Some Twist of Molecular Circuitry Fast Forwards Overnight Sleep Hours: A Systematic Review of Natural Short Sleepers' Genes

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Abstract

This systematic review focuses on different genetic mutations identified in studies on natural short sleepers, who would not be ill-defined as one type of sleep-related disorder. The reviewed literature is from databases such as PubMed, PMC, Scopus, and ResearchGate. Due to the rare prevalence, the number of studies conducted on natural short sleepers is limited. Hence, searching the search of databases was done without any date restriction and included animal studies, since mouse and fly models share similarities with human sleep behaviors. Of the 12 articles analyzed, four conducted two types of studies, animal and human (cross-sectional or randomized-controlled studies), to testify the effects of human mutant genes in familial natural short sleepers via transgenic mouse or fly models. The remaining eight articles mainly focused on one type of study each: animal study (four articles), cross-sectional study (two articles), review (one article), and case report (one article). Hence, those articles brought different perspectives on the natural short sleep phenomenon by identifying intrinsic factors like DEC2, NPSR1, mGluR1, and β1-AR mutant genes. Natural short sleep traits in either point-mutations or single null mutations in those genes have been examined and confirmed its intrinsic nature in affected individuals without any related health concerns. Finally, this review added a potential limitation in these studies, mainly highlighting intrinsic causes since one case study reported an extrinsically triggered short sleep behavior in an older man without any family history. The overall result of the review study suggests that the molecular mechanisms tuned by identified sleep genes can give some potential points of therapeutic intervention in future studies.

Introduction And Background

"Although sleep is an essential process for life, the brain circuits regulating sleep and the cellular and/or molecular mechanisms involved in this complex process are still enigmatic. Sleep or a 'sleep-like' behavior is present in virtually every animal species where it has been studied. Total sleep deprivation can be fatal, and partial deprivation of sleep has serious consequences on cognition, mood, and health." [1]

One of the most frequently asked sleep questions would be the optimal sleep hours for most individuals or the minimum sleep requirement to thrive in their lives. Although the report from Sleep Foundation [www.sleepfoundation.org] says that the average United States (US) adult sleeps about 7.4 hours per day during their work-offs [1]. It also states that the optimal sleep duration for most adults is eight hours each day to sustain their health in general [2]. Prolonged periods of short sleep hours either due to social needs or comorbid pathologic conditions will gradually deteriorate the quality of life as a whole. Most individuals will suffer from daytime sleepiness and ultimately need to catch up with their missed sleep hours during work-offs [3].

In many pieces of literature, the term "short sleep" is often referred to synonymously as sleep deprivation or sleep-wake disorder leading to other chronic medical consequences. However, it is a less popular concept that this term can be composed of two different phenomena of sleep: short sleep phenotype and deprived sleep. The former group is also classified as natural short sleepers (NSS) who usually sleep four to six hours a day without any negative impact on health or daytime drowsiness [2]; meanwhile, insufficient sleep is a pathologic condition needed to be managed and corrected. NSS is also not to be confused with the term familial advanced sleep phase (FASP), or advanced sleep phase (ASP), in which affected individual displays spontaneous early sleep onset and offset times while overall sleep duration is unaffected [4].

Hence, as the topic of sleep is more extensively studied by researchers, the need for clarification of the lexicon of sleep is rising, and it must be handled carefully [5].

Other challenges of studying NSS include (i) screening of other sleep-wake variants with short sleep patterns related to the subject's underlying comorbid medical condition or pharmacological influence [6], (ii) reliability of subjective reports of short sleep patterns, which need to be confirmed by objective

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measurements conducted by wrist actimetry sensors and home EEG units to detect sleep/wake transition and quality of sleep [1], and (iii) recruitment difficulty due to undetected NSS cases due to subject's perception of own phenotypic short sleep behavior as non-problematic and dependence on research subject's interest in sleep research and active involvement [2]. While facing such limitations in human studies, many NSS phenotype research is based on animal studies compared to human sleep behaviors and gene sequencing. The molecular mechanisms of identified genes regulating circadian rhythm, neuronal excitability, neurotransmission, and metabolism can make a good parallel to those of humans with a well-conserved molecular basis of sleep throughout evolution [7,8].

With recent growing interest in developing medical interventions to sleep disturbances and sleep deprivation to alleviate sleep debts and associated pathologies, it is crucial to understand gene-based modulations of sleep quality and quantity, and thus overall sleep homeostasis [1]. It is only after obtaining such solid understanding that outlines for future therapeutic intervention can be drawn. This systematic review, therefore, can give a good overview of the underlying molecular mechanisms of sleep dynamics in NSS ruled by currently identified mutant alleles of DEC2 (basic helix-loop-helix proteins differentiated embryo chondrocyte 2), NPSR1 (neuropeptide S receptor 1), mGluR 1 (metabotropic glutamate receptors of subtype ), and β1-AR (β1-adrenergic receptor) genes in existing reports.

Method

For this systematic review, keywords such as sleep, short sleep phenotype, natural short sleep, DEC2, NPSR1, mGluR1, or ADRB1 were used to search in databases including PubMed, Scopus, PubMed Central (PMC), and ResearchGate. MeSH (Medical subject headings) keyword strategies in PubMed were built for the precise result outcome: each keyword describing gene types such as “DEC2”, “NPSR1”, “mGluR1”, and “ADRB1”, had been paired with the keyword “sleep,” linked by Boolean AND so that the results would be restricted to each gene's function on sleep, out of many other known functions. In addition, the keyword “natural short sleep” was used for each database to detect any potentially missed articles. We searched the relevant articles offered for free with full text extensively without limits on publication dates or study types: articles reviewed include animal studies, cross-sectional studies, a review paper, and even a case report. Our inclusion criteria were set as follows: (i) discussion on natural short sleep phenotype or familial short sleep at least some extent, if not all, or (ii) studies on the regulation of sleep duration or sleep homeostasis on a molecular genetic basis. We removed any duplicates of searched articles from different databases by importing the article list to the Endnote and using its “find duplicate” tool. We strictly excluded those articles on sleep disorders like sleep deprivation, shift work sleep disorder, or advanced sleep phase syndromes, for the precision of our analysis on the term "short sleep phenotype," which is not considered a disease. While some articles were added and cited from the articles of our direct search by using their citation index to supplement the discussion section of our review, no further searching methods like contacting authors, experts, or manufacturers, were sought. Every step taken during this screening process of searched articles followed the PRISMA guideline 2020 as Figure 1 [9] below and the same search method was repeated weekly to stay updated with its last updated search done on September 7, 2021. Lastly, we went through the PRISMA-S checklist 2021 to ensure the good quality of review content.
FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guideline Flow Diagram 2020

Adapted from: Page MJ et al.[9]

DEC2: transcription factor basic helix-loop-helix proteins differentiated embryo chondrocyte 2; NPSR1: neuropeptide S receptor 1; mGluR 5: metabotropic glutamate receptors of subtype 5; ADRB1: β1-adrenergic receptor; PMC: PubMed Central; n: number of studies.

