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*Review*

# Vasopressin in circadian function of SCN

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The suprachiasmatic nucleus (SCN) that acts as the primary circadian pacemaker in mammals is responsible for orchestrating multiple circadian rhythms in every organism. A network structure in the SCN composed of multiple types of neurons orchestrates the circadian rhythms. Despite speculations regarding the working of the clock, the molecular mechanisms governing it is far from clear. The molecular mechanism seems to be woven around the genes present and their linking with the neuromodulators. With the advancement in knowledge regarding the role of neuromodulators in the workings of the clock, especially that of Arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP), the entire picture of the mechanisms involved and therefore the importance of these neuromodulators has changed considerably. AVP seems to be very important for the functioning of the clock and its role has been well established based on the evidence available at present. Enormous research is going on to study the role of AVP and new roles are likely to be assigned to AVP in the execution of function in the SCN. Of late, there have been reports indicating linkage of AVP with jet lag in a positive way, suggesting vasopressin signalling as a possible remedy for ill effects and their improvement. Studies also show circadian rhythm disturbances in mood disorders and the same is related to AVP levels in the SCN. Various findings are thus in accordance with strong suggestions for a critical role for AVP in SCN function.

**Keywords.** Clock function; neuromodulators; neurotransmitters; suprachiasmatic nucleus; vasopressin

**Abbreviations:** AVP, arginine vasopressin; AVP-ir, AVP immunoreactive; BMAL 1, brain-muscle-Arnt-like-protein 1; CCGs, clock controlled genes; *cry1*, cryptochrome 1; *cry2*, cryptochrome 2; CSF, cerebrospinal fluid; DM, dorsomedial; ENK, encephalin; GABA, gamma amino butyric acid; GRP, gastrin releasing peptide; m tim, m timeless; mper, m period; NMS, neuromedin; PACAP, pituitary adenylate cyclase-activating polypeptide; per2, period2; per1, period 1; pk2, prokineticin 2; RGCs, retinal ganglion cells; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; TTFL, transcription-and translational feedback loops; UBR4, ubiquitin protein ligase E3 component N-recognin; VIP, vasoactive intestinal polypeptide; VIP-ir, VIP immunoreactive; VIP-KO, VIP-deficient; VL, ventrolateral; WT, wild type.

## 1. Introduction

The unique nature of Arginine vasopressin (AVP) in the involvement of diverse physiological and behavioural processes is really amazing. Though earlier identified as a hormone and later as a neurotransmitter present in many areas of the body including brain, today it is known to have a role as a neuromodulator in brain especially in the SCN of the hypothalamus. AVP has a specific position in the SCN for more than one reason. The foremost among them is the fact that it is one of the first neurotransmitters to be identified in the SCN (Swaab *et al.* 1975; Vandesande *et al.* 1975; Van den pol and Tsujimoto 1985). AVP containing a sub-population of neurons is a characteristic feature of the SCN in many species including humans. AVP neurons of the SCN have pronounced variation in activity and it can be seen in human post-mortem brains as well. Deterioration of sleep/wake rhythms during aging and


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depression is correlated with the diminished AVP levels in the SCN. Loss of vasopressin neurons of the SCN is also found to be associated with increased activity fragmentation without loss of amplitude in humans. In addition, AVP signalling has been shown to modulate SCN period and phase in a spatially specific manner which makes the master clock interact with downstream tissues and thereby respond to environmental changes (Bedont *et al.* 2018). Moreover, on a broader basis, it has been suggested that AVP neurons form an essential component of the circadian pacemaker cells of the SCN (Mieda *et al.* 2016). All these point towards an inevitable role for AVP in circadian function.

