Review Article

Targeting modulation of noradrenalin release in the brain for amelioration of REMS loss-associated effects

Abhishek Singh, Birendra Nath Mallick
School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

ABSTRACT

Rapid eye movement sleep (REMS) loss affects most of the physiological processes, and it has been proposed that REMS maintains normal physiological processes. Changes in cultural, social, personal traits and life-style severely affect the amount and pattern of sleep, including REMS, which then manifests symptoms in animals, including humans. The effects may vary from simple fatigue and irritability to severe patho-physiological and behavioral deficits such as cognitive and behavioral dysfunctions. It has been a challenge to identify a molecule(s) that may have a potential for treating REMS loss-associated symptoms, which are very diverse. For decades, the critical role of locus coeruleus neurons in regulating REMS has been known, which has further been supported by the fact that the noradrenalin (NA) level is elevated in the brain after REMS loss. In this review, we have collected evidence from the published literature, including those from this laboratory, and argue that factors that affect REMS and vice versa modulate the level of a common molecule, the NA. Further, NA is known to affect the physiological processes affected by REMS loss. Therefore, we propose that modulation of the level of NA in the brain may be targeted for treating REMS loss-related symptoms. Further, we also argue that among the various ways to affect the release of NA-level, targeting α_2 adrenoceptor autoreceptor on the pre-synaptic terminal may be the better option for ameliorating REMS loss-associated symptoms.

Key words: adrenoceptors, locus coeruleus, prazosin, pre- and postsynaptic adrenoceptors, REMS deprivation

Key Messages: Elevated level of NA in the brain is a key molecule that induces REMS loss-associated symptoms. Modulation of presynaptic α_2-adrenoceptors, which are autoreceptors, is a better target and option to counter the elevated level of NA as a treatment of REMS loss-associated symptoms.

Address for Correspondence:
Dr. Birendra Nath Mallick,
School of Life Sciences, Jawaharlal Nehru University,
New Delhi – 110 067, India.
E-mail: remsbnm@yahoo.com

Access this article online

Website: www.intern-med.com

DOI: 10.4103/2224-4018.154288

Quick Response Code:

INTRODUCTION

Rapid eye movement sleep (REMS) is a unique behavioral phenomenon and is an integral component of sleep. Different states of sleep and wakefulness have been objectively identified by the simultaneous presence or absence of associated classical electrophysiological signals recorded from the brain, the electroencephalogram (EEG), eye movements, the electrooculogram (EOG) and muscle tone and the electromyogram (EMG). REMS is classically and objectively identified and quantified by desynchronized EEG, atonia in the antigravity muscles, rapid eye movements and appearance of ponto-geniculo occipital (PGO) waves. Thus, as compared with waking, during REMS the EEG and EOG apparently resemble that associated with waking, while EMG shows an opposite expression. Therefore, this sleep state has also been referred to as "*active sleep*" or "*paradoxical sleep*" or "*desynchronized sleep.*" Further, as this stage is often associated with dreaming, this stage has been termed as dream state of sleep, although it is known that sometimes dream may appear during non-REMS as well. The REMS has been identified in almost all the higher species in evolution recorded so far, including humans.[1-3] To this effect, we reiterate our argument that as one of the primary characteristic features to identify REMS is the recording from the brain the EEG signals, consequently this stage of

sleep has been identified in species higher in evolution possessing developed and evolved brain. As a corollary, it is also obvious that because of a lack of fundamental bio-molecular markers, it is yet to be confirmed if this stage is present, may be even in a rudimentary form in other lower species.

The quantity of REMS varies among species; it is affected by life-style changes and under various psycho-somato-patho-physio-logical altered conditions.[4] Under normal conditions, the quantum of REMS reduces with ageing; however, normally, this stage is never absent through life.[5,6] The essentiality of REMS to maintain normal life processes may be supported by the fact that it is not under voluntary control, it is affected in almost all disorders, its loss is followed by a compensatory rebound increase during the post-deprivation recovery period, its prolonged loss may be fatal and, finally, its basic regulatory mechanism lies at the core of the brainstem as that of controlling other absolutely essential functions for living, e.g. heart rate, respiration, blood pressure and sleep-waking, which, however, may be modulated by other factors.

Involvement of noradrenaline (NA) in REMS-loss associated symptoms

REMS loss is often associated with expressions of a number of specific and nonspecific symptoms, many of which may or may be apparently unrelated. Although it may be difficult to associate REMS loss as an exclusive cause or effect of a disorder, we propose that in the case of REMS disturbance (directly or indirectly as a cause or an effect), the neural mechanism regulating it must be affected. Therefore, targeting a common factor, if any, which is known to be essentially expressed during REMS as well as under conditions of REMS loss, may be targeted to help the sufferer. Altered REMS is one of the common symptoms associated with many disordered states, including hypertension,[7] hyperglycemia, hyper-excitability,[8,9] lack of concentration, memory loss,[10] Alzheimer's disease,[11,12] Parkinson's disease[13] and depression.[14] The level of NA is altered in most of these altered states (dysfunctions) and, interestingly, NA is elevated after REMS loss as well.[15] By and large, NA is at least an important common causative factor inducing many of the REMS deprivation (REMSD)-associated symptoms, including neuronal cytomorphometry,[16-18] apoptosis in brain neurons,[19] increased Na–K ATPase activity[20] and thermoregulatory changes[21] that were prevented by adrenoceptor (AR) antagonists.[22] Therefore, we propose that targeting mechanisms(s) that maintain the NA level in the brain could be a possible way to address treatment of REMS loss-associated symptoms. However, before we proceed to justify in support of our proposition, what role NA plays in REMS regulation needs to be evaluated.

Neural regulation of REMS and its relation with brain level of NA

REMS has a well-regulated cyclic appearance; at least in humans, its frequency and duration per episode increases with the depth of sleep.[6] Lesion, transection and stimulation studies have shown that neurons located in the brainstem are its primary regulators, while neurons in other brain regions modulate REMS by influencing these primary regulators.[23] On the basis of temporal correlation of firing rate of neurons during REMS, neurons have been classified as REM-ON (those are active during REMS) or REM-OFF (those are silent during REMS).[24] It is classically known that REM-ON neurons are presumably ACh-ergic and are concentrated largely within the latero-dorsal tegmentum/pedunculo-pontine tegmentum (LDT/PPT), while the REM-OFF neurons are NA-ergic and largely located in the locus coeruleus (LC).[25] It is important to note that some neurons in other parts of the brain have also been found to behave phenotypically as REM-OFF and REM-ON neurons; however, they have not been studied as extensively as those in LC and LDT/PPT. The LDT/PPT and LC neurons have reciprocal projections,[26,27] which could be a direct connection or through GABA-ergic,[28] glutamatergic or glycinergic[29] interneurons. Additionally, these REMS-related neurons receive projections from widespread areas in the brain, including those involved in regulating sleep and waking (reviewed in[23]). Thus, it is evident that modulation of the activity of REMS-related neurons would be complex and so will be the regulation of REMS.