Results

Initial search results from all databases mentioned were overall 1351 articles, of which 148 duplicates were found. Out of the remaining 1203 articles after duplicate elimination, only 458 records were offered in free full text and chosen to be further screened. Application of our inclusion and exclusion criteria yielded the final 16 articles. Two independent reviewers then assessed these articles via different quality appraisal tools depending on study types of each article: Joanna Briggs Institute (JBI) tools for analytical cross-sectional study (five articles), case report (one article), and randomized-controlled study (one article); the Scale for the Assessment of Narrative Review Articles (SANRA) for narrative reviews (one article); and the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool for animal study (eight articles). Among those, three articles conducted both cross-sectional studies and animal studies, and one article included both randomized-controlled trials and animal studies. Hence, they were evaluated twice for each type of study they discussed by corresponding quality assessment tools. Because no concrete rules on rating the risk of bias are given to all the tools being used, the reviewers’ judgment on ratings for scores earned by studies had been made accordingly on each tool as indicated in Table 1, Table 2, Table 3, Table 4, and Table 5. As a result, we could confirm that all the articles assessed through JBI, SANRA, and SYRCLE’s tools were of low risk of bias, except three animal studies that were of moderate
risk of bias according to SYRCLE’s risk of bias tool [10-12]. The final decision was made to include all 12 articles (with a total of 16 studies) for analyses in our systematic review. A brief overview of key findings from each study included in this review is outlined in Table 6.

| Study             | ITEM 1 | ITEM 2 | ITEM 3 | ITEM 4 | ITEM 5 | ITEM 6 | ITEM 7 | ITEM 8 | % Yes | Average Risk* |
|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|-------|---------------|
| He et al.[1]      | 2009   | Yes    | Yes    | Yes    | Yes    | Unclear| Yes    | Yes    | 87.5  | Low           |
|                   |        | Yes    | Yes    | Yes    | Yes    | Unclear| Yes    | Yes    | 87.5  | Low           |
| Pellegrino et al. [13] | 2014   | Yes    | Yes    | Yes    | Yes    | Unclear| Yes    | Yes    | 75    | Low           |
|                   |        | Yes    | Yes    | Yes    | Yes    | Unclear| Yes    | Yes    | 87.5  | Low           |
| Spada et al.[14]  | 2014   | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | 100   | Low           |
|                   |        | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | 100   | Low           |
| Xing et al. [15]  | 2019   | Yes    | Yes    | Yes    | Unclear| Yes    | Yes    | Yes    | 87.5  | Low           |
|                   |        | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | 100   | Low           |
| Shi et al.[2]     | 2021   | Yes    | Yes    | Yes    | Unclear| Unclear| Yes    | Yes    | 75    | Low           |
|                   |        | Yes    | Yes    | Yes    | No     | Unclear| Yes    | Yes    | 75    | Low           |

**TABLE 1: Joanna Briggs Institute (JBI) Checklist for Cross Sectional Studies**
Adapted from: Critical Appraisal Tools [10]

Study reached equal or more than 70% of yes rated as low risk bias; between 69-50% of yes as moderate risk; and up to 49% or below as high risk.

| Study              | ITEM 1 | ITEM 2 | ITEM 3 | ITEM 4 | ITEM 5 | ITEM 6 | ITEM 7 | ITEM 8 | % Yes | Average Risk* |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|-------|---------------|
| Seystahl et al.[16]| 2014   | Unclear| Yes    | Yes    | Yes    | Yes    | Unclear| Yes    | 75    | Low           |
|                   |        | Unclear| Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | 87.5  | Low           |

**TABLE 2: Joanna Briggs Institute (JBI) Checklist for Case Reports**
Adapted from: Critical Appraisal Tools [10]

Study reached equal or more than 70% of yes rated as low risk bias; between 69-50% of yes as moderate risk; and up to 49% or below as high risk.

| Study              | ITEM 1 | ITEM 2 | ITEM 3 | ITEM 4 | ITEM 5 | ITEM 6 | ITEM 7 | ITEM 8 | ITEM 9 | ITEM 10 | ITEM 11 | ITEM 12 | ITEM 13 | % Yes | Average Risk* |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|---------|-------|---------------|
| Holst et al.[17]   | 2017   | Yes    | Unclear| No     | No     | Unclear| Yes    | Yes    | Yes    | Yes     | Yes     | Yes     | Yes     | Yes    | 69.2  | Low           |
|                   |        | Yes    | Unclear| Unclear| Unclear| Yes    | Yes    | Yes    | Yes    | Yes     | Yes     | Yes     | Yes     | 76.8  | Low           |

**TABLE 3: Joanna Briggs Institute (JBI) Checklist for Randomized Controlled Trial**
Adapted from: Critical Appraisal Tools [10]

Study reached equal or more than 70% of yes rated as low risk bias; between 69-50% of yes as moderate risk; and up to 49% or below as high risk.
TABLE 4: Scale for the Assessment of Narrative Review Articles (SANRA)
Adapted from: Baethge et al.\[11\]

Sum score of 7 or higher is considered as low-risk bias; 6-4 as moderate risk; and 3-0 as high risk

| Study                        | ITEM 1 | ITEM 2 | ITEM 3 | ITEM 4 | ITEM 5 | ITEM 6 | Sum score | Average Risk* |
|-----------------------------|--------|--------|--------|--------|--------|--------|-----------|---------------|
| Kushikata et al. [18]       | 2      | 2      | 1      | 2      | 2      | 0      | 9         | Low           |
|                             | 2      | 2      | 1      | 1      | 2      | 0      | 8         |               |

TABLE 5: The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias (ROB) Tool for Animal Studies
Adapted from: Hooijmans et al.[12]

Sum scores in between 20-14 is defined as low risk bias; 13-7 is moderate risk; and 6-0 is high risk where "yes" scores 2, "unclear" scores 1, and "no" scores 0.