Identification of SCN as a seat of the biological clock came in the year 1972 from two laboratories (Moore and Eichler 1972; Stephan and Zucker 1972). By coincidence, the neurotransmitter function of neuropeptides in general and AVP in particular were also reported in 1970s. A sizable population of vasopressin neurons in the SCN was identified only by 1975 (Swaab *et al.* 1975, Vandesande *et al.* 1975). Central circadian pacemaker has two regions, one region called ventral/ventrolateral (VL) and/or core, and the other subdivision called dorsal/dorsomedial (DM) and/or shell with hardly any clearcut demarcation of the two regions (Albers *et al.* 2017). About 20,000 densely packed neurons with approximately 10,000 in each nucleus (Reppert and Weaver, 2002) are divided into two groups (Herzog 2007) on the basis of their properties. Neurons of the VL region produce VIP, whereas the DM part has large population of AVP-producing neurons (10–30%). The dorsal part also receives strong input from ventral SCN, whereas ventral SCN has little input from dorsal SCN (Moore *et al.* 2002; Yamaguchi *et al.* 2003). A diverse range of neuropeptides are produced by the SCN and there are reports highlighting their location and function in the SCN (Van den pol and Tsujimoto 1985; Lee *et al.* 2013; Reghunandanan and Reghunandanan 2006). This review is not intended to be a comprehensive or exhaustive one regarding the role of all the neuromodulators of the SCN, instead it will focus on AVP since many studies have highlighted the crucial role of AVP and it was felt necessary to explore and bring out the most relevant information. In accordance with the modern view of considering AVP as a neuromodulator from a broad point of view, the discussion will be based as a neuromodulator especially considering the role of AVP in communication and the role in AVP signalling. Gene expression having intimate relation with AVP also is discussed.

## 2. Discussion

### 2.1 *Relevance of AVP in time keeping as of now*

Over the years, advancement in both methodology and techniques used to study the role of AVP in circadian timekeeping has given a definite answer to the role of AVP (Bedont *et al.* 2018; Mieda *et al.* 2016; Raghunandanan *et al.* 1991; Kalsbeek *et al.* 2010). However, role of AVP in the molecular basis of the working of the clock is not yet fully authentic. Nearly one-third of the SCN neurons in the rat synthesize AVP, and it is secreted by the SCN in a circadian pattern (Van den pol and Tsujimoto 1985; Ingram *et al.* 1996; Ingram *et al.* 1998). Among the three types of AVP receptors, V1a, V1b and V2, V1a receptor is the major mediator (Morel *et al.* 1992) for the circadian function carried out by AVP. AVP is found to increase the amplitude of firing rates of neurons of the SCN by activating V1a receptors during subjective day (Mihai *et al.* 1994a, b) and thus enhance the output. On the basis of these reports, it is likely that V1a signalling has an important role in the generation of overt circadian rhythms (Li *et al.* 2009).

An argument was prevalent that the presence of AVP in SCN may not be critical for the expression of many of the circadian rhythms which was supported by studies using AVP-deficient Brattleboro rats showing disturbances in many circadian rhythms. Local application of AVP into the SCN does not affect the free-running circadian wheel-running rhythm in hamsters (Albers *et al.* 1984) as well as entrained circadian food (Reghunandanan *et al.* 1987) and water intake (Reghunandanan *et al.* 1992). However, absence of AVP shows abnormalities of some of the expressed rhythms. One of the reports indicate free-running period of locomotor rhythms being lengthened in Brattleboro rats (Groblewski *et al.* 1981) V1a-deficient mice (Li *et al.* 2009) but not in V1a and V1b-deficient mice (Yamaguchi *et al.*2013). Transplantation studies (Lehman *et al.* 1987; Decoursey and Buggy 1989) have given a positive convincing role for AVP in circadian function.

## 3. AVP functions in the SCN

A variety of approaches ranging from behaviour models to electrophysiological and pharmacological studies have been undertaken (Brown and Nunez 1989; Jansen *et al.* 2000; Jansen *et al.* 2007; Murphy *et al.* 1998; Wideman *et al.* 2000) to establish the role of AVP

signalling and accordingly an array of studies was employed. Circadian variation in the concentration of AVP in cerebrospinal fluid with morning levels about 5 times more as compared to night hours (Reppert *et al.*1981) originates from AVP content of SCN (Jansen *et al.* 2007). Health, cognitive performance and alertness of individuals depends on the functional integrity of the biological clocks (Ramkisoensing and Meijer 2015). The central pacemaker remains at the top of the hierarchy of the organization and integrates light information to ultimately regulate rhythms in gene expression (Barca-Mayo *et al.* 2017). Individual cellular clocks and their integration aided by the presence of neuromodulators contribute to this function. Multiple oscillating neurons are coupled to act as a single circadian unit at the cellular level. Heterogeneity of the neurons, presence of large number of neuromodulators and the genes linking with them along with the requirement of synchronized network are among valid reasons for difficulty in assigning specific functions of the SCN precisely (Loh *et al.* 2015).