In an attempt to explain the neural regulation of REMS, based on single neuronal recording in freely moving normally behaving animals in isolated experiments, a simple model based on the Lotka-Volterra principle explaining the reciprocal interaction between REM-ON and REM-OFF neurons was proposed.[30,31] The temporal relationship of reciprocal behavior of the REM-ON and REM-OFF neurons was confirmed by simultaneous recording of a pair of REM-ON and REM-OFF neuronal activities, along with waking–non-REMS (NREMS) and REMS in chronically prepared freely moving normally behaving cats.[24,30] Subsequent extensive systematic *in vivo* and *in vitro* studies during the past two decades have confirmed the role of GABA-terminals and GABA-interneurons acting pre- and postsynaptically on REMS-related neurons[32-34] for REMS regulation. These findings have been consolidated recently and a working model that activation of a de-activation process is responsible for REMS initiation and regulation has been proposed.[23]

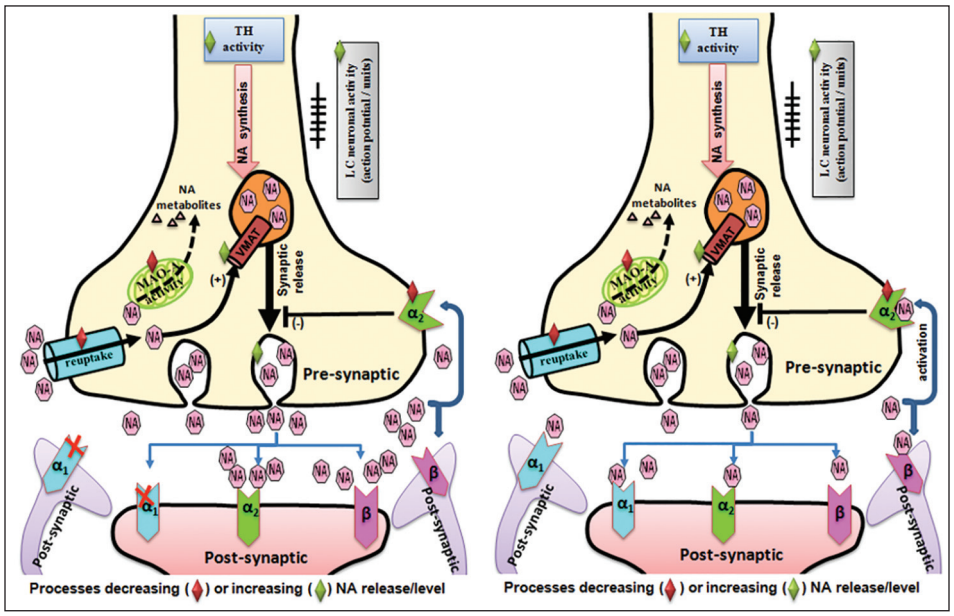

Figure 1: Noradrenalin (NA) concentration at the synapse is ultimately responsible for manifesting its effect. Its action is mediated by NA-level and its action on the postsynaptic adrenoceptors (ARs). However, the level of NA at the synapse is modulated by changes in either or combination of some or all of the following factors: (i) firing rate of NA-ergic neurons and (ii) changes in (a) TH activity, (b) NA transporter activity, (c) MAO activity and (d) number of α2-ARs and their activation of the NA-ergic neurons. Left panel (A) represents that if any one sub-type of receptor (e.g., by antagonist of α1-ARs as shown here) is blocked, relatively more NA becomes available to act on other sub-types of ARs, which may then express nonspecific side-effects (symptom). Although as an example we have shown that by blocking α1-ARs, a similar effect may be evident by blocking any other one type or combination of ARs types Right panel (B) represents action of NA on the pre-synaptic α2-ARs (autoreceptors) and thus modulating the release of NA

Factors affecting LC–NA-ergic neurons modulate REMS and may induce REMS loss-related symptoms

The REMS is a multifactorial complex phenomenon; its regulation is also likely to be multi-dimensional. The role of many neurotransmitters and neuropeptides directly or indirectly have been implicated in the regulation of REMS.[35,36] The LC is the primary site of NA-ergic neurons in the brain.[37] These neurons normally cease activity during REMS;[38,39] however, they do not cease activity during REMSD.[40] On the other hand, if the LC–NA-ergic neurons were kept active for a short- or long-term by electrical stimulation[41,42] or by preventing GABA-ergic inhibitory input to act on them[43] or by increasing the Na–K ATPase activity on the LC neurons,[44] REMS was reduced. Many factors that modulate REMS have been shown or proposed to mediate their action by modulating LC neurons. For example, normally, REMS does not appear during waking because wake–active[45] areas including orexinergic perifornical area (PeF)[46,47] activate, while the NREMS-areas[45] in the brain inhibit[48] the neurons in LC, the site of LC–REM-OFF neurons. Further, neuronal activity is modulated by microinjection of neurotransmitter agonist and antagonist into the LC-altered REMS.[49,50] As the decrease in REMS is due to increased excitation and sustained activity of the LC–REM-OFF NA-ergic neurons, it is imperative that the later would elevate the NA level in the brain during REMSD and vice versa. Also, after REMSD, as tyrosine hydroxylase (TH) is increased and monoamine oxidase (MAO) is decreased, there would be increased NA in the brain.[51-53] The possible mechanism of REMSD-associated elevated synaptic NA level at NA-ergic synapses and the brain at large is shown in Figure 1. Thus, in principle, either by modulating LC–NA-ergic neuronal activity, which in turn would control the quantity of NA-release, or by preventing the action of the elevated NA on potential target(s), REMS loss-associated symptoms may be ameliorated.

Modulation of effect of NA in the brain: A possible therapeutic approach to ameliorate REMS loss-associated symptoms

Normally cessation of NA-ergic REM-OFF neuronal activity is a prerequisite condition for generation and maintenance of REMS.[54] If they do not cease activity, REMS does not appear and as a result of noncessation (i.e., continuation of activity) of LC neurons, there is likely to be elevated level of NA in the brain. This elevated NA in the brain in turn has been reported to induce many, if not most, of the REMS loss-associated symptoms.[16-17,19,55-57] These propositions may be supported by the fact that many of the diseases associated with REMS loss[58] show an elevated level of NA or express symptoms that could be due to elevated level of NA.[59] Therefore, effective neutralization of the action of released NA, particularly at the site of its release/action, could be a natural and preferred choice of therapeutic intervention to counter the REMS loss-induced

effects and associated symptoms. This could be achieved by either or combination of the following:

(i) Blocking the postsynaptic AR to prevent the action of NA;
(ii) By elevating the level of monoamine oxidase that breaks down the released NA;
(iii) By increasing the NA-transporter and reducing the effective concentration of NA at the synaptic sites;
(iv) By modulating the synthesis and release of NA;
(v) By influencing inputs on the LC–NA-ergic neurons thereby altering their activities and release of NA; or
(vi) By targeting the presynaptic ARs at the NA-ergic terminal and thus modulating the release of NA

Various possibilities targeting the release of NA at the terminal, along with their advantages and disadvantages, have been discussed in the following sections considering each one of them as a potential therapeutic approach for the treatment of REMSD-associated symptoms.