| Study                        | ITEM 1 | ITEM 2 | ITEM 3 | ITEM 4 | ITEM 5 | ITEM 6 | ITEM 7 | ITEM 8 | ITEM 9 | ITEM 10 | Sum Score | Average Risk* |
|-----------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-----------|---------------|
| He et al. [3]               | No     | Unclear| Unclear| Yes    | Yes    | Yes    | Unclear| Unclear| Yes    | Unclear | 13        | Moderate      |
|                             | No     | Unclear| Unclear| Yes    | Yes    | Yes    | No     | Unclear| Yes    | Unclear | 11        |               |
| Shahmoradi et al. [19]      | Unclear| Yes    | Unclear| Yes    | Yes    | Yes    | Yes    | Unclear| Yes    | Unclear | 17        | Low          |
|                             | Unclear| Yes    | Unclear| Yes    | Yes    | Yes    | No     | Unclear| Yes    | Unclear | 15        |               |
| Holst et al. [17]           | Yes    | Yes    | Unclear| Unclear| Unclear| Yes    | Yes    | Yes    | Unclear| Yes     | 16        | Low          |
|                             | Yes    | Yes    | Unclear| Unclear| Unclear| Yes    | Yes    | Yes    | Unclear| Yes     | 17        |               |
| Hirans et al. [20]          | Yes    | Yes    | Unclear| Unclear| Unclear| No     | No     | Yes    | Yes    | Unclear | 11        | Moderate      |
|                             | Yes    | Yes    | Unclear| Unclear| Unclear| No     | No     | Yes    | Yes    | Yes     | 15        | Low          |
| Shi et al. [21]             | Yes    | Yes    | Unclear| Unclear| Unclear| Yes    | Yes    | Yes    | Yes    | Unclear | 19        | Low          |
|                             | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Unclear | 19        |               |
| Xing et al. [15]            | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Unclear | 18        | Low          |
|                             | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Yes    | Unclear | 18        |               |
| Aguilar et al. [22]         | Unclear| Yes    | Unclear| Unclear| Unclear| Unclear| Unclear| Yes    | Yes    | Unclear | 14        | Moderate      |
|                             | Unclear| Yes    | Unclear| Unclear| Unclear| Unclear| Yes    | Yes    | Yes    | Unclear | 15        |               |
| Shi et al. [2]              | Yes    | Yes    | Unclear| Yes    | Unclear| Yes    | Yes    | Yes    | Yes    | Unclear | 16        | Low          |
|                             | Yes    | Yes    | Unclear| Yes    | Unclear| Yes    | Yes    | Yes    | Yes    | Unclear | 16        |               |
| Author(s) | Type of Study | Methods | Findings |
|-----------|---------------|---------|----------|
| He et al. (2009) [1] | Cross-sectional study & animal study | Carrier and construct transgenic animal models to testify the effect of this mutation on sleep duration and homeostasis. | Identified hDEC2 P385R point mutation from DNA gene sequences in two carriers of a short sleep family. DEC2 P385R transgenic mouse and fly models displayed the same short sleep patterns. |
| Seystahl et al. (2014) [16] | Case report | To report unexpected arising of short sleep phenotype in patient who underwent ventriculostomy due to his chronic hydrocephalus. | Decompression of the patient’s chronic hydrocephalus may have lowered supratentorial brain pressure in general so that adjacent structures such as the thalamus and hypothalamus might be responsible for the change in sleep need and homeostasis. |
| Pellegrino et al. (2014) [13] | Cross-sectional study | To identify other variants of the DEC2 gene that may induce short sleep phenotype in humans. | Several mutations of the DEC2 gene were identified: p.Tyr362His, p.Pro384Arg, p.Pro384Gln, and p.Ala380Ser. Those mutations reduce the total sleep of carriers, and clock mechanisms involving DEC2 and CLOCK/BMAL1 transactivation must play a role in this alteration. |
| Spada et al. (2014) [14] | Cross-sectional study | Some objective measurements are used to examine the influence of SNP rs324981 in NPSR1 on sleep regulation. | Compared to A-allele carriers, T-allele carriers reported no change in rest and sleep onsets but had much shorter rest and sleep durations. These findings paralleled with previous animal studies in mice and human reports. |
| Shahmoradi et al. (2015) [19] | Animal study | To investigate the relationship between DEC1/DEC2 transcription factors and cognitive function as sleep is known to closely affect memory consolidation. | DEC1 and DEC2 single null mutants did not display any cognitive dysfunctions and thus confirmed functional redundancy of both proteins. Double null DEC1/DEC2 mutants showed enhanced remote fear memory consolidation; however, deterioration of fear memory formation in aging double null mutants implied that chronic elevation of IGF2 signaling might damage cognitive processing. |
| Holst et al. (2017) [17] | Randomized-control trial & animal study | To identify the contribution of mGlur5 to sleep-wake homeostasis. | Upon sleep deprivation, there had been increased bioavailability of mGlur5 in human subjects with the presence of objective markers of sleep need (delta and low frequency <1Hz EEG activity), and mGlur5 KO mice showed severely disturbed sleep homeostasis with poor adaptation to new tasks, and lack of recovery sleep. |
| Reference                  | Study Type                        | Description                                                                                           | Methods                                                                                     | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hirano et al. (2018) [20]  | Animal study                      | To confirm that mutant DEC2 gene (P384R) shortens sleep duration by modulating neuropeptide hormone orexin. | Mouse models (backcrossed to C57BL/6 j10 generations), Cell-based luciferase assay, and immunoprecipitation using plasmid vectors.                                                                 | Mutant DEC2 showed decreased transcriptional repressor activities for orexin expression, thus possibly increasing total arousal states in mammals. DEC2 must be responsible for sleep-duration regulation, at least to some extent, by fluctuating orexin levels.                                                                                                                                                                                                                                                                                                                                                                                                          |
| Shi et al. (2019) [21]     | Animal study                      | To identify additional genes affecting sleep duration to broaden the knowledge of gene and molecular pathways essential for sleep homeostasis in humans. | FNSS family with ADRB1- A187V carriers (n = 15); WT mice (n = 4 – 20); Adrb1- mutant mice (n = 4 – 19) Self-reported sleep diary, SNP genotyping, and exome sequencing. Mouse models (protein extraction and immunoblot analysis, RNA extract PCR analysis, stereotaxic surgery, EEG recording, maze-monitoring, etc.).                                                                 | Mutant ADRB1 was identified in humans with FNSS trait. Mutant Adrb1-A187V mice showed reduced sleep time of 55 minutes per day and increased active time, while human carriers slept 2 hours per day less on average than noncarriers. Hence, ADRB1 mutant neurons in dorsal pons may have increased wake-promoting activities leading to short sleep traits.                                                                                                                                                                                                                                                                                                                                                                                                   |
| Xing et al. (2019) [15]    | Cross-sectional study & animal study | To identify mutant NPSR1 gene in the FNSS family and recreate it in mouse models to confirm the role of the NPSR1/NPS system in sleep regulation. | Carriers in a FNSS family (n=2); Npsr1-KO mice (n = 3); Npsr1- Y206H mice (n = 7 – 12); WT Npsr1 mice (n= 8 – 19) Exome sequencing of FNSS family and mouse models (backcrossed to C57BL/6 j minimum four generations, maze-monitoring, EEG analysis, and mice brain slices and analysis).                                                                 | As a gain-of-function mutation inducing arousal, NPSR1-Y206H transgenic mice had reduced sleep duration similar to human FNSS human subjects. This finding further strengthens the importance of the NPS/PNSR1 system in control of sleep duration.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Aguilar et al. (2020) [22] | Animal study                      | To examine the functions of mGluR5 involved in neural oscillations during sleep, which may reproduce schizophrenia-like behaviors in the absence. | WT mice (n = 8 – 9); mGluR5-KO mice (n = 6 – 12) Mouse models: stereotaxic surgery, EEG analysis (NREM and REM sleep), and a visual analog to the acoustic steady-state response (ASSR) for task-evoked gamma power.                                                                 | mGluR5 KO mice showed loss of sleep spindle density, wake alpha power, and 40-Hz visual task-evoked gamma power and phase locking. Also, a reduction in sigma power (10-15Hz) was observed during NREM sleep transitions. Overall, mGluR5 KO mice reproduced those EEG signals much like to schizophrenia patients.                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Kushikata et al. (2021) [18]| Review                            | To investigate the role of NPS in anesthesia, analgesia, and sleep-wake modulation to pursue better medical care. | N/A N/A                                                                                                                                               | NPS and orexin promote emergence from anesthesia but do not necessarily inhibit the sedation by anesthesia. Hence, anesthetic induction and emergence may not share the same mechanism of action. Also, NPS attenuates not only inflammatory pain via noradrenergic neuronal activity and dopaminergic neurons but also other kinds of pain like neuropathic pain via micro-infusion of NPS into the amygdala. As an indirect inhibitor of sleep-inducing neurons, NPS acts as a wake-promoting substance by activating histaminergic and orexinergic neurons.                                                                                                                                                                                                                                                                                                                                 |
To study the function of mGluR1 in sleep-wake regulation by examining mutant GRM1 carriers and mouse models.

