

# Short Sleep Duration and Erectile Dysfunction: A Review of the Literature

Fuxun Zhang<sup>1,2,\*</sup>, Yang Xiong<sup>1,2,\*</sup>, Feng Qin<sup>1</sup>, Jiahong Yuan<sup>1,2</sup>

<sup>1</sup>Andrology Laboratory, West China Hospital, Sichuan University, Chengdu, People's Republic of China; <sup>2</sup>Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Jiahong Yuan, Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, People's Republic of China, Email [jiuhongyuan2107@163.com](mailto:jiuhongyuan2107@163.com)

**Abstract:** The meaning of sleep has puzzled people for millennia. In modern society, short sleep duration is becoming a global problem. It has been established that short sleep duration can increase the risk of several diseases, such as cardiovascular and metabolic diseases. Currently, a growing body of research has revealed a possible link between sleep disorders and erectile dysfunction (ED). However, the mechanisms linking short sleep duration and ED are largely unknown. Thus, we provide a review of clinical trials and animal studies. In this review, we propose putative pathways connecting short sleep duration and ED, including neuroendocrine pathways and molecular mechanisms, aiming to pave the way for future research. Meanwhile, the assessment and improvement of sleep quality should be recommended in the diagnosis and treatment of ED patients.

**Keywords:** erectile dysfunction, molecular mechanisms, sleep disorder, short sleep duration, signaling pathway

## Introduction

Sleep is vital to life. As a mystery of biology, the roles of sleep have puzzled and intrigued people for millennia.<sup>1</sup> For adults, the recommended sleep duration is 7 to 9 hours, while short sleep duration is defined as habitual sleep time less than 6 hours.<sup>2</sup> Sleep disorders are divided into 7 major diagnostic sections based on International Classification of Sleep Disorders-3 (ICSD-3), including insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders and other sleep disorders.<sup>3</sup> Short sleep duration, as one of the most notable characteristics of sleep disorders and some psychiatric disorders, was received with concern in modern society.<sup>3,4</sup> Meanwhile, it is reported that sleep disorders with short sleep duration appear to have more severe manifestation than those with normal sleep duration.<sup>5,6</sup> Furthermore, it is estimated that the prevalence of short sleep duration has gradually increased, in which 29.1% of US adults reported short sleep duration in 2009, including the habitual short sleepers and those with medical conditions.<sup>7</sup> Although many issues remain unresolved, the association between short sleep duration and many negative health outcomes, such as cardiovascular diseases, metabolic diseases and inflammatory disorders, has been widely investigated.<sup>8,9</sup> Furthermore, several studies have hinted that short sleep may be associated with men's health and sexual function.<sup>10,11</sup>

Erectile dysfunction (ED) is defined as the inability to acquire or maintain penile erection for satisfactory sexual performance.<sup>12</sup> Although ED is not a fatal condition, it bothers a large proportion of males around the world.<sup>13,14</sup> It is suggested that more than 80% of patients with ED have organic etiologies, including vascular, neurological and endocrine factors.<sup>12</sup> However, ED still involves the psychological component, especially in younger males.<sup>15</sup> Thus, it must be pointed out that previous psychological problems and the disturbance of psychosocial process, such as sleep homeostasis, may be involved in the pathophysiology of ED. Similarly, the etiology and pathophysiology of sleep disorders are thought to be associated with a variety of elements and medical conditions.<sup>16</sup> Although ED and sleep disorders are prevalent in modern society, the mainstream in this field almost universally focuses on the relationship between sleep-related breathing disorders

and ED.<sup>17,18</sup> Therefore, current data is not enough to interpret the effects of non-apnea sleep disorders with short sleep duration on erectile function.

Actually, available evidence indicates that short sleep duration might have a negative influence on erectile function.<sup>19,20</sup> However, ED can be either the consequence or the cause of short sleep. Due to the absence of intermediate mechanisms, it is difficult to prove a causal link between short sleep duration and ED. For example, short sleep duration and ED may influence each other via complex interactions or coexist independently in an individual patient. Even so, several pathophysiological mechanisms have been proposed to link sleep duration and medical conditions in recent years.<sup>21,22</sup> Moreover, causal associations of short sleep duration with various diseases seem to dominate in current studies.<sup>8,23</sup> Thus, we reviewed available data on sleep and erection (Table 1) and proposed putative mechanisms underlying causal associations of short sleep duration with ED, in order to facilitate further studies to elucidate the causal link between short sleep duration and ED.

**Table 1** Studies Linking Sleep Duration and Erectile Dysfunction in Humans

References	Cases	Study Objectives	Primary Outcomes	Results
Wu X et al <sup>69</sup>	179	The relationship between sleep quality and ED.	IIEF-5, GAD-7, PHQ-9, PSQI and sleep parameters	Sleep parameters are significantly associated with ED, poor sleep may increase the possibility of ED.
Keller J et al <sup>73</sup>	129	The simultaneous roles of HPA axis, symptoms and HPA genetic variation in cognitive performance.	NR3C1 (GR) and NR3C2 (MR) SNPs	HPA axis activity and genetic variation can predict cognition in depressed subjects.
Abell JG et al <sup>74</sup>	3314	The association of short sleep duration with the diurnal release of cortisol.	Cortisol	Recurrent sleep problems are associated with adverse salivary cortisol patterns throughout the day.
Kumari M et al <sup>75</sup>	2751	The association of short sleep duration and with the cortisol secretion across the day.	Cortisol	Short sleep duration influences cortisol secretion and duration was associated with cortisol awakening response.
von Treuer K et al <sup>76</sup>	9	The levels of cortisol, before, during, and, after one night of sleep deprivation.	Melatonin, cortisol, prolactin, and TSH	Cortisol was significantly higher on the sleep deprivation night.
Leproult R et al <sup>104</sup>	10	The effect of 1 week of sleep restriction on testosterone and cortisol levels.	Cortisol and testosterone	Testosterone levels were lower after sleep restriction than in the rested condition; Daytime cortisol profiles were similar under both conditions.
Kobori Y et al <sup>81</sup>	105	The relationship between sexual function and testosterone and cortisol.	IIEF-5, cortisol and testosterone	The cortisol showed negative correlations with sexual function.
Castro-Diehl C et al <sup>82</sup>	527	The associations of short sleep duration with markers of autonomic tone.	HR and HRV	Short sleep duration was associated with autonomic tone, indicating lower levels of parasympathetic tone and higher levels of sympathetic tone.
Jarrin DC et al <sup>84</sup>	180	The difference of cardiovascular function between patients with short sleep duration and normal sleep duration.	HR and HRV	Short sleepers exhibited significantly dampened parasympathetic activation and increased sympathovagal imbalance compared with normal sleepers.

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Table 1 (Continued).