NA-ergic AR

NA acts through ARs that belong to G-protein-coupled receptor and may give rise to a variety of responses. There are mainly three subtypes of ARs: α_1, α_2 and β-ARs; they share a high degree of amino acid homology, especially within the ligand binding pockets around the transmembrane regions.[60] Ligand-binding residues confer subtype-specific selectivity to a particular receptor. α_1-ARs are further sub-classified as α_{1A}, α_{1B} and α_{1D} types and are coupled to the Gq/11 family.[61] Stimulation of these α_1 ARs recruits signaling pathways involving activation of phospholipase C, D, A2 and MAP kinases and, subsequently, modulate transcriptional activation of early and late response genes. For example, it has been reported to affect the expression and activation of Ca^{2+} channels, Na^+/H^+ exchangers and K^+ channels,[61-64] which in turn are reported to modulate neuronal functions. At least in neurons, NA has been reported to close L-type Ca^{2+}channels by acting on α_1-AR.[65]

The subtypes of β-ARs, viz. β_1, β_2 and β_3, activate effectors by coupling to G_s or G_i molecules in a time- and dose-dependent manner.[66] Although the action of NA on different types of cells might not have been studied, at least in cardiomyocytes, stimulation of β-AR by nonselective agonist results in G_s-mediated enhanced cAMP generation and activation of the related downstream events. The β-AR-mediated effects enhance contractility of the cardiac muscles either by one or in combination with increasing Ca^{2+} influx through L-type Ca^{2+} channels, increased reuptake of Ca^{2+} by disinhibition of sarcoplasmic reticular Ca^{2+}-ATPase and modulation of myofilament Ca^{2+} sensitivity.[67-69] The β_2-ARs can also couple to G_i protein to inhibit the downstream effectors.[70-72]

The α_2-AR family has α_{2a}, α_{2b} and α_{2c} receptor subtypes, and they are encoded by three distinct genes. The α_2-AR couples to the G_i subunit and is involved in the modulation (usually inhibition) of NA release.[73,74] Activation of G_i leads to inhibition of adenylate cyclase, which results in decreased cAMP generation. Coupling to several other signaling pathways has also been reported upon activation of α_2-ARs for modulation of neurotransmitter functions. These include activation of K^+ channels, inhibition of Ca^{2+} channels, activation of Na^+/H^+ antiporter, mobilization of intracellular Ca^{2+} and activation of the mitogen-activated protein kinase (MAPK) cascade.[75-77]

Targeting the postsynaptic α_1-ARs

α_1-ARs are distributed on the neurons throughout the brain, including those in the areas responsible for REMS regulation as such as well as on neurons responsible for functions related to REMS. Presence of α_1-ARs on the wake–active neurons in the pedunculo-pontine tegmentum (PPT)[78] and on thermosensitive neurons in the preoptic area[79] have been reported, which in principle may mediate REMSD-associated changes in brain functions. α_1-AR antagonists like prazosin (PRZ) have been widely used in the treatment of sleep (including REMS) disturbance, hypertension, posttraumatic stress disorder (PTSD) and anxiety.[80] Methoxamine, an α_1-AR agonist, increased wakefulness while decreasing NREMS and REMS,[81] which was reversed by PRZ. In stress-sensitive WKY (Wistar Kyoto) rats, REMS was fragmented by electric shock, and this was prevented by PRZ.[82] Similarly, in lower vertebrate model using zebrafish, PRZ treatment reduced the effect of sleep deprivation on anxiety.[83] REMSD caused many changes, including cellular morphology and biochemical parameters, and molecular expressions of Na–K ATPase have been shown to recover by treatment with PRZ.[17,57,84,85] These studies support that blocking α_1-AR activation could reduce the REMS loss-associated symptoms. Mignot *et al.*[86] investigated the role of central α_1-ARs in cataplexy in genetically modified narcoleptic Doberman pinschers. Treatment of narcoleptic dogs with PRZ exacerbated cataplexy, whereas treatment with α_1-agonist, methoxamine, ameliorated it. However, there are a few conflicting reports as well. For example, oral administration of PRZ shortened quiet waking and REMS but increased active waking and slow wave sleep,[87] whereas other α_1-AR antagonists, thymoxamine and mesoridazine increased REMS in humans.[88,89] Thus, the conditions induced by sleep loss, including REMS-loss, were rescued/recovered by activating/deactivating (as the case may be) the α_1-ARs supporting our contention. These findings suggest that if NA was prevented to act on α_1-ARs, REMS was increased and the REMS loss-associated symptoms were decreased.[90]

Targeting postsynaptic β-AR

Improvement in sleep disturbance-associated mood disorder, severe depression and sleep apnea have been reported by treatment with β-AR blockers in both animals and humans.[91-94] Also, REMSD-associated aggressiveness has been suggested to be mediated by NA acting on β-AR.[95] β-agonist, isoproterenol, suppressed while β-antagonist, propranolol, consistently enhanced REMS episodes.[96] Although the amelioration of REMS loss-associated symptoms could be due to improved REMS, their causal and temporal relationship need validation. Microinjection of isoproterenol into the medial septal region of the basal forebrain significantly increased the time spent in wakefulness, while there was a near-complete suppression of REMS.[97] Based on these findings, it has been postulated that NA released from the LC REM-OFF neurons acts on β-ARs present on REM-ON neurons and inhibits those preventing REMS generation.[50] As a corollary, it has been suggested that β-blockers would withdraw the NA-induced inhibition of the REM-ON neurons and facilitate their activation, leading to the generation of REMS; however, there are differences in specificity of chemicals acting on receptors. For example, Kostis and Rosen (1987)[98] reported that hydrophilic β-blocker (e.g., atenolol) do not affect sleep, while lipophilic β-blocker (e.g., pindolol) disturbs sleep continuity. Similarly, in another study, β-AR blockers, acebutolol and metoprolol, did not show any effect on sleep pattern.[99] Acute administration of β_3-AR agonist, CL316243 reduced while its prolonged treatment did not affect REMS.[100]

Thus, although it has been well established that the adrenergic system plays a significant role in REMS regulation, the precise mechanism of how it (β-blockers in particular) mediates the action needs further study. It may be noted that these drugs are widely used in cases of cardiac arrhythmias and hypertension; however, their associated undesirable side-effects of sleep disturbances and insomnia limits their use.[101] Hence, it is important to understand the use of these chemicals as drugs possibly after classifying patients so that these drugs may be used in combination with other molecules to reduce the side-effects. In addition to the application of agonist and antagonist mentioned above, molecules activating reuptake and/or breakdown of NA by MAO-A [Figure 1] at the synaptic terminal also have been used in the treatment of sleep disturbances.[102-105] In this strategy also, ultimately, the effective level of NA at the synaptic cleft is altered.

