For power spectral analysis, all transition epochs were excluded and signals from both EEG1 and EEG2 electrodes were averaged. Frequencies in the 0-50 Hz range were selected for statistical analysis.

Statistical analyses were performed using GraphPad Prism (version 9.0.2). Time spent in each vigilance state across the 23 h recording and normalized EEG power were analysed by a two-way repeated measures ANOVA with Sidak's multiple comparisons test. Bout number and duration were analysed using 2-tailed *t*-tests. Normalized EEG power was expressed as a percentage of the WT group mean. For all analyses, $P < 0.05$ was considered to be statistically significant.

The sleep/wake profiles of *Hcn1* KO and WT mice were not significantly different regarding the average time spent in the wake (Genotype: $F_{(1, 14)} = 0.1094$, $P = 0.746$; time: $F_{(22, 308)} = 28.42$, $P < 0.001$; interaction: $F_{(22, 308)} = 1.024$, $P = 0.433$, Fig. 1A), NREM (Genotype: $F_{(1, 14)} = 0.3988$, $P = 0.538$; time: $F_{(22, 308)} = 21.65$, $P < 0.001$; interaction: $F_{(22, 308)} = 0.9977$, $P = 0.467$, Fig. 1B) or REM (Genotype: $F_{(1, 14)} = 2.953$, $P = 0.108$; time: $F_{(22, 308)} = 26.74$, $P < 0.001$; interaction: $F_{(22, 308)} = 1.401$, $P = 0.111$, Fig. 1C) vigilance states. Wake bout duration in the inactive phase was significantly shorter in *Hcn1* KO mice ($t = 2.52$, $df = 14$, $P < 0.05$, Fig. 2H) whilst no other bout parameters were significantly affected by genotype ($P > 0.05$, Fig. 2). These data demonstrate that *Hcn1* KO mice did not display a major sleep/wake architecture phenotype.

Hcn1 KO mice showed a reduction in overall EEG power (Genotype: $F_{(1, 14)} = 18.03$, $P = 0.001$; frequency: $F_{(3.704, 51.85)} = 2664$, $P < 0.001$; interaction: $F_{(49, 686)} = 26.78$, $P < 0.001$, Fig. 3A, B) which was particularly prominent in the theta (5-9 Hz) and alpha (9-15 Hz) frequency bands. EEG power was significantly reduced in *Hcn1* KO mice compared with WT for all frequencies between 3 and 20 Hz (Fig. 3A, B).

To further investigate EEG power differences, vigilance state-specific EEG power spectral analysis was performed. *Hcn1* KO mice displayed a general reduction in EEG power during NREM sleep (Genotype: $F_{(1, 14)} = 12.70$, $P = 0.003$; frequency: $F_{(2.721, 38.09)} = 2202$, $P < 0.001$; interaction: $F_{(49, 686)} = 24.69$, $P <$

0.001, Fig. 3C, D) which was particularly prominent in the theta (5-9 Hz) and alpha (9-15 Hz) frequency bands.

During REM sleep, *Hcn1* KO mice exhibited a leftward shift in the peak theta frequencies characteristic of REM sleep (Genotype: $F_{(1, 14)} = 1.952$, $P = 0.184$; frequency: $F_{(2.624, 36.73)} = 803.5$, $P < 0.001$; interaction: $F_{(49, 686)} = 9.331$, $P < 0.001$, Fig. 3E, F). EEG power was increased at 6 Hz but decreased at 8 Hz and 9 Hz in *Hcn1* KO mice compared with WT (Fig. 3E, F).

Hcn1 KO mice also showed a more subtle reduction in EEG power during wakefulness (Genotype: $F_{(1, 14)} = 2.973$, $P = 0.107$; frequency: $F_{(3.226, 45.17)} = 832.9$, $P < 0.001$; interaction: $F_{(49, 686)} = 6.766$, $P < 0.001$, Fig. 3G, H) which was again more evident during the theta (5-9 Hz) and alpha (9-15 Hz) frequency bands.