References	Cases	Study Objectives	Primary Outcomes	Results
Arnal PJ et al <sup>86</sup>	14	The effects of sleep on testosterone, cortisol, prolactin and catecholamines.	Testosterone, cortisol, prolactin and catecholamines	Sleep deprivation was associated with decreased circulating testosterone, cortisol and prolactin; Six nights of sleep extension is insufficient to recover the concentrations of testosterone and cortisol after sleep deprivation.
Lee JY et al <sup>88</sup>	220	The alteration of autonomic activity in patients suffering from ED.	IIEF, HR and HRV	ED Patients showed different HRV parameters compared with healthy controls.
Cunningham GR et al <sup>103</sup>	6	The effects of testosterone replacement on sleep-related erections in patients with hypogonadism.	SREs and serum sex steroid	SREs increase in response to testosterone replacement.
Hirshkowitz M et al <sup>102</sup>	10	The association between sleep-related erections and testosterone.	SREs	Androgen reduction impairs the sleep-related erections, but does not eliminate them in healthy young men after a 12-week trial.
Bain AR et al <sup>110</sup>	30	The association between insufficient sleep and impaired NO-mediated vasodilation.	Forearm blood flow	Short sleep duration is associated with endothelial-dependent vasodilator dysfunction.
Calvin AD et al <sup>111</sup>	16	The effect of sleep restriction on endothelial function in healthy people	Flow-mediated vasodilation	Partial sleep restriction leads to impaired endothelial function in healthy people.
Weil BR et al <sup>115</sup>	80	ET-1 mediated vasoconstriction is greater in short sleepers compared with normal sleepers.	Forearm blood flow	Endothelin-1 mediated vasoconstriction is elevated in adults with short sleep duration
Stockelman KA et al <sup>116</sup>	36	Regular aerobic exercise would improve endothelial vasodilation in adults with short sleep duration.	Forearm blood flow	Short sleep duration is associated with endothelial dysfunction mediated by diminished NO signaling and increased ET-1 vasoconstriction.
Dzierzewski JM et al <sup>120</sup>	135	The relationship between sleep duration, inflammatory markers, and general cognitive functioning.	PSQI and inflammatory markers	Sleep duration moderates the association between inflammation and cognitive functioning.
Wright KP Jr et al <sup>125</sup>	17	The effects of acute sleep deprivation on inflammatory markers and cortisol levels.	Cortisol and inflammatory markers	Sleep deprivation and chronic circadian misalignment modulate the levels of cortisol, and chronic circadian misalignment increases plasma levels of inflammatory markers.
Irwin MR et al <sup>126</sup>	30	The effects of sleep deprivation on inflammatory factors.	IL-6 and TNF- $\alpha$	Sleep deprivation induces the functional alteration of the monocyte in pro-inflammatory cytokine response, and drives cellular immune activation.
Tobaldini E et al <sup>127</sup>	15	Acute sleep deprivation could alter the autonomic and immune response.	Hormones and inflammatory cytokines	Sleep deprivation affects autonomic response and immune modulation independent of the activity of the HPA axis.
Vgontzas AN et al <sup>128</sup>	8	An overall reduced secretion of IL-6 would be associated with a better sleep.	IL-6	Sleep deprivation changes the temporal secretion pattern of circadian IL-6 and increases IL-6 secretion in daytime.

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**Table I** (Continued).

References	Cases	Study Objectives	Primary Outcomes	Results
Dolsen MR et al <sup>129</sup>	165	The associations of inflammatory markers with sleep duration, circadian preference, and health domain.	Inflammatory markers, health domain change, sleep duration and circadian preference	Sleep duration and circadian dysfunction are related to the levels of inflammatory markers and health domain.
Elmenhorst D et al <sup>140</sup>	22	Prolonged wakefulness alters ADORA1 availability in the human brain.	Equilibrium total DVt and BP2	Higher expression of ADORA1 in the human brain after sleep deprivation were demonstrated. ADORA1 appears to be a potential agent in regulation of sleep homeostasis besides the adenosine itself.
Rétey JV et al <sup>145</sup>	119	The function of adenosine and ADA in human sleep homeostasis.	The distribution of genotypes of the ADA and ADORA2A	Adenosine have a direct role in regulation of sleep homeostasis, and the genetic polymorphism of adenosinergic system may lead to the interindividual variation in electrical activity of brain during wakefulness and sleep.
Nilsson EK et al <sup>153</sup>	16	The effects of sleep deprivation on DNA methylation.	DNA methylation profiling	Two specific signaling pathways, the Notch and Wnt signaling pathways, were epigenetically affected by total sleep deprivation.
Huang H et al <sup>159</sup>	796	The relationship between DNA methylation and sleep duration.	Epigenome-wide methylation analysis	Short sleep duration may be associated with significant differential methylation in CpG sites, and NPY appears to be related to the convergence arising in the pathways affecting sleep.

**Abbreviations:** ED, Erectile dysfunction; IIEF, International index of erectile function; GAD-7, General Anxiety Disorder-7 scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; HR, Heart rate; HRV, Heart rate variability; SREs, Sleep-related erections; PET, Positron emission tomography; DVt, Distribution volume; BP2, Binding potential; HPA, Hypothalamic–pituitary–adrenal; ET-1, Endothelin-1; ETA receptor, Endothelin A receptor; ACh, Acetylcholine; NO, Nitric oxide; IL-6, Interleukin-6; TSH, Thyroid stimulating hormone; TNF- $\alpha$ , Tumor necrosis factor- $\alpha$ ; ADA, Adenosine deaminase; ADORA1, Adenosine receptor A1; ADORA2A, Adenosine receptor A2A; DNA, Deoxyribonucleic acid; CpG, Cytosine-phosphate-guanine; GR, Glucocorticoid receptor; MR, Mineralocorticoid receptor; SNP, Single-nucleotide polymorphism.

## Sleep

### Normal Sleep

Sleep is a reversible natural behavior characterized by loss of consciousness, insensitivity toward stimuli, and inhibition of voluntary movements, which can be assessed by physiological, cellular, molecular and genetic levels.<sup>24</sup> Sleep, in both animals and humans, is investigated in the laboratory by recording the activity of cortical neurons, eyes, and muscles using polysomnography (PSG).<sup>1</sup> Meanwhile, sleep is regarded as having many neural functions, such as promoting physiological homeostasis in the brain and maintaining normal mood and cognition.<sup>25</sup> With prolonged wakefulness, the duration and intensity of sleep are increasing, indicating that sleep might be modulated through the sleep homeostasis.<sup>26</sup> Moreover, the circadian system is another component that regulates the timing of sleep independent of prior wakefulness.<sup>27</sup> In mammals, the circadian clock is coordinated by the suprachiasmatic nucleus (SCN) and is responsible for synchronizing circadian rhythm on several body functions and behaviors including sleep and wake.<sup>27,28</sup> Therefore, circadian and homeostatic components play an important role in the regulation of sleep.