K50230 family (n = 9); GRM1-K07331 family (n = 4); WT-mice (n = 16–19); Grm1b R889W mice (n = 4–11); Grm1 S458A mice (n = 4–23)

Exome sequencing and Mouse models (protein extraction and immunoblot analysis, Tango assay, EEG analysis, electrophysiological recording, and RNA sequencing).

Two loss-of-function mutations of GRM1 with the short sleep phenotype had been identified in two FNSS families: K50230 and K07331. Mutant mice displayed a reduction in sleep, and this confirmed role of mGluR1 in sleep regulation.

**TABLE 6: Findings of the Studies Included in the Analysis**

| Table 6: Findings of the Studies Included in the Analysis |
|----------------------------------------------------------|
| hDEC2 (also known as BHLHE41): basic helix-loop-helix family member e41 in human; CLOCK: circadian locomotor output cycles kaput; BMAL1: Brain and Muscle ARNT-Like 1; SNP: single nucleotide polymorphism; EEG: electroencephalography; DEC1: transcription factor basic helix-loop-helix proteins differentiated embryo chondrocyte 1 (also known as SHARP2/BHLHE40); DEC2: transcription factor basic helix-loop-helix proteins differentiated embryo chondrocyte 2 (also known as SHARP1/BHLHE41); WT: wild-type; IGF2: insulin-like growth factor 2; NPSR 1: neuropeptide S receptor 1; NPS: neuropeptide S; FNSS: familial natural short sleep; KO: knock-out; Npsr1: mouse NPSR1 gene; mGluR1: metabotropic glutamate receptor subtype 1; GRM1: metabotropic glutamate receptor 1 gene; Grm1: mouse GRM1 gene; Tango assay: standard arrestin-recruitment assay; mGluR5: metabotropic glutamate receptor subtype 5; HT: heterozygous; PET: positron emission tomography; MRS: magnetic resonance spectroscopy; EMG: electromyogram; PCR: polymerase chain reaction; NREM: non-rapid eye movement; REM: rapid eye movement; ADRB1: β1-adrenergic receptor gene; Adrb1: β1-adrenergic receptor gene in mice; N/A: Not Available. |

**Review**

Continuous studies of NSS from various angles have found a familial tendency of such a trait, and that multiple genes must play a role in quantifying sleep requirements in mammals. In this review, some of the well-defined phenotypic induction of NSS trait in either animal models or human studies ruled by DEC2, NPSR1, mGluR1, and β1-AR gene variants are discussed in separate sections as below.

**Induction of short sleep trait by different single point-mutant variants of DEC2**

Among many other circadian modulating genes like Period Circadian Regulator 2 (PER2), neuronal PAS domain protein 2 (NPAS2), aryl hydrocarbon receptor nuclear translocator-like/Brain and Muscle ARNT-Like 1 (ARNTL/BMAL1), circadian locomotor output cycles kaput (CLOCK), and Cryptochrome Circadian Regulator 1 and 2 (CRY1/CRY2), several studies have found that DEC2 gene is closely related to induction of short sleep duration [1]. CLOCK and BMAL1 transcription factors bind to each other as a heterodimer to activate enhancer box (E-box) element in promotor regions of period genes (PER genes). DEC2, as part of the same transcription family, interacts and suppresses CLOCK and BMAL1 via direct protein-protein interaction with BMAL1 and/or competition for E-box element as briefly described in Figure 2 [23].
An hDEC2 point mutation (P385R) in two affected individuals in a small family first had been identified by He et al. [1]. They displayed a distinct difference in sleep duration from the norm: their habitual shorter sleep time reported was an average of 6.25 hours compared to an average of 8.06 hours in noncarrier family members. Therefore, it was speculated that the specific mutations in the DEC2 gene, which suppress the CLOCK/BMAL1 activation, induce phenotypical short sleep [13]. Further study on the point mutation in DEC2 gene was done in both mouse and fly models by comparing wild-type (WT) and mutant carrier (DEC2-P385R) of missense mutation replacing a proline by arginine in amino acid position 385 in exon 5 of DEC2 [1]. Compared to the WT group, the DEC2-P385R group demonstrated more wakefulness with both shorter non-rapid eye movement (NREM) and rapid eye movement (REM) during sleep and thus shorter sleep duration. Also, sleep deprivation in the DEC2-P385R mice led to slow and incomplete NREM sleep recovery with only slight NREM delta power enhancement implying adaptation to shorter sleep with altered sleep homeostasis [1].

In the study conducted by Pellegrino et al. with luciferase assay and plasmid construction, more variants of the DEC2 gene, yielding p.Tyr362His, p.Pro384Arg, p.Pro384Gln, and p.Ala380Ser were discovered and compared with WT DEC2 gene [13]. In addition to a single variant, p.Pro384Arg had been identified previously by He et al. [1], and a variant p.Ala380Ser had been rarely detected in the European Centre d’Etude du Polymorphisme Humain (CEPH) population without any known sleep data, p.Tyr362His, and p.Pro384Gln were two newly found variant types in their study [13]. Among four DEC2 variants examined, only p.Pro384Gln did not significantly affect its molecular activities compared to WT. However, variants type p.Tyr382His, p.Pro384Arg and p.Ala380Ser showed altered repression activity of DEC2 on CLOCK/BMAL1 activation and would likely shorten the sleep duration and alleviate impacts of sleep deprivation [13]. Furthermore, those variants in DEC2 also had the same effect on the NPAS2-BMAL1 complex [13] where NPAS2, another binding partner of BMAL1, is known to alter sleep-wake quantities and act upon stimuli other than light, in some restricted feeding, as found in studies of NPAS2 knock-out mice [24,25]. Therefore, this finding left an open-ended question of whether DEC2 variants show their functional effects through interaction with CLOCK or NPAS2.