A number of neurotransmitters (Frenkel *et al.* 2017; Moore and Speh 1993; Welsh *et al.* 2010) and neuromodulators working in harmony are responsible for the coherent network-wide circadian oscillations. Basically, the clock can be entrained by light. A small subset of retinal ganglion cells (RGCs), intrinsically photosensitive, project to the SCN for mediating circadian photoentrainment. Many of the RGCs which project to the SCN are capable of releasing vasopressin that too more prominently at the end of the night as compared to the end of the day. Response of the SCN neurons is found to be enhanced by the light-induced AVP release. Further, this projection of RGCs and release of AVP enhances expression of immediate early gene *c-fos* and induction of c-fos (Kornhauser *et al.* 1996) and clock genes *per1* and *per2* (Field *et al.* 2000; Akiyama *et al.* 1999; Yan *et al.* 1999) in the SCN. Possible genes for glutamate and pituitary adenylate cyclase-activating peptide (PACAP) appear to be the clock genes *per1* and *per2*, which are induced in the SCN by light. VIP induces *per1* and *per2* expression in a phase-dependent manner (Nielsen *et al.* 2002), thereby suggesting that VIP is important for the light-induced phase shift at night. Photic entrainment of biological rhythms being dependent on expression of genes, vasopressin thus ultimately comes into play in the expression of circadian rhythms by the clock (Tsuji *et al.* 2017). Mammalian clock governed by genes for its working is in turn is linked with neuromodulators. The period gene and the clock gene both identified in 1971 in fruit fly and mice, respectively, are considered to be the basis of the molecular clock work. Peptides encoded by three clock-controlled genes (CCGs), Prokineticin 2 (PK2), cardiotrophin-like cytokine and AVP have been implicated as critical SCN output molecules to link SCN and its efferent targets (Cheng *et al.* 2002; Jin *et al.* 1999; Kraves and Weitz 2006). Among the CCGs in the mammalian SCN, the gene for the neuropeptide AVP is the most well studied. Luciferase reporter gene assays have shown that CLOCK-BMAL1 heterodimers act through an E-box enhancer in the vasopressin gene to activate transcription and this activation can be inhibited by two proteins mPER and mTIM (Jin *et al.* 1999). From a genetic point of view, there are conflicting reports regarding the influence of AVP signalling on SCN function. However, the first known signalling mechanism capable of organizing molecular clock properties in all directions of the SCN network is reported to be AVP (Bedont *et al.*2018).

Each neuron of the SCN has a self-sustained circadian oscillator (cellular clock) (Welsh *et al.* 2010; Mohawk *et al.* 2012). The present understanding regarding transcriptional/translational feedback loops (TTFL) for the molecular oscillations for the expression of genes and their products inhibiting their own transcription (Dunlap 1999; Takahashi 2016; Hardin 2011) is as follows: This auto-regulatory feedback loop called core loop having clock genes, *per1* and *per2*, *cry1* and *cry2*, Brain-muscle-Arnt-like protein 1 (*BMAL 1*) and their protein products (Reppert and Weaver 2002) take part in the generation of cellular circadian rhythms. The role of individual genes in rhythm generation is reported to be tissue specific. Out of the six clock genes, *clock* and *BMAL 1* are positive elements, whereas *per1*, *per2*, *cry1* and *cry2* are negative elements of the feedback loop. Thus, TTFL define circadian time and this is done by the SCN neurons. Each of the neurons is responsible for the 24 h gene expression and neuronal firing rate (Takahashi *et al.* 2008). In TTFL expression, cryptochrome and period genes are inhibited by their own protein products. *cry1* and *cry2* are essential components of the clock and their loss is reported to stop the clock in the SCN. Individual deletions, however, accelerate and decelerate the transcription process respectively (Edwards *et al.* 2016). AVP receptor signalling is crucial for *Cry*-dependent induction of circadian timing in the SCN (Edwards *et al.* 2016) because pharmacological blockade of AVP receptors abolished the same. Transcription of the period (*per1* and *per2*) and cryptochrome (*cry1* and *cry2*) genes is initiated through the *clock*: *BMAL 1* transcription complex in the TTF loop.