### Hypothalamic–Pituitary–Adrenal Axis and Autonomic Nervous System

Sleep has a regulatory effect on the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS).<sup>29</sup> Different from sleep-related breathing disorders, the exact mechanisms of non-apnea sleep disorders affecting health have not been elucidated. It is reported that short sleep duration could result in hyperarousal characterized by a high level of physiological arousal both in wakefulness and sleep.<sup>30</sup> In particular, patients with short sleep always have

increased activity of the HPA axis and imbalance of ANS.<sup>29,31</sup> Additionally, short sleep is thought to be not only a phenotype of some sleep disorders but a causal risk factor for several diseases.<sup>32</sup>

The HPA axis linking to the circadian rhythm of sleep is primarily regulated by the circadian oscillator.<sup>21</sup> Generally, sleep could inhibit the activity of the HPA axis, and increased HPA axis activity can result in the hyper-arousal and sleep disturbance.<sup>33</sup> The increased plasma concentrations of adrenocorticotrophic hormone (ACTH) and cortisol were found in healthy subjects after one night of sleep deprivation, indicating the nervous hyper-arousal.<sup>34</sup> Moreover, as a shortened sleep in the experimental setting, sleep deprivation in animal models also leads to the increased secretion of inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and recovery sleep following sleep deprivation seems to inhibit these inflammatory cytokines which might be potential mediators of sleepiness.<sup>35,36</sup> Accordingly, the interactions between the HPA axis and inflammatory cytokines might be important to sleep regulation. At the same time, overactivity of the HPA axis could be considered as a potential pathway connecting short sleep and conditions.

The relationship between sleep and ANS is bidirectional. The activity of ANS is influenced by sleep, and changes in different stages of sleep.<sup>37</sup> In all, the neuronal populations associated with the transition of sleep stages have close ties with the nervous area controlling the cardiovascular system.<sup>38</sup> During normal sleep, the heart rate and blood pressure increase at the rapid eye movement (REM) stage and drop at the non-REM sleep stage, demonstrating the oscillation of ANS activity.<sup>39</sup> It is believed that patients with sleep disorders are susceptible to autonomic dysfunction, and most of them have increased sympathetic activity with higher levels of circulating catecholamine and inflammatory markers.<sup>40</sup> Meanwhile, several sleep disorders characterized by short sleep duration might result in unbalancing of ANS activity.<sup>41</sup> Taken together, the abnormal HPA axis and imbalanced ANS may be the main connection link short sleep and other diseases including ED, and the signaling pathway between short sleep duration and ED is complicated and extensive.

## Penile Erection and ED

Penile erection is a complicated physiological process. Generally, sexual stimulation activates the erectile tissue through the non-adrenergic non-cholinergic (NANC) fibers and parasympathetic cholinergic fibers, resulting in the activation of neural nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS), and subsequently release of nitric oxide (NO).<sup>12</sup> NO activates guanylyl cyclase (GC) following entering corpus cavernosum smooth muscle cells (CCSMC), and increases the cyclic guanosine monophosphate (cGMP) level in the cytoplasm, resulting in the decreased intracellular levels of calcium, the relaxation of CCSMC and penile erection. Meanwhile, cGMP could be hydrolyzed by phosphodiesterase (PDE) in CCSMC, leading to the increase of calcium in the cytoplasm and a flaccid penis.<sup>12,42</sup> There are 13 kinds of PDE in corpus cavernosum of human.<sup>43</sup> Among them, the higher expression of PDE5 in corpus cavernosum has been established, and PDE5 inhibitors (PDE5Is) have been widely applied as a therapeutic revolution in the management of ED.<sup>44</sup>

On the contrary, the flaccidity of the penis is maintained by chronic contraction of CCSMC.<sup>45</sup> The molecular mechanism of penile flaccidity is mainly regulated by noradrenaline (NA), endothelin-1 (ET-1), and angiotensin II (Ang-II) signaling, which triggers an increase in intracellular calcium and thereby results in the contraction of CCSMC via the phosphorylation of myosin light chain (MLC).<sup>42,45</sup> However, the contraction of smooth muscle is not paralleled with the levels of intracellular calcium and the phosphorylation of MLC, suggesting the existence of signal pathway which inhibits the smooth muscle relaxation independent of NO.<sup>46</sup> Ras homolog gene family member A (RhoA) is a small GTPase that can activate Rho-associated coiled-coil containing kinase (ROCK). ROCK deactivates the myosin light-chain phosphatase (MLCP) by phosphorylating myosin phosphatase target subunit 1 (MYPT1), or directly phosphorylates the myosin light chain 2 (MLC2), promoting the smooth muscle contraction and penile flaccidity, which is also known as the calcium-sensitized pathway.<sup>47,48</sup>

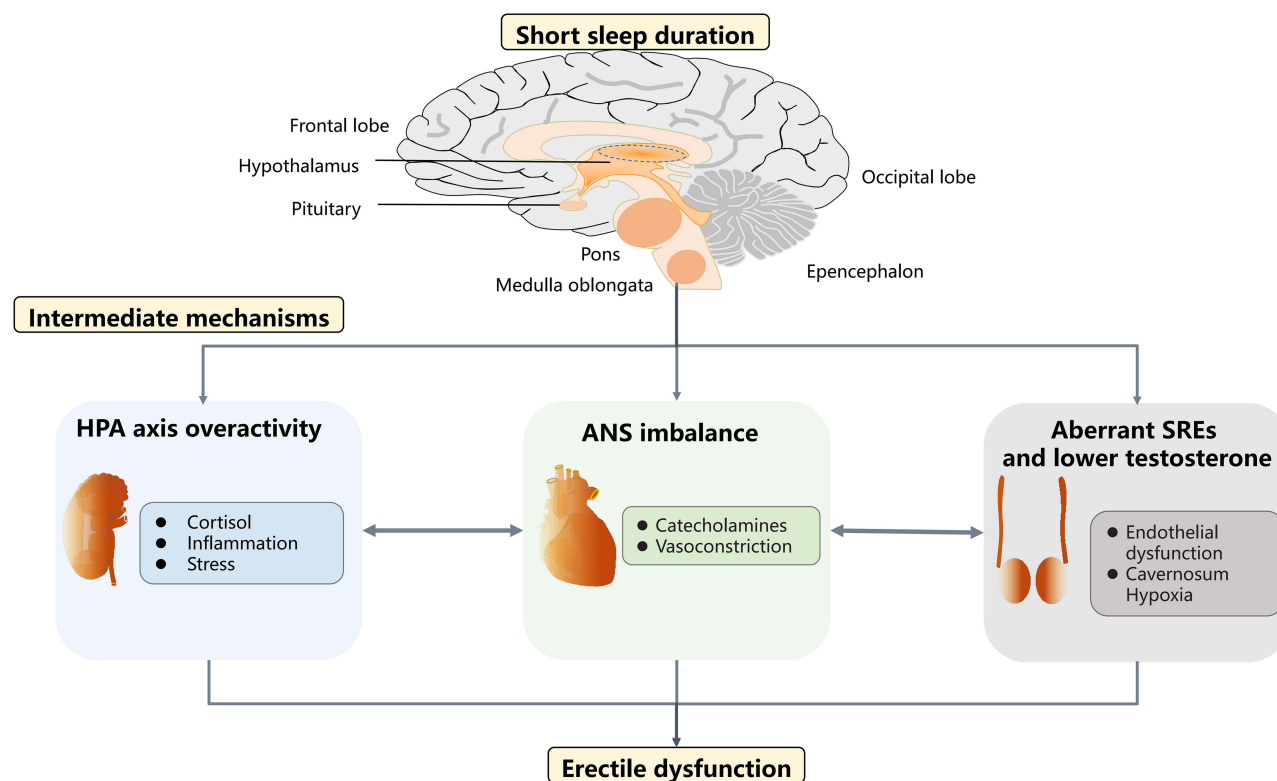
On the other hand, noradrenaline (NA) released from adrenergic nerve binds the adrenergic receptors (ADRs) in corpus cavernosum and leads to a contraction which involves the influx of calcium in CCSMC and calcium-sensitized pathway.<sup>49</sup> It has been demonstrated that penile erection in humans was accompanied by a remarkable decrease of NA in cavernous blood.<sup>50</sup> Meanwhile, current evidence supports the viewpoint that post-synaptic adrenergic receptor  $\alpha 1$  (ADR $\alpha 1$ ) in smooth muscle may play a leading role in contraction.<sup>51</sup> Existing data have demonstrated the potential effect of adenosine in penile erection, priapism, and ED.<sup>52</sup> The role of adenosine is played through its binding to specific

