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PHYSIOLOGICAL REVIEW

Catechol-O-methyltransferase, dopamine, and sleep-wake regulation

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SUMMARY

Sleep and sleep disorders are complex and highly variable phenotypes regulated by many genes and environment. The catechol-O-methyltransferase (*COMT*) gene is an interesting candidate, being one of the major mammalian enzymes involved in the catabolism of catecholamines. The activity of COMT enzyme is genetically polymorphic due to a guanine-to-adenine transition at codon 158, resulting in a valine (Val) to methionine (Met) substitution. Individuals homozygous for the Val allele show higher COMT activity, and lower dopaminergic signaling in prefrontal cortex (PFC) than subjects homozygous for the Met allele. Since COMT has a crucial role in metabolising dopamine, it was suggested that the common functional polymorphism in the *COMT* gene impacts on cognitive function related to PFC, sleep-wake regulation, and potentially on sleep pathologies. The *COMT* Val158Met polymorphism may predict inter-individual differences in brain electroencephalography (EEG) alpha oscillations and recovery processes resulting from partial sleep loss in healthy individuals. The Val158Met polymorphism also exerts a sexual dimorphism and has a strong effect on objective daytime sleepiness in patients with narcolepsy-cataplexy. Since the COMT enzyme inactivates catecholamines, it was hypothesized that the response to stimulant drugs differs between *COMT* genotypes. Modafinil maintained executive functioning performance and vigilant attention throughout sleep deprivation in subjects with Val/Val genotype, but less in those with Met/Met genotype. Also, homozygous Met/Met patients with narcolepsy responded to lower doses of modafinil compared to Val/Val carriers. We review here the critical role of the common functional *COMT* gene polymorphism, COMT enzyme activity, and the prefrontal dopamine levels in the regulation of sleep and wakefulness in normal subjects, in narcolepsy and other sleep-related disorders, and its impact on the response to psychostimulants.

Introduction

Sleep and sleep disorders are complex and highly variable phenotypes regulated by many genes, gene interactions, environment, and gene-environment interactions [1,2]. Current heritability estimates of sleep phenotypes vary between 20 and 40% for habitual sleep duration, to over 90% for the spectral characteristics of the electroencephalography (EEG) in non-rapid eye movement (REM) sleep [3]. However, compared to other complex behaviors, human genetics of both normal and pathological sleep is only starting to be explored. No genome-wide association studies (GWAS), objectively investigating sleep with appropriate and stringent significance thresholds, are currently available. Nevertheless, evidence indicates that polymorphic variants in a number of candidate genes such as circadian locomotor output cycles kaput (*CLOCK*), period, adenosine deaminase, monoamine transporter families, and genes involved in the catabolism of monoamine neurotransmitters affect several characteristics of sleep-wake regulatory processes in both normal and pathological conditions [1,2].

Among the monoaminergic genes that may be involved in trait-like individual differences in sleep, the catechol-O-methyltransferase (*COMT*) gene is an interesting candidate, being one of the major enzymes of the metabolic degradation of catecholamines [4]. *COMT* catalyzes the transfer of a methyl group from S-adenosyl-methionine to a hydroxyl group on a catechol nucleus

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Abbreviations

ADHD	attention deficit hyperactivity disorder
BMI	body mass index
COMT	catechol-O-methyltransferase
CLOCK	circadian locomotor output cycles kaput
CSF	cerebrospinal fluid
DAT	dopamine active transporter
DA	dopamine
EDS	excessive daytime sleepiness
EEG	electroencephalography
ESS	Epworth sleepiness scale
F-DOPA	6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine
GWAS	genome-wide association study
NREM	non rapid eye movement
SNc	substantia nigra pars compacta
SWS	slow wave sleep
VPAG	ventral periaqueductal grey
VTA	ventral tegmental area
MAO-A	monoamine oxidase type A
Met	methionine
MSLT	multiple sleep latency test
PFC	prefrontal cortex
PD	Parkinson's disease
REM	rapid eye movement
RBD	rapid eye movement behavior disorder
SNP	single-nucleotide polymorphism
Val	valine