Targeting the release of NA

Like any other neurotransmitter, NA is released from the presynaptic terminals and it acts on the pre- and postsynaptic receptors for inducing its action. Thus, all other conditions remaining unchanged, the quantity of NA at the synaptic site decides its effect on expressing a behavior. We have discussed above how the effects of the released NA (due to loss of REMS) could be reduced by directly inactivating (NA degradation or re-uptake) the released NA or by preventing the released NA to act on the postsynaptic receptors. Another option of modulating the action of a neurotransmitter at the synaptic site is to modulate the release of neurotransmitter *per se* (NA at this instance) from the presynaptic site, which has also been used in treatment as well as in research.[105-107]

Here, we propose that manipulation of auto-regulatory mechanism of release of neurotransmitter than preventing the action of already released NA possibly would be a better option to maintain the effective level of NA at the synaptic site. This is because use of antagonist of one subtype of AR, although preventing the action of NA on such receptor subtypes, the already released NA remains or becomes available to act on other subtypes of ARs leading to added complications. This is because, for example, under normal conditions, the released quantity of NA will be such that it acts on an optimum number of one or more subtypes of ARs to get a function expressed at an optimum level. However, if a subtype of AR is blocked by its antagonist, the equilibrium of the ligand (NA in this case) to subtypes of receptor (ARs in this instance) would shift and, although a function may get modulated, possibly toward a desired level, other functions may get affected or get biased, expressing undesirable side-effects possibly as compensatory effect(s). This could be due to various reasons including overcoming the threshold of activation of another subtype of ARs, which was not significantly affected under normal condition, under the condition of blocking of one subtype of AR. After blocking one subtype of AR, the available NA might reach the threshold of activation of one or more of other subtypes of ARs expressing undesirable side-effects. This view may be supported by the fact that NA acting on different subtypes of ARs in the same brain area, viz. preoptic area, modulates sleeping-, waking- and thermo-regulation.[108] The literature on experimental as well as clinical practices mentions many such side-effects or associated phenomena that are often ignored due to lack of recorded consistent effects. Although in all cases we do not know the cause and effect relationship, our reasoning offers explanation for the same, which is justifiable and testable. Hence, we propose that in order to target REMS loss-associated induced symptoms, a more effective strategy could be to target modulation of the release of NA itself. However, the limitation is how to design site-specific moderation of release of NA.

Targeting the presynaptic α2 auto receptors

There are many examples where patho-physiologial processes have been reported to be modulated by targeting

the α_2-ARs. Initially, it was believed that α_2-ARs are present exclusively on the presynaptic site; however, recent reports suggest that in addition to the presynaptic site, they are present on the postsynaptic site as well.[60] The unique property of α_2-AR being present on the presynaptic site is that excess NA at the terminal (synaptic cleft) activates these α_2-ARs, preventing further release of NA; thus, the level of NA is auto-regulated at the terminal. The released NA inhibits the influx of calcium ions and thereby prevents further release of NA.[109] As there are collateral feedback inputs on the NA-ergic neurons in the LC,[110] it is likely that the collateral inputs on to itself and rhythmic release of NA due to auto-regulation of NA maintains the rhythmic firing of the LC–REM-OFF neurons and prevents appearance of REMS, especially during waking.[23,30,111]

The α_2-AR agonist, clonidine, has often been used as the treatment to reduce NA release. For example, clonidine and its analogue has been used in treating patient suffering from Crisponi syndrome.[112] In humans, a lower dose of clonidine increased while a higher dose decreased REMS.[113] The findings suggested that before assigning a therapeutic role to an agent, its dose, time and secondary or associated physiological impact should be evaluated. Dexmedetomidine, a more selective α_2-AR agonist than clonidine, has been reported to decrease sleep and reduce c-Fos expression in the LC neurons.[114] The spindles observed under sedation with dexmedetomidine are qualitatively similar to those during natural sleep. However, it has associated problems, e.g. it works even when NA level is severely depleted by various other agents like reserpine and DSP-4.[115] Yohimbine (3 mg/kg), an α_2-AR antagonist, augmented waking and reduced sleep.[116] Activation of α_2-ARs in and around LC reduced NA release and, consequently, reduced NA-mediated effects in the central nervous system.[117,118] α_2-ARs have been shown to be involved in REMS-associated thermoregulatory responses.[119] REMSD-induced increased NA was responsible for impairment in learning and memory in rats, which was significantly improved by treating with α_2-AR agonists.[120]

Proposed model for the treatment of REMSD-associated symptoms

In the brain, the LC is the primary site of NA-ergic neurons. As these neurons project throughout the brain and are responsible for most of NA in the brain, alterations in the activity of these LC–NA-ergic neurons ultimately modulate the level of NA in the brain. These neurons normally cease firing during REMS; however, they do not stop firing upon REMSD. Therefore, during REMS, although normally NA is washed-off from the NA-ergic projected sites, up on REMSD those sites have an increased level of NA. The LC neuronal activities are affected by the inputs they receive from within the brain as well as from the periphery; also, they are influenced by many other physico-chemical factors. Thus, it is understandable that the REMS is affected by wide varieties of inputs originating from within or from external inputs and, upon REMS disturbance, there will be changes in the level of NA in different parts of the brain. This explanation supports the observation that REMS is affected (may be even secondarily) in almost all altered states, e.g. acute fever to chronic and complex psycho-somatic disorders.

Although until now we do not know the exact details, REMS disturbance appears to be a primary cause of many acute to chronic disorders and, depending on the specific neurons that are affected and their projections in the brain, the level of NA would be modulated. This altered NA level would then modulate the physiological activities, which then get expressed as REMSD-associated symptoms. In other case(s) where the level of NA in the brain is elevated as a primary cause, the REMS-loss may be induced as a secondary effect and the associated pathological symptoms are expressed depending on the susceptibility of the neurons affected and their projections where the NA level is increased. Further, as most NA in the brain is released from the LC neurons, which is generally of the REM-OFF type, the REMS is also affected as a secondary/associated effect/response. It is possible that initial change in the level of NA due to REMS-loss could be a compensatory effect, which is often beneficial. However, if the loss is continued, it leads to chronic disorder and the mechanism needs to be understood in detail.