G protein-coupled receptors, including A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>.<sup>53</sup> Among them, adenosine receptor (ADOR) A<sub>2B</sub> appears to be required for vasodilation and erection via cAMP and cGMP induction.<sup>54</sup> In line with previous studies, it was reported that adenosine-induced vasodilation is also mediated through ADOR A<sub>2A</sub> signaling, conversely, ADOR A<sub>1</sub> signaling has an effect on vascular tone regulation.<sup>55</sup> Moreover, the regulation of penile erection has close links with many other agents and signaling pathways, including endothelins-1 (ET-1), TNF- $\alpha$  and reactive oxygen species (ROS).<sup>56,57</sup>

In short, the regulation of normal erectile function is a sophisticated balance of molecular mechanisms and multi-factor process, in which potential risk factors might cause an imbalance and trigger ED (Figure 1). Meanwhile, spinal and central nervous regulation of the penile erection involves various molecules, such as serotonin, dopamine, oxytocin and many peptides. However, most of them are only partly known. Thus, ED is a common but multidimensional psychosomatic disorder and psychological and central nervous components or pathways should not be overlooked.

## Short Sleep Duration and ED

Short sleep duration might be associated with social elements, including but not limited to shift work, intense work mission or unhealthy lifestyles in modern society.<sup>58</sup> Meanwhile, short sleep duration has been demonstrated to be related to a large group of disorders, such as diabetes, hypertension, major depressive disorder, and other morbidities.<sup>59,60</sup> Actually, the relationship between several sleep disorders and ED has been revealed by previous studies.<sup>61,62</sup> However, most of these studies focus on the sleep-related breathing disorders characterized by hypoxaemia, such as obstructive sleep apnea (OSA).<sup>62,63</sup> Actually, short sleep duration as an important phenotype of sleep disorders should be paid more attention. Thus, despite the connection between short sleep duration and ED is mainly based on some circumstantial evidence, it is necessary to explore the putative links between them.



**Figure 1** Putative mechanisms linking short sleep duration and erectile dysfunction. Short sleep duration caused by sleep disorders or lifestyle might provoke the over-activity of the HPA axis, the imbalance of ANS, aberrant SREs and low levels of testosterone. These intermediate mechanisms could lead to unwanted effects on penile erection through varied downstream molecular signaling, including but not limited to endothelial dysfunction, excessive vasoconstriction, inflammation and hypoxia.

**Abbreviations:** HPA axis: Hypothalamic-pituitary-adrenal axis; ANS: Autonomic nervous system; SREs: Sleep-related erections; NPY: Neuropeptide Y.

Shift work, an underlying cause of short sleeper, is a prevalent working schedule in the world, which involves about 20% of the labor force worldwide.<sup>64</sup> Common schedules in shift work comprise standard and non-standard formats, including morning, night, evening shifts, and irregular rotation occurring outside of a standard time in the workday.<sup>65</sup> Similar to sleep disorders, shift work might result in the circadian disturbance, daytime dysfunction, acute sleep loss and short sleep.<sup>64</sup> Although the original researches demonstrated mixed results, shift work might be a risk factor for cancer, stroke and cardio-metabolic diseases.<sup>66</sup> It is suggested that men occupied in shift work have worse penile erection, especially those work night shifts, which may attribute to short sleep and disrupted circadian rhythm.<sup>67</sup> Moreover, men working non-standard shifts are susceptible to short sleep duration and shift work sleep disorders, which are associated with frequent hypogonadal symptoms and poor erectile function.<sup>68</sup> These studies add the growing evidence that sleep is important to erectile function. However, there are some inevitable confounding factors existed in shift work comparing with the short sleep duration, and the situation of the working shift seems to be not completely same with common sleep disorders.

Recently, a prospective cohort study investigated the association between sleep parameters and ED using both questionnaires and sleep monitors, demonstrating that sleep duration, including total sleep duration and deep sleep duration, is significantly different between healthy subjects and ED patients who have significantly shorter sleep time.<sup>69</sup> Meanwhile, some previous studies seem to provide consistent evidence. A longitudinal population-based cohort study conducted a longer follow-up to participants with sleep disorders and found that those with short sleep duration had the increased risk of developing ED after accounting for age and comorbidities.<sup>19</sup> Meanwhile, an investigation performed via Amazon's Mechanical Turk (MTurk) showed a significant relationship between insomnia and sexual function in males after adjustment for other variables about anxious and depressive symptoms.<sup>70</sup> It is reasonable to infer that short sleep might participate in the process of ED among insomnia patients. Similarly, a cross-sectional designed pilot study using mobile health platforms showed an underlying connection between poor sleep quality and ED.<sup>71</sup> In addition, a subgroup analysis of older adults suggested that self-reported sleep duration might be related to sexual dysfunction.<sup>11</sup>

In recent years, although mixed results were concluded usually, more and more studies provided clues that short sleep duration might be a risk factor for ED.<sup>69,72</sup> However, the cross-sectional nature of those studies restrict the establishment of a causal relationship, and impede the development of further research. Accordingly, new insights from experimental evidence involving potential molecular mechanisms are needed.