of major neurotransmitters such as dopamine, epinephrine, and norepinephrine [5]. The human *COMT* gene is located within the q11 band of chromosome 22. The *COMT* enzyme activity is genetically polymorphic in human red blood cells and liver, with a trimodal distribution of low, intermediate, and high level of activity. Segregation analysis from family studies demonstrated that the pattern of inheritance is consistent with the presence of autosomal co-dominant alleles. This polymorphism is mainly due to a 544 guanine-to-adenine transition at codon 158 of the *COMT* gene, resulting in a valine (Val) to methionine (Met) substitution (single-nucleotide polymorphism (SNP) *rs4680*) [6]. The two alleles can be identified by a PCR-based restriction fragment length polymorphism analysis using the restriction enzyme *NlaIII* that detects the digested (Met-M158 or L for low enzyme activity) vs. full length fragment (Val-V158 or H for high enzyme activity). The functional V158M is polymorphic in populations around the world, occurring in almost equal frequencies in Europe and North America with subjects with Met/Met, Val/Val and Met/Val genotype representing respectively 30%, 20% and 50% of the general population [7,8]. Homozygosity for M158 (LL genotype) leads to a three- to four-fold reduction in enzyme activity compared with homozygosity for V158 (HH genotype). Moreover, because the alleles are codominant, heterozygous individuals have an enzyme activity midway between homozygous individuals [9]. Other known, yet less studied, polymorphisms in the *COMT* gene (i.e., *rs2097603* located in the COMT promoter region, *rs737865* located in intron 1, and *rs6267* in exon 3) were reported and may also modify the enzyme activity [10]. A large human postmortem study investigated the effects of several SNPs within the *COMT* gene on mRNA expression and protein levels, and enzyme activity in prefrontal cortex (PFC) tissue that predominantly expresses the membrane-bound isoform of *COMT* [5]. The common V158M polymorphism significantly affected protein abundance and enzyme activity but not the mRNA expression level, suggesting that differences in post-transcriptional modifications resulting in protein integrity and/or stability account for the difference in enzyme activity between alleles. The V158M polymorphism modifies mRNA local stem-loop structures, such that the most stable structure is associated with the lowest protein levels and COMT enzymatic activity [11].

Since COMT has a crucial role in the metabolism of dopamine, it was suggested that its common functional variant impacts on sleep-wake regulation, and potentially sleep pathologies. In addition to its role in the metabolism of endogenous substances, *COMT* may also impact on the efficacy of drugs increasing catecholaminergic tone such as stimulants. We propose here a review focusing on recent advances in our understanding of possible consequences of the variation in the *COMT* gene for normal sleep-wake regulation, sleep pathologies, and pharmacogenetics of sleep.

Importance of the dopamine system in behavioral arousal

The dopamine (DA) system has an established role in regulating motor control, cognition, and the maintenance of behavioral arousal [12]. In contrast to the striatum, the prefrontal cortex expresses low levels of dopamine transporter protein in general and none within synapses [13,14]. Because the dopamine transporter is the most efficient mechanism for clearing released dopamine from extracellular space, the PFC is more dependent on secondary mechanisms, such as the COMT enzyme, for terminating the action of released dopamine. Although the COMT enzyme has a widespread distribution in non-dopaminergic neurons and glia cells, pharmacological studies showed that catabolic flux of synaptic dopamine through the COMT pathway is a characteristic of the PFC [15]. The COMT enzyme accounts for more than 60% of the dopamine degradation in the PFC, but for less than 15% in the striatum [15].

Dopaminergic neurons are quite few in number, a total of around 400,000 in the human brain and their cell bodies are confined to relatively few small brain areas, including the ventral tegmental area (VTA), the substantia nigra pars compacta (SNc), the ventral periaqueductal grey (VPAG), and some hypothalamic areas [16]. The VTA and SNc cells have large efferent and afferent projections with structures involved in sleep-wake regulation, such as the dorsal raphe nucleus, the pedunculopontine and laterodorsal tegmental nuclei, the locus coeruleus, the lateral and posterior hypothalamus, the basal forebrain, and the thalamus [16]. Even though DA neurons in the VTA and the SNc may not distinctly change their mean firing rate across the sleep-wake cycle, they may be involved in the regulation of sleep and waking by modifying their tonic and phasic pattern of discharge in connection with serotonergic, cholinergic, orexinergic, glutamatergic and noradrenergic neurons [17]. Genetically modified mice, in which the dopamine active transporter (*DAT*) gene was deleted, exhibited reduced NREM sleep and prolonged wakefulness when compared to wildtype mice [18]. Moreover, functional genetic variation of the gene encoding DAT in humans modified the rebound in slow wave sleep after sleep deprivation in healthy volunteers [19].