Here we demonstrate that HCN1 channels do not play a major role in sleep architecture, with no significant differences observed between *Hcn1* KO and WT male mice when considering time spent in different vigilance states and minimal effects on bout structure. This is an unexpected but important finding when considering the critical role of HCN1 channels in synchronous neuronal network activity.

Computational modelling suggests that an I_h conductance of sufficient amplitude is required to sustain the spontaneous delta activity in thalamocortical neurons which underpins synchronous slow-wave activity during sleep [9]. This conductance enhances with age and appears to correlate with significant increases in *HCN1* and *HCN2* expression in the dorsal lateral geniculate nucleus, although *HCN1* expression remains substantially lower than other HCN channel isoforms in this region [9]. Combined with our *in vivo* data, this suggests that while HCN channels as a class are important for the initial generation of slow-wave sleep, the HCN1 subtype may play only a minimal role. This does not, however, exclude the possibility of HCN1 channel involvement in other aspects of chronobiology. For example, factors such as the circadian rhythm, responses to anaesthetics and recovery sleep fall outside the scope of this study but may yet be altered by changes to *HCN1*-induced neuronal rhythmicity, and thus warrant further research.

Although we did not see any significant differences in sleep-wake architecture between *Hcn1* KO and WT mice, *Hcn1* KO significantly altered underlying neuronal activity, as demonstrated by alterations in EEG power in all vigilance states, as well as more subtle changes in some states at specific frequencies (Fig. 3). Such data support a role for *HCN1* in underlying neuronal rhythmicity. However, compensatory changes may also occur in the brains of constitutive knockout mice. Indeed, altered I_h *via* HCN1 channel knockout causes compensatory upregulation of the $GABA_A$ receptor alpha-5 subunit in cortical pyramidal neurons [22] which is proposed to help maintain synaptic summation; as another example, mice harbouring a pathogenic *Hcn1* variant that significantly alters I_h kinetics and voltage dependence show significant changes in the cortical expression of the sodium channel genes *Scn2a* and

Scn8a [23]. Of note, whether the expression of other HCN channel subtypes is altered in *Hcn1* knockout mice has not yet been reported.

Our theta power findings differ from Nolan et al., (2004) [24], who reported increased hippocampal theta activity in *Hcn1* KO mice during REM sleep and wheel running. By contrast, we report reduced theta power during wake, enhanced REM sleep theta at 5-6Hz and decreased REM sleep activity at 8Hz and upward (Fig. 3E, F), and REM sleep theta power peak shift from 7 to 6Hz (Fig. 3E) in *Hcn1* KO mice compared to WT. Theta peak shifts are not identifiable in [24], but the overall increased theta power reported in their study differs from ours. The two studies have different recording sites (hippocampus *vs.* cortical surface), however theta and higher frequency power in cortical field potentials likely reflects hippocampal volume conduction, thus this alone is unlikely to explain the different findings. The studies also differ in background mouse strain (129SVEV:C57Bl/6J in [24] *vs.* 129SVEV here). The *Disc1* (disrupted in schizophrenia 1) gene is deleted in 129S strains [25], which reduces hippocampal theta power and, in 129S mice, alters CA1 spike timing fidelity [26], suggesting a possible strain contribution to *Hcn1* KO theta power findings.