During the process protein products of per and cry genes which accumulates in the cytoplasm re-enter the nucleus to inhibit the transcription process (Takahashi *et al.* 2008). Buhr and Takahashi 2013 had reported an elegant mechanism operating in every cell of the body. According to this cellular rhythm are generated by interlocking feedback loops controlling the daily transcription of 'clock genes' and 'clock-controlled genes'. At the core, molecular circadian clock is a delayed negative feedback loop with positive elements which are the transcription factors *CLOCK* and *BMAL 1* during transcription and negative elements *PERIOD* and *CRYPTOCHROME* repressing transcription on a daily basis (Evans 2016).

## 4. Circuitry and signalling mechanism of SCN for time keeping

Authenticity in circuitry and coupling mechanism for the collective time keeping has been elusive so far. An interesting observation has been the participation of the glial cells along with neurons to participate in the regulation of circadian rhythms (Fonken *et al.* 2015; Li *et al.* 2002; Ng *et al.* 2011). Glial cells also display self-sustained circadian rhythm in cellular functions regulated by a 24 h TTFL at the molecular level (Evans 2016).

Astrocytes have (Marpegan *et al.* 2011; Burkeen *et al.* 2011; Womac *et al.* 2009; Prolo *et al.* 2005) persistent circadian clock gene expression and thereby participate in daily rhythms in neurons and behaviour (Tso *et al.* 2017). Barca-Mayo *et al.* (2017) had demonstrated for the first time a role for astrocyte *BMAL 1* in the mediation of circadian locomotor behaviour on the basis of the deletion of *BMAL 1* in astrocytes. Thus, similar to neurons astrocytes also have synchronous circadian oscillators in SCN which modulate daily rhythms in locomotor behaviour. Loss of *BMAL 1* in astrocytes lengthens locomotor period in SCN neurons. In effect astrocytes in the SCN can communicate to neurons to determine circadian rhythms (Tso *et al.* 2017).

VIP, GABA and AVP signalling are among the coupling factors which influence SCN function (Evans 2016). Role of VIP and GABA have been reported in the synchronizing of the SCN neurons (Vosko *et al.* 2007; Wang *et al.* 2014; Evans *et al.* 2013; Irwin and Allen 2010; Mohawk and Takahashi 2011; Granados-Fuentes and Herzog 2013). AVP is traditionally accepted as an output signal (Kalsbeek *et al.* 2010). AVP neurons are found to project within the SCN itself (Castel *et al.* 1990; Romijn *et al.* 1997) and exogenous AVP regulates the activity of the SCN neurons (Ingram *et al.* 1998; Mihai *et al.* 1994a, b; Liou and Albers 1989). This supports and confirms to a great extent the role of AVP in network. AVP receptor mediated changes and re-entrainment almost instantly as reported by Yamaguchi *et al.* (2013), rapid recovery following simulated jet lag in mice lacking *BMAL 1* in the AVP neurons and its reversal by SCN-specific rescue of molecular clock function (Mieda *et al.* 2015) are among some of the results available emphasizing the role of AVP. AVP signalling seems to be an important factor for setting the pace of re-entrainment and causes a change in SCN coupling which allows the entire network to shift rapidly to the new time zone. It is further reported (Maywood *et al.* 2011) that application of AVP can synchronize SCN neurons collected from mice deficient in VIP signaling. Though loss of AVP signaling does not preclude circadian oscillations, absence of AVPR1 and AVPR1b receptors in mice or slice preparations can phase shift more rapidly to resetting ones. This is an indication of weaker coupling across the network (Patton and Hastings 2018). Of late, a direct role for AVP in synchronization has been reported as well (Evans 2016; Yoshikawa *et al.* 2015).