Molecular cloning techniques have characterized two distinct groups of DA receptors: the D1-family that includes the D1 and D5 receptors, and the D2-family including the D2, D3, and D4 receptors. Pharmacological studies showed that systemic administration of a D1 receptor agonist increased wakefulness and reduced both slow wave and REM sleep [20]. In contrast, systemic injection of a D2 receptor agonist induced biphasic effects, with low doses reducing wakefulness and increasing slow wave sleep (WS) and REM sleep, whereas large doses induced the opposite effect [21]. Drugs that antagonize D1 or D2 receptors increased NREM sleep

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and reduced wakefulness [22]. Finally, amphetamine-like stimulants increased wakefulness by blocking catecholamine reuptake from the synaptic cleft and stimulating catecholamine release (i.e., noradrenaline and dopamine) [18]. After electrolytic lesioning of the DA-containing neurons of the SNc and the VTA of the cat, a dissociation was found between behavioral arousal and electrocortical waking [23]. A decrease in electrocortical waking was associated with a large increase in N2 sleep and a smaller increase in SWS. This finding was attributed to the respective interruption of DA pathways. Hence, DA neurons of the VTA seem essential for the maintenance of behavioral arousal, in contrast to noradrenergic neurons of the pons that mostly mediate the tonic cortical activation [23]. Altogether, electrophysiological, genetic, pharmacological, and lesional studies suggest that both DA neurons bursting activity and increased dopaminergic tone contribute to the occurrence of wakefulness and behavioral arousal.

The loss of normal dopaminergic function in humans contributes to several sleep disorders such as restless legs syndrome and REM sleep behavior disorder [24]. In particular, it leads to Parkinson's disease, a neurodegenerative condition associated with disturbed sleep and vigilance [24].

Importance of COMT in frontal cortex and sleep-wake physiology

Mice deficient for the *COMT* gene showed a sexual phenotypic dimorphism with modification in emotional and social behavior [4]. Homozygous *COMT*-deficient female mice displayed impairment in emotional reactivity in the dark/light exploratory model of anxiety. Heterozygous *COMT*-deficient male mice exhibited increased aggressive behavior. Region-specific changes of dopamine levels were reported between *COMT*-deficient male and female mice, with the former having an increased dopamine level in the frontal cortex but not in the striatum or the hypothalamus [4]. The COMT enzyme activity is reduced epigenetically by estrogen with 30% decrease in activity in females compared to males [25]. The Met158 carriers are more sensitive to stress and exhibit higher anxiety and reactivity to lower levels of stress [26]. The *COMT* genotype might also modulate the interaction between prefrontal activity and midbrain dopaminergic function in humans. Individuals homozygous for the Val158 allele show higher COMT activity, have more COMT protein in post-mortem brain tissues, and lower dopaminergic signaling in PFC than subjects homozygous for the Met158 allele [11]. A neuroimaging study performed in healthy volunteers reported that carriers of the Val158 allele had significantly higher midbrain 6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine (F-DOPA) uptake rates compared to homozygous Met158 carriers, indicating decreased dopaminergic tone in Met carriers [27]. Moreover, the regional cerebral blood flow in the PFC was correlated with midbrain dopamine uptake during a working memory challenge test as a function of *COMT* genotype. The *COMT* genotype was associated with performance differences in executive cognitive functions, such that carriers of the variant Met158 showed better executive function (mainly in males), with best performance in Met/Met homozygotes [28]. These findings strongly suggest that genetically-determined variation in COMT activity has neurobiological effects specific to the PFC.