Based on the arguments given above, we propose that diseases associated with REMS loss need to be treated by a combination of factor(s), α_2-ARs agonist, which would reduce the release of NA along with agonist or antagonist of such receptor, which presumably is the primary cause of modulating the LC neurons. It may be a tough call on how to decide on the latter; however, we think that it could be done symptomatically on the basis of expressed symptoms. Although apparently it may be difficult to conceive at present, at least it may be said with certainty that all sleep/REMS disorder patient cannot be treated in the same manner (by the same drug) and, if this is done, including due to self-medication, it would create more complications as is often experienced; however, which might not have been reported as frequently due to a lack of consistent expression of symptoms. Finally, we propose that modulation of NA-release is likely to be the desirable treatment for REMS loss-associated symptoms. This may be achieved by modulating the firing rate of the LC–NA-ergic neurons in combination with or without independently modulating the presynaptic α_2-ARs; however, the challenge is to design such a targeted delivery system to be used as a therapy.

Basic principle of such targeted drug delivery system as a proof of principle

As discussed above, in principle, delivery of α_2-AR agonist to a desired site is the likely solution. However, the challenge is how to deliver the drug to a desired target, e.g. where the NA-ergic inputs are on the postsynaptic neurons possessing specific subtypes of receptors (cholinergic, GABA-ergic, etc. for instance). Subject to experimental verification, we suggest (propose) that the desired α_2-AR agonist could be packaged in liposomes having affinity for the target site where the drug (the cargo) needs to be delivered; the affinity of the designed molecules on the liposomes could be made of various combinations. Once such designed liposomes (the vehicles) are targeted at specific sites, the drug (the cargo) will be delivered at the desired site; the vehicle may be designed as per need.

CONCLUSION

REMS is a complex behavioral phenomenon and its loss affects various psycho–patho-physio-logical processes. NA level is elevated in the brain upon REMS-loss, which has been reported to be responsible for inducing several REMS loss-associated symptoms. We propose that reduction of NA-release either by modulating the NA-ergic neuronal firing rate alone or in combination with activating the presynaptic α_2-ARs is likely to be preferred and promising strategies for treating REMS loss-associated symptoms. Subject to confirmation, as a proof of principle, we have also proposed a possible approach for targeted drug delivery.

REFERENCES

1. McNamara P, Capellini I, Harris E, Nunn CL, Barton RA, Preston B. The Phylogeny of Sleep Database: A New Resource for Sleep Scientists. Open Sleep J 2008;1:11-4.
2. Capellini I, Barton RA, McNamara P, Preston BT, Nunn CL. Phylogenetic analysis of the ecology and evolution of mammalian sleep. Evolution 2008;62:1764-76.
3. Siegel JM. Phylogeny and the function of REM sleep. Behav Brain Res 1995;69:29-34.
4. Kushida CA. Sleep Deprivation; basic science, physiology and behavior. Vol. 192. New York: Marcel-Dekker; 2005.
5. Jouvet-Mounier D, Astic L, Lacote D. Ontogenesis of the states of sleep in rat, cat, and guinea pig during the first postnatal month. Dev Psychobiol 1970;2:216-39.
6. Roffwarg HP, Muzio JN, Dement WC. Ontogenetic development of the human sleep-dream cycle. Science 1966;152:604-19.
7. Horne RS, De Preu ND, Berger PJ, Walker AM. Arousal responses to hypertension in lambs: Effect of sinoaortic denervation. Am J Physiol 1991;260:H1283-9.
8. Hess CW, Mills KR, Murray NM, Schriefer TN. Excitability of the human motor cortex is enhanced during REM sleep. Neurosci Lett 1987;82:47-52.
9. Placidi F, Zannino S, Albanese M, Romigi A, Izzi F, Marciani MG, *et al*. Increased cortical excitability after selective REM sleep deprivation in healthy humans: A transcranial magnetic stimulation study. Sleep Med 2013;14:288-92.
10. Stickgold R. The role of REM sleep in memory comsolidation, enhancement and integration, in Rapid Eye Movement Sleep-Regulation and Function, Mallick BN, Pandi-Perumal SR, McCarley RW, Morrison AR, editors. Cambridge, England: Cambridge University Press; 2010.
11. Haglund M, Sjobeck M, Englund E. Locus ceruleus degeneration is ubiquitous in Alzheimer's disease: Possible implications for diagnosis and treatment. Neuropathology 2006;26:528-32.
12. Chalermpalanupap T, Kinkead B, Hu WT, Kummer MP, Hammerschmidt T, Heneka MT, *et al*. Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. Alzheimers Res Ther 2013;5:21.
13. Del Tredici K, Braak H. Dysfunction of the locus coeruleus-norepinephrine system and related circuitry in Parkinson's disease-related dementia. J Neurol Neurosurg Psychiatry 2013;84:774-83.
14. Berridge CW, Dunn AJ. DSP-4-induced depletion of brain norepinephrine produces opposite effects on exploratory behavior 3 and 14 days after treatment. Psychopharmacology (Berl) 1990;100:504-8.
15. Gottesmann C. Noradrenaline involvement in basic and higher integrated REM sleep processes. Prog Neurobiol 2008;85:237-72.
16. Majumdar S, Mallick BN. Cytomorphometric changes in rat brain neurons after rapid eye movement sleep deprivation. Neuroscience 2005;135:679-90.
17. Ranjan A, Biswas S, Mallick BN. Cytomorphometric changes in the dorsal raphe neurons after rapid eye movement sleep deprivation are mediated by noradrenalin in rats. Behav Brain Funct 2010;6:62.
18. Majumdar S, Faisal M, Madan V, Mallick BN. Increased turnover of Na-K ATPase molecules in rat brain after rapid eye movement sleep deprivation. J Neurosci Res 2003;73:870-5.
19. Biswas S, Mishra P, Mallick BN. Increased apoptosis in rat brain after rapid eye movement sleep loss. Neuroscience 2006;142:315-31.
20. Gulyani S, Mallick BN. Effect of rapid eye movement sleep deprivation on rat brain Na-K ATPase activity. J Sleep Res 1993;2:45-50.
21. Jaiswal MK, Mallick BN. Prazosin modulates rapid eye movement sleep deprivation-induced changes in body temperature in rats. J Sleep Res 2009;18:349-56.
22. Mallick BN, Singh A. REM sleep loss increases brain excitability: Role of noradrenaline and its mechanism of action. Sleep Med Rev 2011;15:165-78.
23. Mallick BN, Singh A, Khanday MA. Activation of inactivation process initiates rapid eye movement sleep. Prog Neurobiol 2012;97:259-76.
24. Mallick BN, Thankachan S, Islam F. Differential responses of brain stem neurons during spontaneous and stimulation-induced desynchronization of the cortical eeg in freely moving cats. Sleep Res Online 1998;1:132-46.
25. Chu NS, Bloom FE. Activity patterns of catecholamine-containing pontine neurons in the dorso-lateral tegmentum of unrestrained cats. J Neurobiol 1974;5:527-44.
26. Cedarbaum JM, Aghajanian GK. Afferent projections to the rat locus coeruleus as determined by a retrograde tracing technique. J Comp Neurol 1978;178:1-16.
27. Jones BE, Yang TZ. The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. J Comp Neurol 1985;242:56-92.
28. Berod A, Chat M, Paut L, Tappaz M. Catecholaminergic and GABAergic anatomical relationship in the rat substantia nigra, locus coeruleus, and hypothalamic median eminence: Immunocytochemical visualization of biosynthetic enzymes on serial semithin plastic-embedded sections. J Histochem Cytochem 1984;32:1331-8.
29. Somogyi J. Llewellyn-Smith, IJ. Patterns of colocalization of GABA, glutamate and glycine immunoreactivities in terminals that synapse on dendrites of noradrenergic neurons in rat locus coeruleus. Eur J Neurosci 2001;14:219-28.
30. Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: Reciprocal discharge by two brainstem neuronal groups. Science 1975;189:55-8.
31. Sakai K, Sastre JP, Kanamori N, Jouvet M. State-specific neurons in pontomedullary reticular formation with special reference to the postural atonia during paradoxical slep in the cat, in Brain mechanism and perceptual awareness, Pompeiano O, Marsan CA, editors. New York: Raven Press; 1981.
32. Pal D, Mallick BN. Role of noradrenergic and GABA-ergic inputs in pedunculopontine tegmentum for regulation of rapid eye movement sleep in rats. Neuropharmacology 2006;51:1-11.
33. Pal D, Mallick BN. GABA in pedunculopontine tegmentum increases rapid eye movement sleep in freely moving rats: Possible role of GABA-ergic inputs from substantia nigra pars reticulata. Neuroscience 2009;164:404-14.
34. Kaur S, Saxena RN, Mallick BN. GABAergic neurons in prepositus hypoglossi regulate REM sleep by its action on locus coeruleus in freely moving rats. Synapse 2001;42:141-50.