### 4.1 *SCN networking and coupling*

Coupling between the SCN neurons and a variety of neuropeptide-mediated networking is the hallmark of the functioning of the SCN. Two exciting state-of -the-art genetic tools (Mieda *et al.* 2015; Lee *et al.* 2015) to investigate further into the mechanisms comes to mind and is worthwhile to consider. Mice with a *BMAL 1* deletion, specific to AVP-producing neurons, have shown marked lengthening in the free-running period and activity time of behavioural rhythms (Mieda *et al.* 2015). Mice in which *BMAL 1* was deleted specifically in AVP neurons was one of the tools used to study the nature of coupling. *BMAL 1* being one of the specific and essential transcription factors of the TTFL and *BMAL 1*-dependent oscillations of AVP neurons being able to modulate the coupling, its absence from the SCN neurons has been considered to be sufficient for the extinction of the circadian behavioural rhythm in mice (Bunger *et al.* 2000). Lee *et al.* (2015) had reported that neuropeptide neuromedin S (NMS) acts as cellular pacemaker to regulate circadian period, based on their observations of blocking synaptic transmission from NMS neurons and abolishing the molecular clock of NMS neurons, leading to *in vivo*

disruption of circadian rhythms. Loh *et al.* (2015) have given an authentication to the coordination by neurons using genetic tools and to establish the requirement of neurocircuits of SCN for the generation of circadian rhythmic behaviour. A new era has thus opened up regarding the microcircuits of the SCN for studying pacemaker function and this is likely to gain further momentum.

A number of oscillating cells present in the SCN are coupled to each other and provide coherent output rhythms (Mohawk *et al.* 2012). Network dynamics of gene expression is possible with intercellular communication only. Neuropeptides in distinct regions of the SCN have different functional roles (Vadnie and McClung 2017). Numerous mechanisms which include specific neurotransmitters, gap junctions, astrocytes and GABAergic signalling (Welsh *et al.* 2010; Vadnie and McClung 2017; Brancaccio *et al.* 2014) contribute to the coupling among SCN neurons. Diverse paracrine signals contribute to the molecular circadian cycling (Maywood *et al.* 2011). Cells of the SCN synchronize not only to each other but also to local environmental cycles for coherent daily behavioural pattern (Granados-Fuentes and Herzog 2013). Although studies involving neuromodulators have indicated VIP as a primary synchronizer, others like GABA, AVP and Gastrin releasing peptide (GRP) have equally important role in synchronizing mechanism. In addition, ProK2 and other unidentified ones may function in concert and in combination to contribute differentially for mediating the output of cellular oscillations in AVP neurons (Mieda *et al.* 2015) to achieve coupling. Cell - autonomous transcription -based clock with circuit level interactions perform synchronization in the neurons. Synchronization process requires not only neuropeptide signalling but also a close interdependent reciprocal relation between molecular clockwork and rhythmic electrical activity (Herzog *et al.* 2017). Rhythmic electrical activity depends on the daytime $Na^+$ and night time $K^+$ drag.