As the COMT enzyme plays an important role in the breakdown of cortical catecholamines in the PFC, an impact of the Val158Met polymorphism on normal sleep-wake regulation was hypothesized. In male homozygous Val carriers, alpha-peak-frequency in wakefulness was 1.4 Hz slower than in homozygous Met carriers [29]. Moreover, the two genotypes showed a stable and frequency-specific inter-individual difference in brain alpha oscillations, mainly in the 11–13 Hz band. Val/Val allele carriers exhibited less EEG 11–13 Hz power than Met/Met homozygotes in wakefulness, NREM sleep, and REM sleep. This difference resisted to both, the effects of sleep deprivation (40 h prolonged wakefulness) and modafinil. It is currently not known whether the observed effects of the Val158Met polymorphism on the EEG alpha-activity have any bearing on *COMT* genotype-dependent differences in cognitive functions. Although it was previously suggested that individuals with faster alpha-peak frequency and higher upper alpha-band power may show better cognitive and memory performance [30], such associations need to be interpreted with caution (discussed in [29]). Another study reported that Met/Met subjects show a greater decline in slow-wave EEG energy during five consecutive days of partial sleep deprivation compared to the Val/Val and the Val/Met subjects, despite comparable baseline values [31]. No cognitive (i.e., executive function performance) differences were found between the different genotypes, with similar subjective and physiological sleepiness in response to chronic sleep loss.

Some evidence suggests an inverted U-shaped relationship between dopaminergic tone in the PFC and distinct PFC-dependent brain functions [32]. Whether such a relationship may exist for sleep-wake physiology is currently unknown. A recent long-term actigraphy study revealed that Val/Val and Met/Met homozygotes habitually prolonged sleep on rest days compared to workdays, whereas Val/Met heterozygotes did not significantly extend their sleep length on weekends [33]. These data are consistent with an inverted U-shaped relationship between *COMT* genotype-dependent differences in PFC dopamine and the accumulation of a sleep debt during the workdays. Controlled intervention studies in appropriate study samples are needed to formally test this hypothesis. Collectively, the available findings in healthy individuals suggest that the Val158Met polymorphism of the *COMT* gene predicts inter-individual differences in distinct aspects of sleep-wake physiology.

Impact of COMT in narcolepsy and other sleep-related disorders

Narcolepsy is a disabling neurological disorder characterized by two major symptoms, excessive daytime sleepiness (EDS) and cataplexy. Narcolepsy is one of the most studied sleep disorders at the molecular level with a demonstrated marked decrease in hypocretin-1 levels in the cerebrospinal fluid (CSF), together with a decreased number of hypocretin neurons in postmortem brain tissues [34]. While hypocretin deficiency underlies narcolepsy, strong excitatory projections of hypocretin neurons to the noradrenergic, dopaminergic, serotonergic, histaminergic, and cholinergic neurons lead to abnormal dopaminergic/noradrenergic neurotransmission that may relate to the clinical symptoms [34–36]. Genetic studies in narcoleptic mice showed that dopamine transmission modulates cataplexy and sleep attacks by different receptor mechanisms [37]. Hence, activation of D1-like receptors decreased sleep attacks without affecting cataplexy but activation of D2-like receptors aggravated cataplexy without any effect on sleep attacks [37].

To test the hypothesis that the noradrenergic/dopaminergic systems are critically involved in human narcolepsy and to a larger extent than the serotonergic system, we analyzed two polymorphisms of monoamine oxidase type A (MAO-A, i.e., a major enzyme that degrades monoamines and particularly serotonin) and the functional (Val158Met) polymorphism of the *COMT* gene in patients with typical narcolepsy-cataplexy (38 females and 59 males) and ethnically matched normal controls (59 females and 82 males) [38]. The study revealed no association between either the genotype or the allele frequencies of *MAO-A* and *COMT* genes in narcolepsy. However, the *COMT* genotype distribution differed