35. Monti JM, Pandi- Perumal SR, Sinton CM, editors. Neurochemistry of sleep wakefulness. Cambridge: Cambridge University Press; 2008.
36. Mallick BN, Pandi-Permual SR, McCarley RW, Morrison AR, editors. Rapid Eye Movement Sleep – Regulation and Function. Cambridge: Cambridge University Press; 2011.
37. Dahlstrom A, Fuxe K. Localization of monoamines in the lower brain stem. Experientia 1964;20:398-9.
38. Aston-Jones G, Bloom FE. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1981;1:876-86.
39. Jacobs BL. Single unit activity of locus coeruleus neurons in behaving animals. Prog Neurobiol 1986;27:183-94.
40. Mallick BN, Siegel JM, Fahringer H. Changes in pontine unit activity with REM sleep deprivation. Brain Res 1990;515:94-8.
41. Kaitin KI, Bliwise DL, Gleason C, Nino-Murcia G, Dement WC, Libet B. Sleep disturbance produced by electrical stimulation of the locus coeruleus in a human subject. Biol Psychiatry 1986;21:710-6.
42. Singh S, Mallick BN. Mild electrical stimulation of pontine tegmentum around locus coeruleus reduces rapid eye movement sleep in rats. Neurosci Res 1996;24:227-35.
43. Kaur S, Panchal M, Faisal M, Madan V, Nangia P, Mallick BN. Long term blocking of GABA-A receptor in locus coeruleus by bilateral microinfusion of picrotoxin reduced rapid eye movement sleep and increased brain Na-K ATPase activity in freely moving normally behaving rats. Behav Brain Res 2004;151:185-90.
44. Jaiswal MK, Dvela M, Lichtstein D, Mallick BN. Endogenous ouabain-like compounds in locus coeruleus modulate rapid eye movement sleep in rats. J Sleep Res 2010;19:183-91.
45. Thankachan S, Islam F, Mallick BN. Role of wake inducing brain stem area on rapid eye movement sleep regulation in freely moving cats. Brain Res Bull 2001;55:43-9.
46. Choudhary RC, Khanday MA, Mitra A, Mallick BN. Perifornical orexinergic neurons modulate REM sleep by influencing locus coeruleus neurons in rats. Neuroscience 2014;279:33-43.
47. Alam MA, Mallick BN. Glutamic acid stimulation of the perifornical-lateral hypothalamic area promotes arousal and inhibits non-REM/REM sleep. Neurosci Lett 2008;439:281-6.
48. Mallick BN, Thankachan S, Islam F. Influence of hypnogenic brain areas on wakefulness- and rapid-eye-movement sleep-related neurons in the brainstem of freely moving cats. J Neurosci Res 2004;75: 133-42.
49. Mallick BN, Kaur S, Saxena RN. Interactions between cholinergic and GABAergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats. Neuroscience 2001;104:467-85.
50. Mallick BN, Singh S, Pal D. Role of alpha and beta adrenoceptors in locus coeruleus stimulation-induced reduction in rapid eye movement sleep in freely moving rats. Behav Brain Res 2005;158:9-21.
51. Thakkar, M, Mallick, BN. Effect of rapid eye movement sleep deprivation on rat brain monoamine oxidases. Neuroscience 1993;55:677-83.
52. Basheer R, Magner M, McCarley RW, Shiromani PJ. REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. Brain Res Mol Brain Res 1998;57:235-40.
53. Majumdar S, Mallick BN. Increased levels of tyrosine hydroxylase and glutamic acid decarboxylase in locus coeruleus neurons after rapid eye movement sleep deprivation in rats. Neurosci Lett 2003;338:193-6.
54. Pal D, Mallick BN. Neural mechanism of rapid eye movement sleep generation with reference to REM-OFF neurons in locus coeruleus. Indian J Med Res 2007;125:721-39.
55. Mallick BN, Majumdar S, Faisal M, Yadav V, Madan V, Pal D. Role of norepinephrine in the regulation of rapid eye movement sleep. J Biosci 2002;27:539-51.
56. Mallick BN, Jha SK, Islam F. Presence of alpha-1 adrenoreceptors on thermosensitive neurons in the medial preoptico-anterior hypothalamic area in rats. Neuropharmacology 2002;42:697-705.
57. Baskey G, Singh A, Sharma R, Mallick BN. REM sleep deprivation-induced noradrenaline stimulates neuronal and inhibits glial Na-K ATPase in rat brain: In vivo and in vitro studies. Neurochem Int 2009;54:65-71.
58. Keshavan MS, Reynolds CF, Kupfer DJ. Electroencephalographic sleep in schizophrenia: A critical review. Compr Psychiatry 1990;31: 34-47.
59. Lake CR, Sternberg DE, van Kammen DP, Ballenger JC, Ziegler MG, Post RM, *et al*. Schizophrenia: Elevated cerebrospinal fluid norepinephrine. Science 1980;207:331-3.