The changes observed in EEG spectral activity could be predicted to have functional consequences. For example, reduced alpha and beta power may suggest disruption in functions such as perceptual decision processes, attention, and motor execution [27-29]. However, *Hcn1* forebrain-specific KO mice did not differ from control animals in a prepulse inhibition (PPI) task [24]. Given the deficit in alpha power in *Hcn1* KO mice, it would be of interest to determine the concurrence of evoked alpha oscillations with PPI in these animals, as is seen in humans [30]. As a further example, reduced hippocampal theta power is known to have negative effects on hippocampal learning and memory [31, 32]. *Hcn1* KO mice had impaired learning and memory of fast, coordinated motor movements, believed to be a cerebellar phenotype, however, no deficits in spatial localisation and memory were detected [19]. In contrast, forebrain-specific *Hcn1* KO mice showed enhanced hippocampal-dependent learning and memory, thought to be due to enhanced long-term potentiation [24]; but also displayed impaired performance on a delayed non-match to place task, which interrogates working memory and interference resolution [33]. These findings highlight the complex and subtle roles of HCN1 channels in different types of learning and memory. Our data suggest that these changes to learning and memory are likely independent of sleep duration-dependent encoding.

Our data also provides further insight into the role of HCN1 channels in the altered levels of consciousness induced by sedation and general anaesthesia. The fact that *Hcn1* KO had no significant effect on time spent in different vigilance states initially suggests that the mechanism through which HCN1 channel block mediates sedation and anaesthesia does not involve the alteration of vigilance states, and thus is separate from sleep. This is perhaps not unexpected considering that, although HCN channels are relevant in both contexts, anaesthetic-induced loss of consciousness is a distinct state from

native sleep (described in detail in [11]). It is important to note, however, that temporary inhibition of HCN1 channel activity due to drug administration is different from constitutive HCN1 channel knockout throughout development, and could result in very different neuronal and network function. As such, it remains plausible that drug-induced HCN1 channel block may indeed alter vigilance states, though further research is required to clarify this point.

In summary, we have demonstrated that HCN1 channels do not play a major role in sleep-wake architecture in male mice. Further studies are required to determine if this is also the case in female mice. Our data thus suggest that the role of HCN1 channel block in sedation and anaesthesia is distinct from the modulation of vigilance states. Finally, *Hcn1* KO did cause significant changes to underlying EEG activity, providing hints to its possible roles in brain functions such as perception, learning and memory.

Funding sources

DH and LHJ are supported by the Australian Government NHMRC (1105284, 2003370). LEB acknowledges the support of an Australian Government Research Training Program Scholarship.

Declarations of interest

No authors report disclosures relevant to the manuscript.

Figure Captions

Figure 1. Sleep/wake profile of *Hcn1* KO mice.

A-C*,** Minutes spent in wake (A***), NREM (***B***) and REM (***C***) vigilance states per hour across a 23 h recording in *Hcn1* KO and WT mice. Dark shade represents the active phase. Data are means ± SEM. n = 8 per group.

Figure 2. Number and duration of sleep-wake vigilance state bouts in *Hcn1* KO mice.

A-L, Mean number (***A-F***) and duration (***G-L***) of bouts of wake (***A, B, G, H***), NREM (***C, D, I, J***) and REM sleep (***E, F, K, L***) during the active (12 hours of recording) and inactive (11 hours of recording) phases in WT and *Hcn1* KO mice. Data are means ± SEM. n = 8 per group, *P < 0.05 by Student's t-test.

Figure 3. Altered EEG power in *Hcn1* KO mice.

A-H*,** Overall normalized EEG power (A, B***) and vigilance state-specific normalized EEG power for NREM (***C, D***), REM (***E, F***) and wake (***G, H***) in *Hcn1* KO and WT mice. Data are expressed as a percentage of the WT group in ***B***, ***D***, ***F*** and ***H***. Data are means ± SEM. n = 8 per group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. WT, by repeated measures two-way ANOVA with Sidak's multiple comparisons test.