As He et al. [1] previously introduced a family with natural short sleep trait in their study, similar findings were illustrated in twin study by Pellegrino et al. [13]. The carrier twin had a much shorter total sleep time (299.3 min) than his noncarrier brother (364.7 min); meanwhile, no difference in NREM sleep duration was noted. Along with higher delta power, a measure of sleep drive, the carrier twin also showed minimal behavioral and metabolic impairment in response to sleep loss compared to the noncarrier by reporting significantly fewer average lapses of performance alertness and almost the same BMI reading (23.9 kg/m2).
levels are increased in neurons expressing NPSR1 for neurotransmission modulation by NPS[14,41,42].

The tuberomammillary nucleus, in which wake-promoting orexin and histamine are expressed, respectively, found in some areas for sleep induction and in hypothalamic areas such as the perifornical region and the posterior hypothalamus.[14,34,40].

The brain: it can be primarily found in the sleep-wake system of the hypothalamus and thalamus and also be found throughout the brainstem neurons adjacent to the locus coeruleus in the parabrachial nucleus and principal sensory trigeminal nucleus.[34,35].

Orexin, also called hypocretin (Hcrt), is a neuropeptide known for its role in regulating arousal[35]. Lower circulating Hcrt and fewer Hcrt receptors cause decreased arousal at certain times of day and nighttime fragmentation of sleep architecture[35]. In a further study of the role of DEC2 protein[20], DEC1 and DEC 2 also form a complex with MyoD1 and E12/47, the other set of transcription factors, to bind to another E-box sequence (CAG CTG) in the promoter region of Hcrt. In this region, DEC2 represses MyoD1 activating prepro-orexin gene expression. Therefore, fluctuations of Hcrt levels are controlled by DEC2 expressions oscillating in a circadian rhythm in the hypothalamus and cerebrospinal fluid[35,36]. In vitro studies[35] found that altered binding of mutant DEC2-P385R to E12 and DNA resulted in the reduced repressive activity of DEC2, and it was suggested that MyoD1/E12 heteromer involved in the recruitment of DEC2 to the binding site, E-box. Interestingly, DEC2 effect cancellation can occur due to overexpressed E12 or E47, which might be competing with MyoD1 binding to E-boxes, and thus unable to form a heteromer (MyoD1/E12) for the DEC2 recruitment. Or it might be due to the inability of DEC2 to replace overexpressed E12/47 in E-box binding sites. Hence, this DEC2 identified function in sleep regulation via Hcrt could make DEC2 a good target for modulating orexinergic signaling and could be used in inventing new treatment of insomnia patients[20].

NPS/NPSR1 signaling and reduction of sleep duration by a gain-of-function mutation in NPSR1

The neuropeptide S (NPS) is highly expressed in brainstem neurons adjacent to the locus coeruleus in the parabrachial nucleus and principal sensory trigeminal nucleus[14,37,38]. The ascending arousal network is distributed over the locus coeruleus and the parabrachial nucleus areas, while the trigeminal sensory nucleus is also influenced by the sleep-wake cycle[39,40]. Unlike specific distributions of NPS, neuropeptide S receptor (NPSR1), a G-protein coupled receptor, is more extensively distributed throughout the brain: it can be primarily found in the sleep-wake system of the hypothalamus and thalamus and also observed in the cortex and the amygdala as illustrated in Figure 3. More importantly, NPSR1 can be found in some areas for sleep induction and in hypothalamic areas such as the perifornical region and the tuberomammillary nucleus, in which wake-promoting orexin and histamine are expressed, respectively[14,41,42]. Protein kinases are activated upon NPS binding to NPSR1, and intracellular cAMP and Ca^2+ levels are increased in neurons expressing NPSR1 for neurotransmission modulation by NPS[37].
Most studies in the single nucleotide polymorphism (SNP) rs324981 (triplet position 107 of the NPSR1 gene on chromosome 7p14.3) had been done in mouse models, making a parallel to NPS/NPSR1 functions in humans [14]. The T-allele of the SNP replaces the asparagine with isoleucine in the active center of the NPSR1-binding site, which consequently increases sensitivity to its ligand, NPS, up to tenfold [43]. Based on a previous similar study done by Gottlieb et al. [44] conducted via subjective measurement of sleep with two single questionnaires, Spada et al. [14] replicated the study with an objective measure of sleep via actinography. They again examined homozygous T-allele carriers who showed a reduction in sleep duration than A-allele carriers but had no significant difference in sleep onset. However, underlying functional mechanisms of this alteration of sleep duration were to be further investigated.

Further study on NPS/NPSR1 mutation in human and mouse models by Xing et al. [15] demonstrated the mutation NPSR1-Y206H in mice with shorter sleep duration as well as resistance to memory loss in response to sleep deprivation, and similar corresponding homologous mutation in people with familial natural short sleeper (FNSS) trait. They stated that NPSR1-Y206H mice to be a gain of function mutation due to absence of sleep phenotype in NPSR1 knock-out (KO) mice and their better response upon NPS administration inducing wakefulness and hyperactivity. NPS also has been known to facilitate learning and memory [45], elicit anxiolytic [37], and have antinociceptive effects [46]. Hence, other than the short sleep trait, NPSR1-Y206H could also be responsible for at least some of the seemingly protective traits for carrier subjects, although it is yet unknown that whether these traits are from efficient sleep or regulation by different NPS/NPSR1 signaling. These findings, as a result, make NPS/NPSR1 system a good therapeutic target for sleep improvement and treatment for sleep-related disorders in humans [15].

In various sites of its action, NPS administration can facilitate emergence from anesthetic agents without interrupting their sedative effects [47]; attenuate inflammatory or neuropathic pain via noradrenergic and dopaminergic neurons, or amygdala [48], respectively; and also modulate sleep-wake status through histaminergic and orexinergic neurons [18]. GABAergic neuron with its inhibitory function in sleep regulation, in the ventrolateral preoptic area (VLPO), is facilitated by NPS, which works as an indirect inhibitor of sleep-inducing neurons in this manner. In the other study, NPS administration (0.1 and 1nmol, icv) markedly raised wakefulness for about two hours of duration, and it was evaluated by increased high-frequency activities (14.5-60 Hz) detected in EEG measurement [49]. Induction of c-Fos (Fos proto-oncogene) expression by NPS injection in areas of abundant NPSR1 expressions such as histaminergic neurons and orexinergic neurons promote wakefulness and quantified sleep rhythm in sleep-wake associated brain structures [18]. Though with yet unknown mechanism, endogenous NPS showed inhibitory action on NREM sleep during light phase but no effect on REM sleep, implying that those two sleep statues must be regulated differently [50].