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between male and female narcoleptics, with a higher number of males with the Val/Met genotype (LH genotype). Moreover, female narcoleptics with high COMT activity (Val158 or HH genotype) fell asleep twice faster than those with low COMT activity (Met158 or LL genotype) during the multiple sleep latency test (MSLT). The opposite was true for men. Independent of gender, *COMT* genotype significantly affected the presence or absence of sleep paralysis, sleep latency at night, and the number of sleep-onset REM periods during the MSLT. This study was the first genetic evidence for the critical involvement of the dopaminergic/noradrenergic system in human narcolepsy and confirmed previous findings in the canine model of the disease [39]. Thus, Val158Met polymorphism of *COMT* has a sexual dimorphism and a strong effect on EDS in patients with narcolepsy. However, recent genome-wide association studies in narcolepsy could not confirm this association when designed as case–control studies without taking into account gender and endophenotype such as the severity of EDS [40–42]. Recently an European case-control GWAS performed in narcolepsy-cataplexy looked for genetic variants and clinical traits [43]. The sample was relatively small to obtain enough power to detect a genome-wide significant signal. Neither the top hits nor the alleles of the functional COMT gene polymorphism (rs4680) were associated with the severity of EDS assessed by MSLT [43].

As patients with Parkinson's disease (PD) also suffer from EDS and sudden sleep attacks, a few studies searched for an association between *COMT* genotype and daytime sleepiness in PD. A first study ($n = 46$) suggested that PD patients with Met158 allele had higher levels of sleepiness measured with the Epworth sleepiness scale (ESS) when compared to the group with Val allele only (ESS>10, 40% vs 9.1%) [44]. However, a larger study including 240 patients with PD with and without episodes of sudden asleep attacks matched for anti-PD medication, disease duration, sex, and age, did not support a clinically relevant effect of the *COMT* genotype on daytime sleepiness in PD [45]. However, no study investigated the relationship between *COMT* genotype and EDS assessed with objective measures (i.e., MSLT) in PD. Another study revealed no association between *COMT* Val/Met polymorphism and restless legs syndrome, and no association with gender, age of onset, and family history [46]. To our knowledge, association studies between the *COMT* gene variants and idiopathic rapid eye movement behavior disorder (RBD), NREM parasomnias, and chronic insomnia are lacking.

Pharmacogenetics of the COMT gene

Drug response varies between subjects and may relate to body composition and weight, age and gender, but also to inter-individual differences in the constitutive pathways involved. Genetic factors are now being recognized as key determinants of inter-individual and inter-ethnic differences in drug metabolism. These include polymorphisms of the cytochrome P450 enzyme and of the monoaminergic genes. In addition to its role in the metabolism of endogenous substances, *COMT* gene variants might be important for the metabolism of catecholaminergic drugs used to treat several sleep disorders [47].

Since COMT inactivates norepinephrine and dopamine via methyl-conjugation, it was suggested that it may impact the response to stimulant drugs. Modafinil (diphenyl-methyl sulfinyl-2-acetamide) was shown to promote vigilance without producing dependence and abuse. The biochemical mechanisms and the brain regions involved in vigilance-promoting effects of modafinil are not fully understood. One study, however, demonstrated that *DAT* knock-out mice were unresponsive to the wake-promoting action of catecholaminergic drugs (i.e., amphetamine and modafinil), a finding consistant with the involvement of a dopaminergic mechanism [18]. A positron emission tomography study recently measured the acute effects of modafinil on the availability of extracellular dopamine and dopamine transporter in the male human brain [48]. Main results indicated that modafinil blocked dopamine transporters and increased dopamine in the putamen, the caudate, and the nucleus accumbens. Furthermore, modafinil intake (200 mg) during sleep deprivation in healthy volunteers affected distinct EEG frequency bands in NREM sleep in a *DAT*-genotype-dependent manner [19].