60. Angela M, Finch VS, Robert M. The Adrenergic receptors: In the 21st Century. Perez DM, editor. Totowa, New Jersey: Humana Press; 2006.
61. Zhong H, Minneman KP. Alpha1-adrenoceptor subtypes. Eur J Pharmacol 1999;375:261-76.
62. Graham RM, Perez DM, Hwa J, Piascik MT. alpha 1-adrenergic receptor subtypes. Molecular structure, function, and signaling. Circ Res 1996;78:737-49.
63. Macrez-Lepretre N, Kalkbrenner F, Schultz G, Mironneau J. Distinct functions of Gq and G11 proteins in coupling alpha1-adrenoreceptors to Ca2+ release and Ca2+ entry in rat portal vein myocytes. J Biol Chem 1997;272:5261-8.
64. Wu D, Katz A, Lee CH, Simon MI. Activation of phospholipase C by alpha 1-adrenergic receptors is mediated by the alpha subunits of Gq family. J Biol Chem 1992;267:25798-802.
65. Das G, Gopalakrishnan A, Faisal M, Mallick BN. Stimulatory role of calcium in rapid eye movement sleep deprivation-induced noradrenaline-mediated increase in Na-K-ATPase activity in rat brain. Neuroscience 2008;155:76-89.
66. Green SA, Holt BD, Liggett SB. Beta 1- and beta 2-adrenergic receptors display subtype-selective coupling to Gs. Mol Pharmacol 1992;41:889-93.
67. Sulakhe PV, Vo XT. Regulation of phospholamban and troponin-I phosphorylation in the intact rat cardiomyocytes by adrenergic and cholinergic stimuli: Roles of cyclic nucleotides, calcium, protein kinases and phosphatases and depolarization. Mol Cell Biochem 1995;149-150:103-26.
68. Gerhardstein BL, Puri TS, Chien AJ, Hosey MM. Identification of the sites phosphorylated by cyclic AMP-dependent protein kinase on the beta 2 subunit of L-type voltage-dependent calcium channels. Biochemistry 1999;38:10361-70.
69. Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, Rosemblit N, *et al*. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): Defective regulation in failing hearts. Cell 2000;101:365-76.
70. Oshima N, Onimaru H, Yamamoto K, Takechi H, Nishida Y, Oda T, *et al*. Expression and functions of beta- and beta-adrenergic receptors on the bulbospinal neurons in the rostral ventrolateral medulla. Hypertens Res 2014;37:976-83.
71. Meitzen J, Luoma JI, Stern CM, Mermelstein PG. beta1-Adrenergic receptors activate two distinct signaling pathways in striatal neurons. J Neurochem 2011;116:984-95.
72. Kompa AR, Gu XH, Evans BA, Summers RJ. Desensitization of cardiac beta-adrenoceptor signaling with heart failure produced by myocardial infarction in the rat. Evidence for the role of Gi but not Gs or phosphorylating proteins. J Mol Cell Cardiol 1999;31:1185-201.
73. Lawler OA, Miggin SM, Kinsella BT. Protein kinase A-mediated phosphorylation of serine 357 of the mouse prostacyclin receptor regulates its coupling to G(s)-, to G(i)-, and to G(q)-coupled effector signaling. J Biol Chem 2001;276:33596-607.
74. Balkin TJ, O'Donnell VM, Wesensten N, McCann U, Belenky G. Comparison of the daytime sleep and performance effects of zolpidem versus triazolam. Psychopharmacology (Berl) 1992;107:83-8.
75. Aghajanian GK, VanderMaelen CP. alpha 2-adrenoceptor-mediated hyperpolarization of locus coeruleus neurons: Intracellular studies in vivo. Science 1982;215:1394-6.
76. Isom LL, Cragoe EJ Jr, Limbird LE. Alpha 2-adrenergic receptors accelerate Na+/H+ exchange in neuroblastoma X glioma cells. J Biol Chem 1987;262:6750-7.
77. Michel MC, Brass LF, Williams A, Bokoch GM, LaMorte VJ, Motulsky HJ. Alpha 2-adrenergic receptor stimulation mobilizes intracellular Ca2+ in human erythroleukemia cells. J Biol Chem 1989;264:4986-91.
78. Datta S, Siwek DF. Single cell activity patterns of pedunculopontine tegmentum neurons across the sleep-wake cycle in the freely moving rats. J Neurosci Res 2002;70:611-21.
79. Jha SK, Mallick BN. Presence of alpha-1 norepinephrinergic and GABA-A receptors on medial preoptic hypothalamus thermosensitive neurons and their role in integrating brainstem ascending reticular activating system inputs in thermoregulation in rats. Neuroscience 2009;158:833-44.
80. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, *et al*. A parallel group placebo controlled study of prazosin for trauma

nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry 2007;61:928-34.
81. Hilakivi I, Leppavuori A. Effects of methoxamine, and alpha-1 adrenoceptor agonist, and prazosin, an alpha-1 antagonist, on the stages of the sleep-waking cycle in the cat. Acta Physiol Scand 1984;120:363-72.
82. Laitman BM, Gajewski ND, Mann GL, Kubin L, Morrison AR, Ross RJ. The alpha1 adrenoceptor antagonist prazosin enhances sleep continuity in fear-conditioned Wistar-Kyoto rats. Prog Neuropsychopharmacol Biol Psychiatry 2014;49:7-15.
83. Singh A, Subhashini N, Sharma S, Mallick BN. Involvement of the alpha1-adrenoceptor in sleep-waking and sleep loss-induced anxiety behavior in zebrafish. Neuroscience 2013;245:136-47.
84. Das G, Mallick BN. Noradrenaline acting on alpha1-adrenoceptor mediates REM sleep deprivation-induced increased membrane potential in rat brain synaptosomes. Neurochem Int 2008;52:734-40.
85. Mallick BN, Adya HV, Faisal M. Norepinephrine-stimulated increase in Na+, K+-ATPase activity in the rat brain is mediated through alpha1A-adrenoceptor possibly by dephosphorylation of the enzyme. J Neurochem 2000;74:1574-8.
86. Mignot E, Guilleminault C, Bowersox S, Frusthofer B, Nishino S, Maddaluno J, *et al*. Central alpha 1 adrenoceptor subtypes in narcolepsy-cataplexy: A disorder of REM sleep. Brain Res 1989;490:186-91.
87. Kleinlogel H. Effects of the selective alpha 1-adrenoceptor blocker prazosin on EEG sleep and waking stages in the rat. Neuropsychobiology 1989;21:100-3.
88. Oswald I, Thacore VR, Adam K, Brezinova V. Apha-adrenergic receptor blockade increases human REM sleep. Br J Clin Pharmacol 1975;2:107-10.
89. Loew DM, Spiegel R. Polygraphic sleep studies in rats and humans: Their use in psychopharmacological research. Arzneimittelforschung 1976;26:1032-5.
90. Makela JP, Hilakivi IT. Effect of alpha-adrenoceptor blockade on sleep and wakefulness in the rat. Pharmacol Biochem Behav 1986;24:613-6.
91. Hilakivi I. The role of beta- and alpha-adrenoceptors in the regulation of the stages of the sleep-waking cycle in the cat. Brain Res 1983;277:109-18.
92. Mendelson WB, Gillin JC, Dawson, SD, Lewy, AJ, Wyatt, RJ. Effects of melatonin and propranolol on sleep of the rat. Brain Res 1980;201:240-4.
93. Dunleavy DL, MacLean AW, Oswald I. Debrisoquine, guanethidine, propranolol and human sleep. Psychopharmacologia 1971;21:101-10.
94. Bender W, Greil W, Ruther E, Schnelle K. Effects of the beta-adrenoceptor blocking agent sotalol on CNS: Sleep, EEG, and psychophysiological parameters. J Clin Pharmacol 1979;19:505-12.
95. Troncone LR, Tufik S. Effects of selective adrenoceptor agonists and antagonists on aggressive behavior elicited by apomorphine, DL-dopa and fusaric acid in REM-sleep-deprived rats. Physiol Behav 1991;50:173-8.
96. Tononi G, Pompeiano M, Pompeiano O. Modulation of desynchronized sleep through microinjection of beta-adrenergic agonists and antagonists in the dorsal pontine tegmentum of the cat. Pflugers Arch 1989;415:142-9.
97. Berridge CW, Foote SL. Enhancement of behavioral and electroencephalographic indices of waking following stimulation of noradrenergic beta-receptors within the medial septal region of the basal forebrain. J Neurosci 1996;16:6999-7009.
98. Kostis JB, Rosen RC. Central nervous system effects of beta-adrenergic-blocking drugs: The role of ancillary properties. Circulation 1987;75:204-12.
99. Kayed K, Godtlibsen OB. Effects of the beta-adrenoceptor antagonists acebutolol and metoprolol on sleep pattern in normal subjects. Eur J Clin Pharmacol 1977;12:323-6.
100. Conley RK, Li J, Ivarsson M, Hutson PH. Effect of the beta3 adrenoceptor agonist CL 316243 on hypothalamic 5-HT synthesis and suppression of REM sleep in the rat. J Psychopharmacol 2007;21:597-602.
101. Cruickshank JM. Beta-blockers and heart failure. Indian Heart J 2010;62:101-10.
102. Monroe RR, Heath RG, Mickle WA, Miller W. A comparison of cortical and subcortical brain waves in normal, barbiturate, reserpine, and chlorpromazine sleep. Ann N Y Acad Sci 1955;61:56-71.
103. Hartmann E, Cravens J. The effects of long term administration of psychotropic drugs on human sleep. I. Methodology and the effects of placebo. Psychopharmacologia 1973;33:153-67.
104. Stern WC, Morgane PJ. Effects of reserpine on sleep and brain biogenic amine levels in the cat. Psychopharmacologia 1973;28:275-86.
105. Hublin C, Partinen M, Heinonen EH, Puukka P, Salmi T. Selegiline in the treatment of narcolepsy. Neurology 1994;44:2095-101.
106. Goodwin FK, Bunney WE Jr. Depressions following reserpine: A reevaluation. Semin Psychiatry 1971;3:435-48.
107. Gaillard JM, de St Hilaire-Kafi S. Sleep, depression and the effects of antidepressant drugs. Acta Psychiatr Belg 1985;85:561-7.
108. Mallick BN, Alam MN. Different types of norepinephrinergic receptors are involved in preoptic area mediated independent modulation of sleep-wakefulness and body temperature. Brain Res 1992;591:8-19.
109. Bowyer JF, Weiner N. Alpha-2 adrenergic inhibition of Ca(++)-evoked [3H]norepinephrine release from synaptosomes is blocked by depolarization. J Pharmacol Exp Ther 1990;253:1063-9.
110. Aghajanian GK, Cedarbaum JM, Wang RY. Evidence for norepinephrine-mediated collateral inhibition of locus coeruleus neurons. Brain Res 1977;136:570-7.
111. Steriade M, McCarley RW. Brainstem control of wakefulness and sleep. New York: Plennum Press; 1990.
112. Herholz J, Crisponi L, Mallick BN, Rutsch F. Successful treatment of cold-induced sweating in Crisponi syndrome and its possible mechanism of action. Dev Med Child Neurol 2010;52:494-7.
113. Miyazaki S, Uchida S, Mukai J, Nishihara K. Clonidine effects on all-night human sleep: Opposite action of low- and medium-dose clonidine on human NREM-REM sleep proportion. Psychiatry Clin Neurosci 2004;58:138-44.
114. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003;98:428-36.
115. Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. Anesthesiology 1988;69:818-23.
116. Pellejero T, Monti JM, Baglietto J, Jantos H, Pazos S, Cichevski V, *et al*. Effects of methoxamine and alpha-adrenoceptor antagonists, prazosin and yohimbine, on the sleep-wake cycle of the rat. Sleep 1984;7:365-72.
117. Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. Anesthesiology 1989;71:75-9.
118. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. Anesthesiology 1992;76:948-52.
119. Raasch W, Jungbluth B, Schafer U, Hauser W, Dominiak P. Norepinephrine release is reduced by I(1)-receptors in addition to alpha(2)-adrenoceptors. Ann N Y Acad Sci 2003;1009:270-3.
120. Groch S, Wilhelm I, Diekelmann S, Sayk F, Gais S, Born J. Contribution of norepinephrine to emotional memory consolidation during sleep. Psychoneuroendocrinology 2011;36:1342-50.

How to cite this article: Singh A, Mallick BN. Targeting modulation of noradrenalin release in the brain for amelioration of REMS loss-associated effects. J Transl Intern Med 2015;3:8-16.
Source of Support: Funding from the JC Bose Fellowship, UGC and UPEII are acknowledged. The UGC extended fellowship to AS, **Conflict of Interest:** NIL.