**Loss-of-function mutations in mGluR1 and mGluR5 subtypes lead to different outcomes**

The group I metabotropic glutamate receptors (mGluR1 and mGluR5 subtypes) are involved in the regulation of normal cellular activity and synaptic plasticity, as well as sleep homeostasis (by mGluR5), and many of them are coupled with different Homer isoforms for binding and are distinctively regulated [51,52]. During sleep, synapses are loosened by Homer1a (sleep regulator) and mGluR1/mGluR5 via signaling of neuromodulators promoting sleep-wake cycles [53], as depicted in Figure 4.
FIGURE 4: Periodic Changes of Neural Excitability and Synaptic Strength

During the wake period, mGluR1/mGluR5 binds to long-form Homer proteins (tetramer of Homer1a) to anchor IP3R in ER and Shank at the base of PSD, thus increasing calcium release for neuronal excitability and upregulating AMPAR for strengthening synapses, respectively. During sleep, mGluR1/mGluR5 is agonized by Homer1a monomer and dissociated from IP3R and Shank, which, in turn, decreasing neural excitability and synaptic strength.[51]

mGluR1/5: Group I metabotropic glutamate receptors; Homer1a: Homer protein homolog 1 a; AMPAR: AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptor; IP3R: 1,4,5-triphosphate receptor; PSD: postsynaptic density; Shank: Shank protein; ER: endoplasmic reticulum.

In another study [2], two rare independent mutations, K50230 and K07331, of the glutamate metabotropic receptor 1 gene (GRM1) had been identified in two unrelated FNSS families. K50230 altered the arginine into a tryptophan at position 889 in the C-terminal intracellular domain of the isoform GRM1b-R889W, and K07331 substituted the serine into an alanine at position 458 in the N-terminal extracellular domain yielding the isoform GRM1-S458A. Despite their different mutant domains, those two mutations of mGluR1 shared similar functional changes, but both were comparable to WT mGluR1. Loss-of-function mutation in mutant mGluR1 showed decreased activation of extracellular-signal regulated kinase (ERK) pathway, which had been known to lengthen the sleep duration of mouse models; hence, shortened sleep duration with similar amounts in both mutant strains was observed in mice. The difference was that the mixture of WT and mGluR1b-S458A receptors, compared to mGluR1b-S458A alone, restored activity to a level consistent with a loss-of-function of mutant receptor whereas mixing WT and mGluR1b-R889W with 1:1 ratio showed decreased activity compared to WT or mGluR1b-R889W alone, implying a dominant-negative effect. Among variants of mGluR1 like mGluR1a, mGluR1b, mGluR1d, and mGluR1E55, mGluR1a isoform with the longest C-terminal domain had a strong intrinsic activity that could overcome the effect of mutant S458A [2] and was playing a dominant role, which could restore all cerebellar defects of mGluR1-KO mice. At the same time, mGluR1b could show only partial recovery of such defects [54]. Nonetheless, human subjects with FNSS carried heterozygous mutations with an expectation of a 1:2:1 ratio of WT-WT, W-Mut, and Mut-Mut, respectively, and displayed decreased receptor activities in both mutant types in vivo.

The degree of shortened sleep length (~25 min less) induced by mGluR1, however, was less evident compared to other known mutations causing changes in sleep duration such as Adrb1-A187V (mouse ADRB1-A187V) (55 min less) and Npsr1-Y206H (mouse NPSR1-Y206H) (71 min less) in mice. A similar trend was noted in human models: 132 min less in ADRB1-A187V, 180 min less in NPSR1-Y206H, and ~100 min less in GRM1 mutant carrier humans.[2,15,21]. Furthermore, no change in delta power in mouse carrier models was observed, whereas both Adrb1-A187V and Npsr1-Y206H mice showed an increased delta power at the end of the active phase and beginning of the resting phase. This finding was somewhat unexpected because mGluRs have been known to regulate sleep homeostasis [53]. It is, however, essential to note that human carriers with FNSS traits are healthy without any consequences observed in the
In this review, various genetic factors shortening sleep duration or sleep need in humans were studied together with their possible underlying mechanisms. However, there are some limitations on studies of NSS phenotype in humans. For instance, though there had been more examinable human subjects with NSS, the numbers are still somewhat small due to difficulty in finding such subjects with NSS traits, excluding those with pathological sleep shortages. Although animal models were incorporated in the study due to similarities shared by human and mouse models (or even Drosophila), sleep behaviors in those two models are not the same, as mentioned by Shi et al. [48]. The influences brought by sleep mutant genes may be different in different species, leading to some ambiguity.

Also, a recent case study by Seystahl et al. [16] opens a new possibility of extrinsic factors leading to NSS. In the study, they encountered a 59-year-old male patient suffering from chronic hydrocephalus, with rather an average sleep duration (seven to eight hours) [58]. After the third ventriculostomy to relieve his hydrocephalus, however, he reported a substantial decrease in sleep need of four to five hours without feeling fatigued or excessive sleepiness during daytime [16]. It was a fascinating case since the patient had no family history of NSS, and his neuropsychological examination confirmed no cognitive or physical consequences from the new onset of short sleep at least over 17 months (as per his last follow-up visit) [16]. Seystahl et al. [16] suspected that decompression of the wake-promoting histaminergic neurons in the tuberomammillary nucleus, due to their proximity to the third ventricle, might have induced altered gene expression involving sleep regulation and homeostasis [21].