## Putative Pathways Linking Short Sleep Duration and ED

### Hypothalamic–Pituitary–Adrenal Axis

The HPA axis consists of stimulating and inhibitory loops involving the pituitary and adrenal glands, which regulate the secretion of glucocorticoids, such as the cortisol released from the adrenal cortex.<sup>73</sup> It is pointed out that short sleep duration, recurrent sleep disturbance and chronic insomnia symptoms are associated with cortisol-secreting patterns throughout the day.<sup>74,75</sup> In humans, short sleep duration induced by sleep deprivation or restriction results in some higher levels of cortisol with the circadian variation.<sup>76</sup> Although mixed results were concluded in studies on sleep-deprived animal models, sleep deprivation procedures have a tendency to affect the levels of corticosterone of rodents.<sup>29,77</sup> In short, the changes of cortisol secretion in short sleepers may reflect the dysfunction of the HPA axis, and have adverse effects on erectile function.

Actually, cortisol plays an important role in maintaining the tone of vascular smooth muscles (VSMCs) via increasing vascular responses to vasoconstrictors.<sup>78</sup> It is proven that sustained elevation of serum cortisol facilitates the contraction of coronary VSMCs by enhancing RhoA/ROCK signaling pathway.<sup>79</sup> Conversely, adrenalectomized animal models show decreased responsiveness to the administration of vasoactive agents, which are similar to Addisonian in humans.<sup>80</sup> With regard to sexual function, it has been reported that the levels of serum cortisol are negatively correlated with some domains of the International Index of Erectile Function-5 (IIEF-5) score and males with high levels of serum cortisol might be vulnerable to ED.<sup>81</sup> Although this was previously interpreted as a stress-related outcome due to the relationship between the HPA axis and stress, we hold the opinion that the disordered the HPA axis might be an important cog

between sleep disorders and ED (Figure 1). Meanwhile, short sleep, stress and disordered HPA axis may coexist inevitably and have the complex interplay in sleep-related conditions.

## Autonomic Nervous System

The ANS imbalance as a potential risk factor for various diseases has been widely investigated.<sup>21</sup> Short sleep duration is found to be involved changes in the ANS characterized by lower levels of parasympathetic tone and global sympathetic overactivity.<sup>82</sup> Meanwhile, most data reveal that short sleepers are susceptible to have increased sympathetic activity, which could be carried into the daytime, as well as altered autonomic function following short sleep duration might result in serious repercussions for well-being and health condition.<sup>83,84</sup> On the other hand, short sleep duration always co-occurs with the increased levels of circulating blood catecholamines, which might mediate some adverse effects of sleep disorders on erectile function.<sup>85,86</sup> It is established that noradrenaline could regulate the influx of  $\text{Ca}^{2+}$  into smooth muscle cells and inhibits the penile erection via  $\alpha$ -adrenergic receptors.<sup>87</sup> Therefore, the autonomic imbalance towards sympathetic activity might take part in the association of short sleep with ED. However, the parasympathetic nervous system also plays an important role in regulation of erectile function, which seems to be under-researched in the context of autonomic dysregulation with excessive parasympathetic activity.

It is demonstrated that ED patients exhibit different heart rate variation (HRV) parameters compared with controls, suggesting that not only sympathetic but also general imbalance of the ANS might be an underlying cause of ED.<sup>88</sup> Meanwhile, patients with some diseases that directly lead to collective autonomic dysfunction and neuropathy, such as primary autonomic failure and diabetes, are prone to ED.<sup>89</sup> Sometimes autonomic imbalance is implicated in higher levels of both the parasympathetic and sympathetic system, which is inconsistent with the fact that sexual stimulation results in the penile tumescence through release of NO from parasympathetic cholinergic fibers.<sup>40</sup> However, it should be noted that parasympathetic activity is different from the single effect of cholinergic transmitters, and other neurotransmitters may be co-released from nervous terminals.<sup>90</sup> Actually, co-released transmitters from imbalanced global autonomic function might produce mixed effects on the regulation of erectile function, which might become a risk factor for ED. Given the regulation of ANS is under the control of the central nervous system, we hypothesized that putative pathways linking sleep disorders and ED might involve in the autonomic dysregulation with sympathetic or parasympathetic over-activity (Figure 1). Generally speaking, the evaluation of autonomic function, such as HRV analysis, can provide valuable information for the diagnosis of patients with both sleep disorders and ED.

Dopamine as the main catecholamine in the central nervous system is considered to be involved in sexual function.<sup>91</sup> It is suggested that dopamine might participate in the somatic and autonomic regulation of penile erection, which has been illustrated through animal experiments.<sup>92</sup> The involvement of dopamine in erectile function has been proven by previous studies in which penile erection could be induced using dopamine receptor agonists.<sup>93</sup> Moreover, impaired dopaminergic neurons and dopamine D2 receptor signaling at the nucleus accumbens might result in the inhibition of erectile function and sexual arousal.<sup>94</sup> In the periphery, however, the role of dopamine receptors in the regulation of erectile function is less certain, which still requires further research.

## Sleep-Related Erection and Testosterone

Sleep-related erections (SREs) are undesirable penile erections that appear cyclically during REM sleep in normal healthy men from infancy to old age.<sup>95</sup> SREs testing as a part of polysomnographic technique in sleep medicine has been used in the evaluation and classification of ED for a long time.<sup>96</sup> Despite the well-researched mechanisms of REM sleep, the exact mechanism of SREs remains unclear. On the other hand, impaired SREs might be an indicator of some medical conditions at the early stage.<sup>95,97</sup> In this regard, the impaired SREs have been observed in patients with diabetes, renal disease, hypertension, hypogonadism and some sleep disorders.<sup>98</sup> Meanwhile, it is reported that SREs are diminished in those with major depressive disorders characterized by REM sleep alterations.<sup>98</sup> Significantly, an abnormal extension of SREs, so-called sleep-related painful erection (SRPE), characterized by penile pain during REM sleep could cause sleep fragmentation or sleep deprivation, which is a rare and poorly recognized condition.<sup>99</sup> However, the sleep-related painful erection seems to be a reason rather than a consequence of poor sleep. Together with these findings, we hypothesize that the short sleep duration might reduce the frequency of REM sleep and SREs. Furthermore, decreased SREs may lead to

the insufficiency of arterial inflow, and the accumulation of metabolite in erectile tissue, which induces the hypoxemic and acidotic damage of cavernosum, and subsequently impairs the erectile function.

It has been established that androgens, especially testosterone, could influence erectile function via both central and peripheral effects, especially in the maintenance of libido.<sup>100</sup> Reduced levels of testosterone in males always lead to a decline in sexual interest and erectile function, while administration of testosterone recovers libido and sexual activity in hypogonadal males.<sup>101</sup> Meanwhile, testosterone as an important factor associated with SREs has been investigated in male sexual function.<sup>102</sup> It is demonstrated that reduced levels of androgen via administration of luteinizing-hormone releasing-hormone agonists in young adult males do not eliminate but adversely affect the SREs, and the cessation of testosterone replacement in hypogonadal males triggers the similar descending of SREs measurements.<sup>102,103</sup> Moreover, sleep restriction and sleep fragmentation are associated with lower levels of testosterone, which might be explained by the fact that the major secretion of daily testosterone in males appears in sleep.<sup>86,104</sup> Thus, it is reasonable to assume that short sleep can directly reduce SREs, not just because of disturbed REM sleep, but also because of decreased testosterone levels. Taken together, we speculate that reduced testosterone and impaired SREs might be also involved in the connection between short sleep and ED (Figure 1).