References

[1] A.M.L. Coenen, W.H.I.M. Drinkenburg, Animal models for information processing during sleep, Int J Psychophysiol 46(3) (2002) 163-175.
[2] M. Steriade, R.C. Dossi, A. Nuñez, Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: Cortically induced synchronization and brainstem cholinergic suppression, J Neurosci 11(10) (1991) 3200-3217.
[3] A. Eban-Rothschild, L. Appelbaum, L. de Lecea, Neuronal Mechanisms for Sleep/Wake Regulation and Modulatory Drive, Neuropsychopharmacology 43(5) (2018) 937-952.
[4] B. Santoro, S. Chen, A. Lüthi, P. Pavlidis, G.P. Shumyatsky, G.R. Tibbs, S.A. Siegelbaum, Molecular and functional heterogeneity of hyperpolarization-activated pacemaker channels in the mouse CNS, J Neurosci 20(14) (2000) 5264-5275.
[5] M. Biel, C. Wahl-Schott, S. Michalakis, X. Zong, Hyperpolarization-activated cation channels: from genes to function, Physiol Rev 89(3) (2009) 847-885.
[6] T. Notomi, R. Shigemoto, Immunohistochemical localization of Ih channel subunits, HCN1-4, in the rat brain, J Comp Neurol 471(3) (2004) 241-276.
[7] I. de Andrés, M. Garzón, F. Reinoso-Suárez, Functional Anatomy of Non-REM Sleep, Front Neurol 2 (2011) 70.
[8] D.S. Uygun, C. Yang, E.R. Tilli, F. Katsuki, E.L. Hodges, J.T. McKenna, . . . R. Basheer, Knockdown of GABAA alpha3 subunits on thalamic reticular neurons enhances deep sleep in mice, Nat Commun 13(1) (2022) 2246.
[9] T. Kanyshkova, M. Pawlowski, P. Meuth, C. Dube, R.A. Bender, A.L. Brewster, . . . T. Budde, Postnatal expression pattern of HCN channel isoforms in thalamic neurons: relationship to maturation of thalamocortical oscillations, J Neurosci 29(27) (2009) 8847-8857.
[10] B. Hutcheon, R.M. Miura, E. Puil, Subthreshold Membrane Resonance in Neocortical Neurons, J Neurophysiol 76(2) (1996) 683-697.
[11] E.N. Brown, R. Lydic, N.D. Schiff, General anesthesia, sleep, and coma, N Engl J Med 363(27) (2010) 2638-2650.
[12] U. Rudolph, B. Antkowiak, Molecular and neuronal substrates for general anaesthetics, Nat Rev Neurosci 5(9) (2004) 709-720.
[13] A.K. Lyashchenko, K.J. Redd, J. Yang, G.R. Tibbs, Propofol inhibits HCN1 pacemaker channels by selective association with the closed states of the membrane embedded channel core, J Physiol 583(Pt 1) (2007) 37-56.
[14] X. Chen, S. Shu, D.A. Bayliss, HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine, J Neurosci 29(3) (2009) 600-609.
[15] X. Chen, S. Shu, D.P. Kennedy, S.C. Willcox, D.A. Bayliss, Subunit-specific effects of isoflurane on neuronal Ih in HCN1 knockout mice, J Neurophysiol 101(1) (2009) 129-140.
[16] Z. Huang, M.C. Walker, M.M. Shah, Loss of dendritic HCN1 subunits enhances cortical excitability and epileptogenesis, J Neurosci 29(35) (2009) 10979-10988.
[17] C. Marini, A. Porro, A. Rastetter, C. Dalle, I. Rivolta, D. Bauer, . . . C. Depienne, HCN1 mutation spectrum: from neonatal epileptic encephalopathy to benign generalized epilepsy and beyond, Brain 141(11) (2018) 3160-3178.
[18] C. Nava, C. Dalle, A. Rastetter, P. Striano, C.G. de Kovel, R. Nabbout, . . . C. Depienne, De novo mutations in HCN1 cause early infantile epileptic encephalopathy, Nat Genet 46(6) (2014) 640-645.
[19] M.F. Nolan, G. Malleret, K.H. Lee, E. Gibbs, J.T. Dudman, B. Santoro, . . . A. Morozov, The Hyperpolarization-Activated HCN1 Channel Is Important for Motor Learning and Neuronal Integration by Cerebellar Purkinje Cells, Cell 115(551-564) (2003) 551-564.
[20] R.J. Keenan, H. Daykin, J. Chu, L. Cornthwaite-Duncan, G. Allocca, D. Hoyer, L.H. Jacobson, Differential sleep/wake response and sex differences following acute suvorexant, MK-1064 and zolpidem administration in the rTg4510 mouse model of tauopathy, Br J Pharmacol 179(13) (2022) 3403-3417.