Modafinil is an effective treatment for narcolepsy; however substantial number of patients display none or only partial response. As detailed above, the dopamine metabolism pathway and in particular the COMT enzyme are putative targets for the stimulant effects of modafinil. We hypothesized that functional polymorphism of the *COMT* gene may influence the clinical response to modafinil in narcolepsy. We included a population of 84 patients with narcolepsy-cataplexy (mean age at 48.21 ± 19.25 y) treated with modafinil for 7.49 ± 4.35 y and receiving a minimum daily dose of 100–600 mg (mean daily dose at 307 ± 109 mg) [49]. The effect of modafinil on EDS was established on the basis of clinical investigation made at each visit and scored as 2 for good response (striking improvement up to disappearance of EDS), 1 for moderate response (intermediate improvement) and 0 when no effect was observed. We also determined the daily dose at maximum efficacy in each patient. Seventy-seven patients were classified as responders to modafinil (i.e., 52 good and 25 moderate responders) and only 7 as non-responders. The *COMT* genotype distribution differed between gender according to the response to modafinil. In women, 30 out of 32 narcoleptics (96.8%) were good or moderate responders against 46 out of 52 men (88.5%). In addition, patients with Val/Val (HH) genotype responded less efficiently to modafinil than patients with Met/Met or Met/Val (LL or HL) genotypes. The optimal daily dose of modafinil differed between gender with nearly 100 mg per day less in women (daily dose at 262.50 ± 16.65 mg for women and 343.34 ± 17.50 mg for men). Finally, the distribution of *COMT* genotype interacted with the optimal daily dose, such that patients with Met/Met genotype had less daily dose than the others. To summarize, the response to modafinil-based treatment of EDS differs between gender and *COMT* genotypes, with narcolepsy patients with higher dopaminergic tone (Met/Met genotype, low COMT enzyme activity) responding to lower doses of modafinil compared to patients with Val/Val genotype. These results strengthen the involvement of the dopaminergic pathway in the mechanism of action of modafinil.

Studies in healthy men also reported an impact of the V158M *COMT* polymorphism on the efficacy of modafinil in improving EDS after sleep deprivation [50]. A placebo-controlled, double-blind, randomized crossover study showed that modafinil attenuated the progression of sleepiness and EEG 5–8 Hz activity during sleep deprivation in both Val/Val and Met/Met allele carriers. However, the V158M *COMT* polymorphism modulated the effects of modafinil on the NREM sleep in the recovery period after prolonged wakefulness with increased power in 3.0–6.75 Hz and >16.75 Hz in subjects with Val/Val genotype. Further results showed that modafinil maintained baseline executive function performance and vigilance throughout sleep deprivation in subjects with Val/Val genotype in contrast to those with Met/Met genotype [51]. Although these results highlight the role of dopaminergic mechanisms in impaired waking functions after sleep loss, the significance of the genotype-dependent changes after modafinil in EEG activity in NREM sleep remains to be elucidated. Together with recent findings [19], the available data suggest that genetic variation in the dopamine transporter *DAT* (i.e., the 10-repeat allele homozygotes for the variant SNP-*rs28363170* having 20% reduced DAT availability in the striatum compared to homozygous 9-repeat and heterozygous allele carriers) rather than in *COMT* modulates sleep homeostasis in healthy humans.

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The clinical benefits of other psychostimulants such as amphetamine are quite variable, from positive effects on sleep-wake cycle, mood and cognition in some subjects, to negative responses in others [52]. Inter-individual differences may relate to genetic variants in monoaminergic genes. Hence, amphetamine enhanced the efficiency of PFC function in healthy volunteers with Val/Val *COMT* genotype (i.e., low prefrontal synaptic dopamine at baseline) in contrast to subjects with Met/Met genotype, without any effect on low-to-moderate cognitive processing but with unexpected deterioration on higher processing [53]. The latter findings showed a different response curve to increasing dopamine signaling in the PFC depending on the COMT genotype, with a shift of dopamine signaling from the lower end of the normal range to a higher level on the theoretical inverted U-shaped curve. The excess of dopamine effects in the PFC depending on the M158V *COMT* polymorphism may also be relevant for increased risk of side effects of psychostimulants, especially in Met/Met carriers with the recent example of children affected with attention deficit hyperactivity disorder (ADHD) treated with methylphenidate [54]. Finally, the interaction of pharmacological COMT inhibition (with entacapone or tolcapone) with sleep-wake regulatory mechanisms in genetically characterized volunteers or patients is unknown.