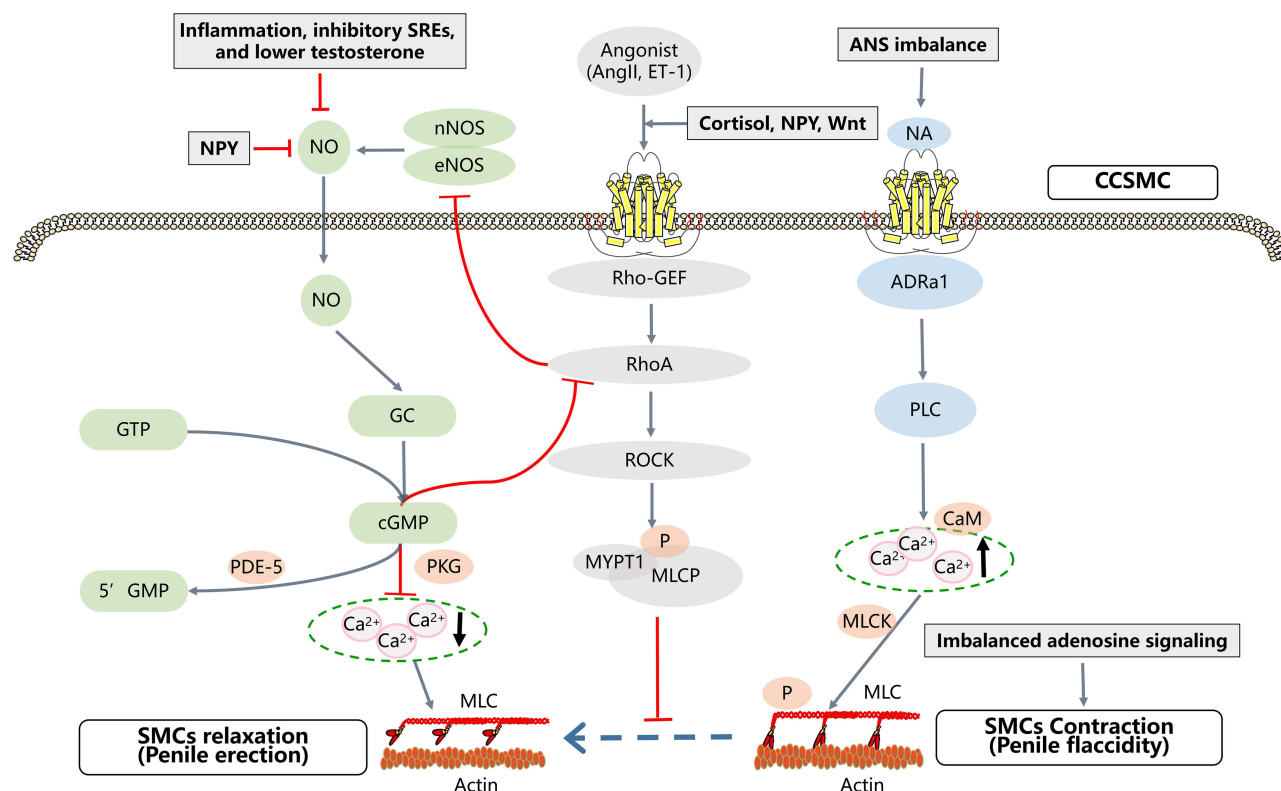
## Possible Molecular Mechanisms Between Short Sleep Duration and ED Endothelial Dysfunction

Current evidence suggests that short sleep duration might be implicated with the risk of cardiovascular diseases, and sufficient sleep duration has the role of protection for cardiovascular health.<sup>105</sup> Previous studies based on animal models have manifested the consistent results that sleep deprivation is involved in deteriorated cardiovascular function.<sup>106,107</sup> Meanwhile, several factors are associated with the maintenance of vascular homeostasis, including NO, ET-1 and angiotensin signaling, which are also important for erectile function. It is demonstrated that sleep deprivation could induce endothelial dysfunction, increased blood pressure and oxidative stress in experimental models.<sup>108</sup> Meanwhile, it is reported that sleep deprivation led to impaired erectile dysfunction in rats through down-regulation of NO/cGMP signaling, which was abolished by supplementation of glutamine.<sup>109</sup>

In humans, short sleep duration damages the endothelial function through diminishing NO bioavailability and inhibiting the NO-cGMP pathway, which is measured by a reduction in forearm blood flow.<sup>110,111</sup> Similarly, the total sleep deprivation seems to drive an attenuation in endothelial-dependent vasodilation, and this endothelial dysfunction is dependent on altered NO signaling and independent of sympathetic signaling.<sup>112</sup> However, ED patients with some psychiatric disorders characterized by short sleep duration, such as major depression disorders or post-trauma stress disorders, always show poor response to PDE5I therapy.<sup>113,114</sup> This inconsistency suggests that other signaling pathways may concurrently participate in the pathophysiology of ED in short sleepers.

It is reported that adults with short sleep duration may have higher levels of ET-1 that is associated with increased vascular tone and cardiovascular risk.<sup>115</sup> On the contrary, non-pharmacological interventions, such as regular aerobic exercise, can reduce the levels of ET-1 and improve endothelial vasodilation in subjects with habitual insufficient sleep.<sup>116</sup> Meanwhile, the circadian of angiotensin (Ang)-converting enzyme (ACE) has been demonstrated in subjects with normal blood pressure and uncomplicated hypertension and could be modified through sleep deprivation.<sup>117,118</sup> The circulatory Ang II and tissue angiotensin type-1 (AT1) receptor expression have revealed circadian rhythmicity, indicating the intimate links between sleep and renin-angiotensin-aldosterone system (RAAS).<sup>119</sup> Interestingly, Ang II and ET-1 also are agonists in corpus cavernosum, activating the RhoA/ROCK signaling pathway that inhibits the penile erection. Furthermore, several inflammatory markers including intercellular adhesion molecule 1 (sICAM-1), interleukin-6 (IL-6), C-reactive protein (CRP) and TNF- $\alpha$  may mediate the association between sleep duration and endothelial function.<sup>120,121</sup>

As discussed above, endothelial dysfunction may be the probable pathway linking short sleep duration and ED (Figure 1 and 2); however, many factors are involved in endothelial homeostasis related to erectile function, highlighting a complex relationship between sleep duration and endothelial-dependent erection. Consequently, this may support the above-mentioned unsatisfactory treatment of PDE5I in patients with short sleep duration.