[21] G. Allocca, S. Ma, D. Martelli, M. Cerri, F. Del Vecchio, S. Bastianini, . . . A.L. Gundlach, Validation of 'Somnivore', a Machine Learning Algorithm for Automated Scoring and Analysis of Polysomnography Data, Front Neurosci 13 (2019) 207.
[22] X. Chen, S. Shu, L.C. Schwartz, C. Sun, J. Kapur, D.A. Bayliss, Homeostatic regulation of synaptic excitability: tonic GABA(A) receptor currents replace I(h) in cortical pyramidal neurons of HCN1 knock-out mice, J Neurosci 30(7) (2010) 2611-2622.
[23] L.E. Bleakley, C.E. McKenzie, M.S. Soh, I.C. Forster, P. Pinares-Garcia, A. Sedo, . . . C.A. Reid, Cation leak underlies neuronal excitability in an HCN1 developmental and epileptic encephalopathy, Brain 144(7) (2021) 2060-2073.
[24] M.F. Nolan, G. Malleret, J.T. Dudman, D.L. Buhl, B. Santoro, E. Gibbs, . . . A. Morozov, A behavioral role for dendritic integration: HCN1 channels constrain spatial memory and plasticity at inputs to distal dendrites of CA1 pyramidal neurons, Cell 119(5) (2004) 719-732.
[25] S.J. Clapcote, J.C. Roder, Deletion polymorphism of Disc1 is common to all 129 mouse substrains: implications for gene-targeting studies of brain function, Genetics 173(4) (2006) 2407-2410.
[26] T. Adeyelu, A. Shrestha, P.A. Adeniyi, C.C. Lee, O.M. Ogundele, CA1 Spike Timing is Impaired in the 129S Inbred Strain During Cognitive Tasks, Neuroscience 484 (2022) 119-138.
[27] J. Samaha, L. Iemi, S. Haegens, N.A. Busch, Spontaneous Brain Oscillations and Perceptual Decision-Making, Trends Cogn Sci 24(8) (2020) 639-653.
[28] P.C. Shih, C.J. Steele, V.V. Nikulin, C. Gundlach, J. Kruse, A. Villringer, B. Sehm, Alpha and beta neural oscillations differentially reflect age-related differences in bilateral coordination, Neurobiol Aging 104 (2021) 82-91.
[29] A.M. Harris, P.E. Dux, C.N. Jones, J.B. Mattingley, Distinct roles of theta and alpha oscillations in the involuntary capture of goal-directed attention, Neuroimage 152 (2017) 171-183.
[30] K.K. Kedzior, M. Koch, C. Basar-Eroglu, Auditory-evoked EEG oscillations associated with prepulse inhibition (PPI) of auditory startle reflex in healthy humans, Brain Res 1163 (2007) 111-118.
[31] M.E. Hasselmo, C.E. Stern, Theta rhythm and the encoding and retrieval of space and time, Neuroimage 85 Pt 2 (2014) 656-666.
[32] J. Winson, Loss of hippocampal theta rhythm results in spatial memory deficit in the rat, Science 201(4351) (1978) 160-163.
[33] S.J. Thuault, G. Malleret, C.M. Constantinople, R. Nicholls, I. Chen, J. Zhu, . . . E.R. Kandel, Prefrontal cortex HCN1 channels enable intrinsic persistent neural firing and executive memory function, J Neurosci 33(34) (2013) 13583-13599.