While admitting a preeminent role for VIP in circadian cellular synchrony, contribution from AVP augments this action. Cellular synchronized pace making is dependent on VIP-ergic signalling, but in the absence of this, AVP can contribute. AVP maintains high amplitude output from SCN in addition to modulating SCN re-entrainment (Kalsbeek *et al.* 2010; Li *et al.* 2009; Yamaguchi *et al.* 2013). A new understanding about the core mechanism operating in the clock has opened up with the identification of Ubiquitin Protein Ligase E3 Component N-Recognin 4 (UBR4) expressed in the AVP ergic neurons seen throughout the rostro caudal extent of the SCN. Its level shows variation with time of day (Ling *et al.* 2014). Light signals in the early subjective night increases the number of UBR4 expressing cells among the SCN neurons. UBR4 expression declines throughout the subjective day when levels of *per1* and *per2* rise in the cytoplasm. When nuclear levels of *per1* and *per2* peak in early subjective night, this also coincides with the sharp rise in the UBR4 expression. Thus, UBR4 acting within AVP ergic neurons participates and influence clock timing mechanism (Ling *et al.* 2014). Circadian clock gene expression being more pronounced in the shell region, it is regarded as a rhythmic compartment with core part being identified as a site for photic and non-photic integration (Hamada *et al.* 2004). VIP and AVP are responsible for integrating the cellular circadian rhythms (Evans 2016; Maywood *et al.* 2011) in different ways and to different extent. VIP in the SCN mediates the light signal from Retinohypothalamic tract (RHT) to the AVP containing neurons for its production (Ibata *et al.* 1993; Morin and Allen 2006) in such a way that its production is seriously affected by light (Francl *et al.* 2010). Lack of VIP signalling can also be critical to disturb circadian behaviour. Circadian behaviour rhythms are also dependent on the AVP containing neurons of the SCN, especially for the coupling of the activity onset and offset (Mieda *et al.* 2015). AVP could thus be regarded as a mediator of SCN neuronal network involved in build-up of cell clusters (Yamaguchi *et al.* 2013). Varadarajan *et al.* 2018 had studied the contacts among many of the peptidergically heterogeneous neurons VIP, Gastrin releasing peptide (GRP) and calretinin of the core and AVP and met enkephalin (ENK) of the shell. It was observed that AVP to VIP neuron contacts are less as compared to VIP to AVP which is numerous in wild type (WT) mice. In case of VIP-deficient (VIP-KO) mice AVP expressed is reduced in SCN and the number of appositions onto other peptidergic cell types is similar to the control WT mice. On the basis of these observations it was pointed out that VIP has an important role in modulating AVP expression levels in the SCN and there is peptidergic cell type communication among the above-mentioned neurons of the core and shell in the SCN. This may also be taken as an indication of the vital role for VIP in determining AVP expression levels in SCN, as reported in the first analysis of the mouse SCN connectome network (Varadarajan *et al.* 2018). AVP has a significant role in synchronization as suggested (Li *et al.* 2009) since loss of V1a and V1b receptors can be responsible for loosening of coupling. It is also seen that abolishing the

molecular clock in AVP expressing cells leads to weak coupling between neurons and also lengthened period of behavioural rhythms (Mieda *et al.* 2015).

## 5. Circadian rhythm misalignment

In today's society with its 24 h schedule, shift work becomes unavoidable. Similarly, people travelling to different time zones are subjected to jet lag. Circadian rhythm misalignment is seen in both shift work and jet lag. Enormous after-effects of shift work and jet lag have been reported that have resulted in serious problems. In both cases, desynchronization of the body's circadian rhythms and consequent misalignment between the circadian clock and external solar time occurs. In terms of external manifestations, weight gain and obesity, diabetes and increased cancer risk (Kondratova and Kondratov 2012; Kyriacou and Hastings 2010; Dardente and Cermakian 2007) exists. As of now, exposure to sunlight, use of jet lag pills and other methods are available. In this context comes the correction effects of vasopressin in decreasing the above-mentioned ill effects to a great extent, which is supported by the observation of vasopressin signalling as a possible therapeutic target. AVP can act as an important time-dependent mediator for light information function from retina to SCN. This action fits very well with the vasopressin jet lag linkage suggested (Yamaguchi *et al.* 2013). Blockade of V1a and V1b receptors in the SCN resulted in accelerated recovery from jet lag. Further, increasing evidences are available showing V1a receptor signalling in the generation of overt circadian rhythms. Coherent circadian rhythms depend on intracellular communication between SCN and its target neurons. Apart from exposure to light, neuromodulators and intracellular calcium concentration are the factors (Irwin and Allen 2010) for the light-induced modulation of gene expression in the SCN. Ca homeostasis in the SCN neurons is at least partially regulated by AVP and this is important for SCN neuronal synchronization. Calcium finds place in signal transduction pathways for photic entrainment and forms an essential component of the feedback loops that generate circadian rhythms (Lundkvist and Block 2005; Lundkvist *et al.* 2005). AVP has been shown to induce elevations of calcium level during the day and night in the SCN neurons (Irwin and Allen 2010). Thus, neuropeptides along with Ca levels contribute for the SCN synchronization and modulation of light input changes of the clock. This aspect can also be considered in relation to the remedial improvements seen in jet lag and other complications of circadian rhythms on exposure to bright light, which has been thus incorporated as one of the measures to overcome jet lag.