As a result, intrinsic factors ruled by genetic variants discussed in this review do not fully outline the whole picture of the NSS phenomenon in humans. More extensive research in this area must be done, and novel approaches to the topic of NSS from different angles still await.
Conclusions
Excluding from a category of sleep-wake disorders, the natural short sleep phenotype is not per se considered an illness, endangering one's health or well-being. People with the NSS trait do not experience the medical consequences driven by short sleep duration. This sleeping habit is not meant to be practiced or learned upon one’s desire, but rather is an intrinsic nature that lasts lifelong. There already had been several identified genetic factors that bring out this short sleep phenomenon of humans and other mammals. To date, the most well-known genes triggering shortening of sleep duration or sleep need, if mutated, are DEC2, NPSR1, mGluR1, and B1-AR genes. Not necessarily knocked out its functions completely, each gene has its unique point-mutation, either upregulating or downregulating its function involving the circadian clock without causing any significant changes in the other biological systems. As a result, each molecular genetic mechanism underlying the NSS trait has therapeutic potential for managing deep-seated sleep-wake disorders or related cognitive dysfunctions. At a glance, this systematic review gives a general overview of accomplishments from the previous research works on NSS until today, with yet many unknowns. It, therefore, may suggest some directions in which future research on sleep could be heading towards.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. He Y, Jones CR, Fujiki N, et al.: The transcriptional repressor DEC2 regulates sleep length in mammals. Science. 2009, 325:866-70. 10.1126/science.1174443
2. Shi G, Yin C, Fan Z, et al.: Mutations in metabotropic glutamate receptor 1 contribute to natural short sleep trait. Curr Biol. 2021, 31:13-24.e4. 10.1016/j.cub.2020.09.071
3. Roenneberg T: Chronobiology: the human sleep project. Nature. 2013, 498:427-8. 10.1038/498427a
4. Zhang L, Plätcke LJ, Fu YH: Diversity of human clock genotypes and consequences. Prog Mol Biol Transl Sci. 2013, 119:51-81. 10.1016/B978-0-12-396971-2.00003-8
5. Grandner MA, Patel NP, Gehmann PR, Perlis ML, Pack AI: Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. Sleep Med Rev. 2010, 14:239-47. 10.1016/smrv.2009.08.001
6. Hsu PK, Plätcke LJ, Fu YH: Genetics of human sleep behavioral phenotypes. Methods Enzymol. 2015, 552:209-24. 10.1016/bs.mie.2014.10.046
7. Sehgal A, Mignot E: Genetics of sleep and sleep disorders. Cell. 2011, 146:194-207. 10.1016/j.cell.2011.07.004
8. Zhang L, Fu YH: The molecular genetics of human sleep. Eur J Neurosci. 2020, 51:422-8. 10.1111/ejn.14132
9. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021, 372:n71. 10.1136/bmj.n71
10. Critical Appraisal Tools. (2021). Accessed: September 9, 2021: https://bi.jbi.global/critical-appraisal-tools.
11. Baethge C, Goldbeck-Wood S, Mertens S: SGNRA-a scale for the quality assessment of narrative review articles. Res Integ Peer Rev. 2019, 4.5. 10.1186/s41073-019-0064-8
12. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW: SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014, 14:43. 10.1186/1471-2288-14-43
13. Pellegrino R, Kavukli IH, Goel N, et al.: A novel BHLHE41 variant is associated with short sleep and resistance to sleep deprivation in humans. Sleep. 2014, 37:1327-36. 10.5665/sleep.3924
14. Spada J, Sander C, Burkhardt R, et al.: Genetic association of objective sleep phenotypes with a functional polymorphism in the neuropeptide S receptor gene. PLoS One. 2014, 9:e98769. 10.1371/journal.pone.0098769
15. Xing L, Shi G, Mostovoy Y, et al.: Mutant neuropeptide S receptor reduces sleep duration with preserved memory consolidation. Sci Transl Med. 2019, 11:145-55. 10.1126/scitranslmed.aaa2014
16. Seystahl K, Königcke H, Sürucü O, Baumann CR, Poryazova R: Development of a short sleeper phenotype after third ventriculostomy in a patient with ependymal cysts. J Clin Sleep Med. 2014, 10:211-3. 10.5664/jcsm.3458
17. Holst SC, Sousek A, Hefli K, et al.: Cerebral mGluRS availability contributes to elevated sleep need and behavioral adjustment after sleep deprivation. Elife. 2017, 6:e28751. 10.7554/eLife.28751
18. Kushikata T, Hirota K, Saito J, Takekawa D: Roles of neuropeptide S in anesthesia, analgesia, and sleep. Pharmaceuticals (Basel). 2021, 14:483. 10.3390/ph14050483
19. Shahmorad A, Radyushklin K, Rossner MJ. Enhanced memory consolidation in mice lacking the circadian modulators SHARP1 and -2 caused by elevated lgt2 signaling in the cortex. Proc Natl Acad Sci U S A. 2015, 112:E3582-9. 10.1073/pnas.1423995112

20. Hirano A, Hsu PK, Zhang L, et al.: DEC2 modulates orexin expression and regulates sleep. Proc Natl Acad Sci U S A. 2018, 115:3434-9. 10.1073/pnas.1801693115

21. Shi G, Xing L, Wu D, et al.: A rare mutation of β1-adrenergic receptor affects sleep/wake behaviors. Neuron. 2019, 103:1044-1055.e7. 10.1016/j.neuron.2019.07.026

22. Aguilar DD, Streekert RE, Basheer R, McNally JM. Alterations in sleep, sleep spindle, and EEG power in mGLUR5 knockout mice. J Neurophysiol. 2020, 123:22-33. 10.1152/jn.00332.2019

23. Honma S, Kawamoto T, Takagi Y, et al.: Dec1 and Dec2 are regulators of the mammalian molecular clock. Nature. 2002, 419:841-4. 10.1038/nature01123

24. Franken P, Dudley CA, Estill SJ, Barakat M, Thomason P, O'Hara BF, McKnight SL. NPAS2 as a transcriptional regulator of non-rapid eye movement sleep: genotype and sex interactions. Proc Natl Acad Sci U S A. 2006, 103:7118-23. 10.1073/pnas.06020010103

25. Franken P, Dijk DJ. Circadian clock genes and sleep homeostasis. Eur J Neurosci. 2009, 29:1820-9. 10.1111/j.1460-9568.2009.06723.x

26. Alldabal L, Bahamman AS. Metabolic, endocrine, and immune consequences of sleep deprivation. Open Respir Med J. 2011, 5:3:1:43. 10.2174/1874306411005010031

27. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010, 11:114-26. 10.1038/nrn2762

28. Ji D, Wilson MA. Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci. 2007, 10:100-7. 10.1038/nrn1825

29. Kelleher PJ, Govindarajan A, Jung HY, Kang H, Tonegawa S. Translational control by MAPK signaling in long-term synaptic plasticity and memory. Cell, 2011, 146:47-59. 10.1016/j.cell.2011.01.015

30. Orban PC, Chapman PF, Brambilla R. Is the Ras-MAPK signalling pathway necessary for long-term memory formation? Trends Neurosci. 1999, 22:38:44. 10.1016/S0166-2236(99)01306-x

31. Philips GT, Ye X, Kopec AM, Carew TJ. MAPK establishes a molecular context that defines effective training conditions for long-term memory formation. J Neurosci. 2013, 33:7565-73. 10.1523/JNEUROSCI.5651-12.2013

32. Baier PC, Brzozka MM, Shahmorad A, et al.: Mice lacking the circadian modulators SHARP1 and SHARP2 display altered sleep and mixed state endophenotypes of psychiatric disorders. PLoS One. 2014, 9:e110510. 10.1371/journal.pone.0110310

33. Sato F, Kawamoto T, Fujimoto K, et al.: Functional analysis of the basic helix-loop-helix transcription factor DEC1 in circadian regulation. Interaction with Bmal1. Eur J Biochem. 2004, 271:4409-19. 10.1111/j.1432-1033.2004.04379.x

34. Rossner MJ, Oster H, Wichert SP, et al.: Disturbed clockwork resetting in Sharp-1 and Sharp-2 single and double mutant mice. PLoS One. 2008, 3:e2762. 10.1371/journal.pone.0002762