**Figure 2** Principal molecular mechanisms of penile erection, and possible targets by which short sleep duration impairing the erectile function. The molecular mechanisms of penile erection involve a balance of signaling between relaxation and contraction of CCSMC. Generally, the NOS-NO-cGMP signaling pathway is considered as the most important mechanism of penile erection, involving the PKG activation and decreased intracellular levels of calcium. On the contrary, penile flaccidity is mainly regulated by the NA, ET-1, and AngII signaling, involving increasing levels of intracellular calcium. Meanwhile, RhoA/ROCK signaling known as the calcium-sensitized pathway, and NA-ADRA1 signaling are crucial to regulate the chronic contraction of CCSMC. In all, ROCK deactivates the MLCP by phosphorylating MYPT1, or directly phosphorylates the MLC2, promoting the contraction of CCSMC. Additionally, the adenosine signaling pathway also has a role in the regulation of erectile function. In short, the short sleep duration might break the balance between the signaling pathways associated with penile erection and flaccidity, resulting in ED.

**Abbreviations:** ED: Erectile dysfunction; HPA axis: Hypothalamic-pituitary-adrenal axis; ANS: Autonomic nervous system; SREs: Sleep-related erections; NPY: Neuropeptide Y; CCSMC: Corpus cavernosum smooth muscle cell; SMCs: smooth muscle cells; nNOS, Neuronal nitric oxide synthase; eNOS: Endothelial nitric oxide synthase; NO, Nitric oxide; NANC fibers: non-adrenergic non-cholinergic fibers; GC: Guanylyl cyclase; PKG: Protein kinase G; cGMP: Cyclic guanosine monophosphate; PDE: phosphodiesterase; NA: Noradrenaline; ET-1: Endothelin-1; Ang II: Angiotensin II; ADRa1: adrenergic receptor  $\alpha$ -1; RhoA: Ras homolog gene family member A; Rho-GEF: Rho guanine exchange factor; ROCK: Rho-associated coiled-coil containing kinase; MLC: Myosin light chain; MLCP: Myosin light-chain phosphatase; MYPT1: Myosin phosphatase target subunit 1; MLC2: myosin light-chain 2; MLCK: Myosin light-chain kinase; CaM: Calmodulin;

## Inflammation

Inflammation is considered as an important mechanism connecting the sleep and the development of various conditions.<sup>122,123</sup> Actually, there is a lot of evidence that poor sleep contributes to the increases of inflammatory markers.<sup>124,125</sup> Among them, shorter sleep duration was reportedly associated with higher levels of CRP.<sup>124</sup> Meanwhile, the sleep deprivation of a night might result in significantly increased monocyte production of IL-6 and TNF- $\alpha$  in the morning compared with normal sleep, which may be mediated by the nuclear factor kappa B (NF- $\kappa$ B) inflammatory signaling and hormone response pathways.<sup>126</sup> Moreover, an increased level of interferon  $\gamma$  (IFN- $\gamma$ ) has been observed in real-life models after a night of sleep deprivation with unchanged levels of TNF- $\alpha$ , interleukin-2 (IL-2) and interleukin-10 (IL-10).<sup>127</sup>

Although inconsistent data on inflammatory markers after sleep deprivation are reported in previous studies, several markers, such as IL-6 and CRP, appear to have more consistent results.<sup>124,128</sup> On the other hand, longitudinal analyses have indicated that effective intervention, such as recovery sleep, might decrease the levels of baseline inflammatory markers and health risk.<sup>129</sup> In the clinical setting, the IL-6 and CRP have been shown to be associated with vascular risk and coronary heart disease.<sup>130,131</sup> Meanwhile, IL-6 seems to mediate the vascular contraction through inhibiting the endothelium-dependent NO-cGMP pathway in animal models.<sup>132</sup>

In agreement with cardiovascular diseases, increased circulating levels of inflammatory cytokines are found to be associated with the presence and severity of ED.<sup>133</sup> Similar findings have been reported in studies on the molecular mechanisms between chronic pelvic pain syndrome (CPPS) and ED. Rat models of CPPS via experimental autoimmune prostatitis seem to have higher levels of serum inflammatory compounds, including IL-6, CRP and TNF- $\alpha$ , and have reduced eNOS expression in corpus cavernosum and impaired erectile function.<sup>134</sup> Furthermore, increased levels of IL-6 are found at 24 hours after the prostatectomy in clinical data, and the inhibition of IL-6 could attenuate ED in animal models of cavernous nerve dissection.<sup>135</sup> Accordingly, the systemic inflammatory state might be a plausible explanation for the relationship between short sleep and ED (Figure 1 and 2). Given the crosstalk between inflammation and endothelial dysfunction, it might be necessary in order to incorporate the inflammatory markers into the diagnostic work-up of patients with ED who suffered sleep problems, in order to pursue essential benefits from treatment.

## Adenosine

The neurotransmitter adenosine links neuronal activity, sleep, energy metabolism and penile erection.<sup>52,136</sup> Adenosine signaling may be a common pathway for several sleep factors, and adenosine A<sub>1</sub> receptor and adenosine A<sub>2A</sub> receptor are reportedly implicated in the regulation of sleep homeostasis through excitation of sleep active neurons.<sup>137</sup> In this regard, central and systemic delivery of adenosine could provoke sleepiness, while caffeine serving as antagonists to both adenosine A<sub>1</sub> and A<sub>2A</sub> receptors could counteract the sleepiness caused by adenosine signaling.<sup>137,138</sup> Moreover, adenosine concentration significantly increases in the basal forebrain, which might be a central area associated with the facilitation of recovery sleep following prolonged wakefulness or sleep deprivation.<sup>136,139</sup> Additionally, the up-regulation of adenosine A<sub>1</sub> receptor in cortical and subcortical regions after sleep deprivation has been shown in vivo evidence, suggesting that short sleep could result in alteration of gene transcription associated with the homeostatic sleep regulation and even other cellular functions.<sup>140</sup>

Similar to NO, adenosine characterized by potent vasodilation and short half-life has been demonstrated to relax the cavernosal smooth muscles and subsequently promote the penile erection.<sup>141</sup> Different cellular functions of adenosine receptors have been described. In all, adenosine receptors A<sub>1</sub> and A<sub>3</sub> coupling to adenylyl cyclase at the inhibitory G protein subunit (G $\alpha_i$ ) serve to decrease the intracellular cAMP, and adenosine receptors A<sub>2A</sub> and A<sub>2B</sub> coupling to adenylyl cyclase at the G protein stimulatory subunit (G $\alpha_s$ ) could increase the levels of intracellular cAMP.<sup>142</sup> Previous studies have identified the distinct roles of adenosine receptors in cavernosal smooth muscles utilizing four adenosine receptors-deficient mice administrated by different dosages of adenosine.<sup>54</sup> Among them, adenosine receptor A<sub>2B</sub> is required for adenosine signaling to induce penile erection, as well as adenosine receptor A<sub>1</sub> is enriched on neurons and its downstream signaling appears to reduce the NE release and facilitate penile erection.<sup>143</sup>