Conclusion

The importance of a genetic contribution to healthy sleep and sleep pathologies is increasingly recognized. The monoaminergic genes, and particularly the *COMT* gene, play a critical role in the regulation of human behavior. Some of the variants of the *COMT* gene are functional, easily detectable, and significantly related to the metabolism of dopamine, which underlies the pathogenesis of a significant number of brain disorders. Val158Met is considered to be the main functional *COMT* variant; however other known but less studied, polymorphisms and haplotypes in the *COMT* gene were reported [10,55], and thus may also lead to *COMT*-dependent phenotypes. Nevertheless, the *COMT* gene is probably not a gene for a particular disease but might have some critical effects on prefrontal cognitive performance, behavioral profile, sleep architecture, sleep EEG, vulnerability to sleep loss, and response to stimulant treatment. A better understanding of the genetic basis of variability in drug responses is needed to further use the pharmacogenetic tools for personalized treatment. Finally, gene–gene and gene-environment interactions with epigenetic mechanisms should also be considered to understand the variability in genetic relative risk for a given individual.

Practice points

1) Several aspects of sleep differ in their regulation and each of these aspects is likely to be under genetic control.
2) Catechol-O-methyltransferase (COMT) is one of the major enzymes involved in the site-specific metabolic degradation of catecholamines. The COMT enzyme accounts for more than 60% of the dopamine degradation in the prefrontal cortex, but for less than 15% in the striatum.
3) The level of COMT enzyme activity is genetically polymorphic mainly due to a Guanine-to-Adenine transition at codon 158, resulting in a valine (Val) to methionine (Met) substitution. Individuals homozygous for the Val158 allele show higher COMT activity, and lower dopaminergic signaling in prefrontal cortex than individuals homozygous for the Met158 allele.
4) The COMT enzyme activity is reduced epigenetically by estrogen with the enzyme activity being 30% lower in females than in males.
5) The variation in COMT activity may have neurobiological effects specific to the prefrontal cortex: Individuals homozygous for Met158 have better performances than Val158 homozygotes in excecutive cognitive functions.
6) The COMT Val158Met polymorphism may predict inter-individual differences in brain EEG alpha oscillations and in sleep rebound resulting from partial sleep loss in healthy individuals.
7) The COMT Val158Met polymorphism exerts a sexual dimorphism and a strong effect on objective daytime sleepiness in patients with narcolepsy-cataplexy.
8) The response to stimulant drugs may differ between COMT genotypes. Modafinil allows better executive function performance and better vigilance throughout sleep deprivation in normal subjects with Val/Val genotype than in those with other genotypes. Patients with narcolepsy having higher dopamine levels (Met/Met genotype) respond to lower doses of modafinil compared to other genotypes.

Research agenda

1) Because the levels of dopamine decrease in the brain with aging, the impact of COMT gene variants on prefrontal cognitive functions should be larger in older adults and needs further investigations.
2) Whether the functional COMT gene polymorphism impacts different endophenotypes of emotional and social behavior and sleep in healthy subjects of different ages and gender remains to be investigated.
3) Molecular techniques including mainly genome-wide linkage and association studies are required to validate the contribution of the functional COMT gene polymorphisms on the severity of daytime sleepiness assessed with objective measures (i.e., MSLT) in hypersomnia disorders.
4) The impact of the COMT Val158Met polymorphism in brain alpha EEG oscillations assessed in healthy subjects during wakefulness needs to be explored in pathological conditions as a function of age and gender.
5) The level of COMT enzyme activity as a biomarker to differentiate the variable sleep rebound after sleep loss needs to be confirmed in healthy subjects as a function of age and gender, and to be studied in neuropsychiatric disorders.
6) The COMT enzyme plays an important role in the metabolism of catecholaminergic drugs used to treat many brain disorders. Further pharmacogenetic and pharmacogenomic studies are required to confirm the role of COMT gene in the response to modafinil in narcolepsy, but also to other stimulant drugs and in other hypersomnias of central origin.
7) To better understand the role of dopamine in the regulation of sleep-wake behavior and to further elucidate the potential underlying epigenetic mechanisms linked to COMT gene, the interactions between the COMT and other genes (i.e., DAT gene) as well as with environmental factors need further investigations.

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