Kori *et al.* (2017) had advanced a theoretical concept called 'jet lag separatrix' using a mathematical model. Their report suggests a two-step re-entrainment to overcome jet lag by applying 4 h shift of LD cycle in a span of two successive days instead of a single 8 h shift which was the one followed earlier (Yamaguchi *et al.* 2013). When given in these two steps it required fewer days than when given in a single 8 h shift. This they had successfully tested in mice and found to be beneficial. Oscillatory amplitude of the clock genes of the SCN substantially dampened just after advancing LD cycle by 8 h as reported by Yamaguchi *et al.* (2013) was observed in the 4 h two-step as well. Considerable disruption of the cell-to-cell synchrony may be responsible for damped oscillations in clock gene expression seen. Mice genetically lacking V1a and V1b receptors, which are receptors for AVP in the SCN, were reported to be showing (Kori *et al.*2017) subtle dampening of the clock gene after advancing of the LD cycle. Three closely interrelated concepts of strong intercellular coupling in the SCN, large desynchronization just after advancing of LD cycle among SCN neurons and slow adaptation to the new LD cycle were put forward by Kori *et al.* (2017) to explain the jet lag effects.

## 6. AVP of SCN and probable linkage with mood disorders

Various studies in animals and clinical studies in humans have shown a linkage between the SCN and mood disorders. Further analysis shows AVP participation in mood disorders. Anxiety like behaviour is observed with phase advances and delays in experiments with mice. In human studies, jet lag due to eastward and westward journeys has opposing effects on mood. Environmental and genetic circadian rhythm disruptions (Vadnie and McClung 2017) can be observed in mood disorders. Circadian genes linkage with mood disorders have been reported (Soria *et al.* 2010; Utge *et al.* 2010; Lavebratt *et al.* 2009; McGrath *et al.* 2009). It is interesting to note that both in favour and against a casual role for SCN in mood disorders are available (Vadnie and McClung 2017) in the clinical and preclinical studies. Zhou *et al.* (2001) had reported increased AVP immunoreactive cells, but decreased AVP mRNA in the SCN of people with depression or bipolar disorder. This is due to a decrease in AVP

transport and release in patients with mood disorders, thereby showing a build-up of AVP in SCN neurons. In yet another study, Wu *et al.* (2017), while investigating the role of GABA in the SCN in relation to changes in AVP in the SCN had also seen a significant increase in AVP-ir, especially in female subjects. The results were interpreted by them as the increase in AVP-ir accounting for a higher vulnerability to depression in women. Whatever may be the indication or derivation, positive and some negative in mood disorders from these studies, the fact remains that SCN disturbances seen in mood disorders are mediated by AVP at least partially if not fully as per the present-day state of knowledge.

## 7. Conclusions

The pivotal role of AVP in pacemaker function has been highlighted. This is based on the function of AVP as well as the altered circadian state seen in the SCN. Altered morphology in SCN as regards to the AVP and VIP neuronal numbers with no decrease in the expression levels of AVP and VIP mRNA is another important point identified. AVP in the circadian rhythms generated within SCN comes from the expression of AVP in many SCN neurons, many retinal cells projecting to the SCN. The inbuilt mechanism for communication in the mammalian circadian timing system is for the efficient communication between the environment and the central pacemaker SCN, as well as with downstream clocks in the body (Astiz *et al.* 2019). Knowledge about the circadian network entrainment has implications for the possible manipulation of the clock system in therapeutic procedure. AVP signalling as a possible therapeutic target cannot be ignored. Coordination among the neurons of the SCN using genetic tools and the role of subsequent neural circuits involving AVP are all pointing towards the same: AVP has both direct and indirect involvement in synchronization function of SCN. Various mechanisms available for the communication for clock to clock and to the external world are far from being understood completely. Cellular clocks of the SCN contribute for the stable expression of the rhythms. Looking forward, there is a need for a more detailed investigation into the various aspects of the AVP function based on network and coupling. This has been addressed to some extent in a recent study (Mieda 2019) in which the emerging role of AVP neurons based on genetic manipulation in mice was discused. A decrease in the AVP-ir neurons along with VIP-ir neurons in the SCN of individuals suffering from type 2 diabetes leading to circadian misalignment is yet another report (Hogenboom *et al.* 2019) in the same direction. In conclusion, one cannot stop investigating the ever-increasing involvement of neuromodulators and AVP, in particular, in making overt expression.

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