35. Desanauad F, Murillo-Rodriguez E, Lin L, et al.: The diurnal rhythm of hypocretin in young and old F344 rats. Sleep, 2004, 27:851-6. 10.1093/sleep/27.5.851

36. Justinussen JL, Holm A, Kornum BR. Disturbed clockwork resetting in Sharp-1 and Sharp-2 single and double mutants. J Neurophysiol. 2004, 92:1033-40. 10.1152/jn.1995.73.6.2486

37. Kohlmeier KA, Soja PJ, Kristensen MP. Functional analysis of the basic helix-loop-helix transcription factor DEC1 in circadian regulation. Interaction with Bmal1. Eur J Biochem. 2004, 271:4409-19. 10.1111/j.1432-1033.2004.04379.x

38. Xu YL, Reinschreid RK, Hultron-Resendiz S, et al.: Neuropeptide S: a neuropeptide promoting arousal and anti-anxiety-like effects. Neuron. 2004, 43:487-97. 10.1016/j.neuron.2004.08.005

39. Zhao P, Shao YF, Zhang M, Fan K, Kong XP, Wang R, Hou YP. Neuropeptide S promotes wakefulness through activation of the posterior hypothalamic histaminergic and orexinergic neurons. Neuroscience. 2012, 207:218-26. 10.1016/j.neuroscience.2012.01.022

40. Caims BE, Fragoso MC, Soja PJ. Activity of rostral trigeminal sensory neurons in the cat during wakefulness and sleep. J Neurophysiol. 1995, 73:2486-98. 10.1152/jn.1995.73.6.2486

41. Kohlmeier KA, Soja PJ, Kristensen MP. Disparate cholinergic currents in rat principal trigeminal sensory nucleus neurons mediated by M1 and M2 receptors: a possible mechanism for selective gating of afferent sensory neurotransmission. Eur J Neurosci. 2006, 23:3245-58. 10.1111/j.1460-9568.2006.04875.x

42. Sutcliffe JG, de Lecea L. The hypocretins: setting the arousal threshold. Nat Rev Neurosci. 2002, 3:339-49. 10.1038/nrn808

43. Xu YL, Gall CM, Jackson VR, Civelli O, Reinschreid RK. Distribution of neuropeptide S receptor mRNA and neurochemical characteristics of neuropeptide S-expressing neurons in the rat brain. J Comp Neurol. 2007, 500:84-102. 10.1002/cne.21159

44. Reinschreid RK, Xu YL, Okamura N, et al.: Pharmacological characterization of human and murine neuropeptide S receptor variants. J Pharmacol Exp Ther. 2005, 315:1388-45. 10.1124/jpet.105.093427

45. Gottlieb DJ, O'Connor GT, Wilk JB. Genome-wide association of sleep and circadian phenotypes. BMC Med Genet. 2007, 8:S9. 10.1186/1471-2250-8-S1-S9

46. Han RW, Yin XQ, Chang M, Peng YL, Li W, Wang R. Neuropeptide S facilitates spatial memory and mitigates spatial memory impairment induced by n-methyl-D-aspartate receptor antagonist in mice. Neurosci Lett. 2009, 455:74-7. 10.1016/j.neulet.2009.03.023

47. Li W, Chang M, Peng YL, Gao YH, Zhang JN, Han RW, Wang R. Neuropeptide S produces antiinociceptive effects at the supraspinal level in mice. Regul Pept. 2009, 152:205-6. 10.1016/j.regpep.2009.03.013

48. Kushikata T, Yoshida H, Kudo M, Salvadori S, Calo G, Hirota K. The effects of neuropeptide S on general anesthesia in rats. Anesth Analg. 2011, 112:845-9. 10.1213/ANE.0b013e3182b0950d

49. Yang F, Peng L, Luo J, Yi H, Xu X. Intra-amygdala microinfusion of neuropeptide S attenuates neuropathic pain and suppresses the response of spinal microglia and astrocytes after spinal nerve ligation in rats. Peptides. 2016, 82:26-34. 10.1016/j.peptides.2016.05.005

50. Chauveau F, Claverie D, Lardant E, et al.: Neuropeptide S promotes wakefulness through the inhibition of sleep-promoting ventrolateral preoptic nucleus neurons. Sleep. 2020, 43:1099:300. 10.1093/sleep/zsz189

51. Oishi M, Kushikata T, Niwa H, et al.: Endogenous neuropeptide S tone influences sleep-wake rhythm in rats. Neurosci Lett. 2014, 581:94-7. 10.1016/j.neulet.2014.08.031

52. Bertaso F, Roussignol G, Worley P, Bockaert J, Fagni L, Ango F. Homer1a-dependent crosstalk between
52. Maret S, Dorsaz S, Gurcel L, et al.: Homer1a is a core brain molecular correlate of sleep loss. Proc Natl Acad Sci U S A. 2007, 104:20090-5. 10.1073/pnas.0710131104
53. Diering GH, Nirujogi RS, Roth RH, Worley PF, Pandey A, Huganir RL: Homer1a drives homeostatic scaling-down of excitatory synapses during sleep. Science. 2017, 355:511-5. 10.1126/science.aai8355
54. Ohtani Y, Miyata M, Hashimoto K, et al.: The synaptic targeting of mGluR1 by its carboxyl-terminal domain is crucial for cerebellar function. J Neurosci. 2014, 34:2702-12. 10.1523/JNEUROSCI.3542-13.2014
55. Ribeiro FM, Paquet M, Cregan SP, Ferguson SS: Group I metabotropic glutamate receptor signalling and its implication in neurological disease. CNS Neurol Disord Drug Targets. 2010, 9:574-9. 10.2174/187152710793361612
56. Ahnaou A, Langlois X, Steckler T, Bartolome-Nebreda JM, Drinkenburg WH: Negative versus positive allosteric modulation of metabotropic glutamate receptors (mGluR5): indices for potential pro-cognitive drug properties based on EEG network oscillations and sleep-wake organization in rats. Psychopharmacology (Berl). 2015, 232:1107-22. 10.1007/s00213-014-3746-4
57. Marshall L, Helgadóttir H, Mölle M, Born J: Boosting slow oscillations during sleep potentiates memory. Nature. 2006, 444:610-3. 10.1038/nature05278
58. Huber KM, Roder JC, Bear MF: Chemical induction of mGluR5- and protein synthesis–dependent long-term depression in hippocampal area CA1. J Neurophysiol. 2001, 86:321-5. 10.1152/jn.2001.86.1.321
59. Lu YM, Jia Z, Janus C, Henderson JT, Gerlai R, Wojtowicz JM, Roder JC: Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. J Neurosci. 1997, 17:5196-205. 10.1523/JNEUROSCI.17-13-05196.1997
60. Kerridge CW, Schmeichel BE, España RA: Noradrenergic modulation of wakefulness/arousal. Sleep Med Rev. 2012, 16:187-97. 10.1016/j.smrv.2011.12.003