Several stressful factors, such as hypoxia, could increase extracellular adenosine, which is paralleled to the effects of sleep deprivation on the central nervous system.<sup>144</sup> Despite increased extracellular adenosine seems to be inconsistent with ED, it needs to be highlighted that the expression of adenosine receptors and adenosine deaminase (ADA) might play a major part in regulation of erectile function. Moreover, it is reported that the genetic variant of ADA might be correlated to reduced metabolism of adenosine during deep sleep.<sup>145</sup> Thus, we hypothesized that short sleep may break the balance between adenosine metabolism and adenosine receptor signaling, leading to impaired erectile function (Figure 2). From another perspective, short sleep duration may result in cavernosal hypoxemia through decreasing arterial oxygen during sleep via disturbing the sleep-related erections, which might induce the accumulation of adenosine and lower the affinity of adenosine receptor A<sub>2B</sub> to adenosine. Eventually, downstream signaling related to penile erection is suppressed.

## Wnt Proteins

In recent years, Wnt signaling pathway has become a fundamental growth control pathway, ranging from neoplasm to animal evolution. There are 19 Wnt genes in mammals, and mutated Wnt pathway components are thought to be implicated in various diseases.<sup>146</sup> The Wnt signaling pathway is commonly classified into  $\beta$ -catenin dependent and  $\beta$ -catenin independent pathways, which have various downstream signaling pathways.<sup>147</sup> Among them, RhoA/ROCK signaling plays a key role in  $\beta$ -catenin independent pathway and mediates pathophysiological mechanisms of several

Wnt-related diseases, such as hypertension.<sup>148</sup> In diabetic ED models, aberrant expression of Wnts in the corpus cavernosum has been identified, suggesting that Wnt signaling might contribute to the development of ED.<sup>149</sup> Meanwhile, the inhibition of Wnt signaling via Dickkopf3 (DKK3) could improve the erectile function in diabetic models through restoring the cavernous vascular integrity and endothelial function.<sup>150</sup> Hence, the Wnt pathway may represent a potential target in the management of ED.

It is reported that the disturbance of circadian rhythms could enhance the signaling of WNT/ $\beta$ -catenin pathway in autism spectrum disorder (ASD) characterized by sleep disorders.<sup>151</sup> Meanwhile, Wnt signaling pathway has been shown to be associated with clock gene brain and muscle Arnt-like 1 (Bmal1) in regulation of adipocyte development.<sup>152</sup> In gene set enrichment analysis, Wnt signaling pathways have been detected to be enriched in the distinctly methylated genes altered by total acute sleep deprivation in human subjects.<sup>153</sup> In short, WNT/ $\beta$ -catenin pathway might be involved the connection between short sleep duration and ED, and the downstream unwanted effects on erectile function may be mediated by the RhoA/ROCK pathway (Figure 2).

## Neuropeptide Y

Neuropeptide Y (NPY) consisting of 36 amino acids is co-released with noradrenaline (NA) from sympathetic nerve on electrical stimulation.<sup>154</sup> Except for human and pig bone marrow, many organs have been found to express NPY, including heart, liver, adrenal gland and urogenital tracts.<sup>155,156</sup> Among them, the adrenal medulla characterized by abundant sympathetic innervation is thought to be the major source of circulating NPY, which might be an important factor related to sleep regulation and homeostatic balance.<sup>156,157</sup> It is reported that chronic sleep deprivation serving as a stressor significantly increases NPY expression in the hypothalamus, which might mediate the connection between sleep disorders and various diseases.<sup>158</sup> Meanwhile, it is presumed that short sleep duration in humans might be associated with significant differential methylation in cytosine-phosphate-guanine (CpG) sites, and NPY appears to be related to the convergence arising in the pathways affecting sleep.<sup>159</sup> Moreover, NPY has been shown to ameliorate the hyperdynamic circulation in cirrhotic animal models through splanchnic vasoconstriction by activating RhoA/ROCK signaling and inhibiting NO signaling.<sup>160</sup>

Actually, NPY localized with sympathetic perivascular nerve is also distributed in erectile tissues around helicine arteries with a high density.<sup>161</sup> NPY has been found to have bidirectional effects on penile resistance arteries via different NPY receptors (Y-receptors), of which Y<sub>1</sub>/Y<sub>2</sub>-postsynaptic receptors are involved in the enhancement of noradrenaline vasoconstriction and Y<sub>2</sub>-presynaptic receptors associated with the inhibition of noradrenaline release.<sup>162</sup> Meanwhile, Y<sub>1</sub> receptor as a G protein-coupled receptor could strengthen the responses of small arteries to other vasoconstrictors through inhibiting the cAMP signaling and depolarizing the smooth muscles in arteries.<sup>163</sup> Additionally, a recent study indicates that the production of NPY is under the control of the autonomic nervous in osteocyte.<sup>164</sup> Thus, we believe that NPY signaling may intermediate the crosstalk between short sleep duration and ED, involving autonomic dysfunction and the RhoA/ROCK signaling pathway (Figure 1 and 2).

## Summary

Sleep problems have prompted much public concern around the world. Short sleep duration as a central feature of sleep disorders is significantly associated with many diseases and health risks. Although the assumption that short sleep duration may impair erectile function has long existed, the underlying mechanisms are inconclusive and require further elucidation. Current data from clinical studies and animal models appear to support the crosstalk between sleep duration and penile erection. However, the causal link between short sleep and ED is not validated. This review summarized possible mechanisms linking short sleep duration and ED and provided clues for future investigations in this field. In short, we hypothesize that short sleep duration may be an independent risk factor of ED for certain subgroups. Meanwhile, neuroendocrine systems, various molecular mechanisms and signaling pathways may participate in the process of ED in patients with short sleep duration, and the improvement sleep quality and habits may be conducive to the treatment of ED. However, the negative influence of sleep disorders on erectile function is complicated, and the role of short sleep duration is just a part of it, which is a key limitation of this review.

In the future, a clear understanding of the molecular mechanisms linking short sleep duration and impaired erectile function will be required based on clinical and experimental studies. Among them, detailed knowledge of central transmitters involves both sleep duration and penile erection will be important. At the same time, it should be noted that current pharmacotherapy for ED may be ineffective in dealing with the underlying motivators that suppress erectile function in males. More importantly, short sleep duration as a risk factor appears to be potentially modifiable and curative compared to vascular and nervous lesion. Thus, we hold the opinion that the assessment of sleep quality should be incorporated into the diagnostic work-up of ED, and the treatment options for ED patients with short sleep duration should comprise not only the PDE5Is but also the measures for improvement of sleep quality.

## Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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## Disclosure

The authors report no conflicts of interest in this work.

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