GENERAL DISCUSSION

A fundamental property of the mammalian clock is that it is based on a neural network which enables the organism to adjust to environmental cycles. For the functioning of the SCN as a clock, it is of major importance that the network shows plasticity. With this thesis I show that the output of the circadian system as an ensemble is more than the sum of electrical activities of its individual cells. In aging for example while the unified electrical activity output is still rhythmic, individual cells lose their circadian rhythmicity in many of their variables to a large extent. Although the rhythm of every single cell participates in forming the coherent output, the output is more than sum of the individuals. Therefore if a subpopulation of cells are defected, the ensemble output can still be functional, but modified. Here I discuss the cellular and network properties of the SCN in aging and photoperiodism based on the data presented in **chapters 3** to **6**.

AGING

Hypothalamic nuclei, including the SCN, are crucial for the neuroendocrine interaction between the central nervous system and the periphery by controlling the metabolism and relaying the environmental signals to other brain regions and downstream tissues. Recently many studies provide evidence revealing a clear role for hypothalamus in aging process as one of the control centers for aging and longevity (Zhang et al., 2013; Satoh and Imai, 2014). In **chapters 3** and **4** properties of aged SCN network and neurons were investigated to clarify the role of this hypothalamic nucleus in the aging process.

Aging Phenotype in the SCN

The data in **chapters 3 and 4** indicate that aging affects the SCN from cellular toward the behavioral level. The behavioral activity and the sleep-wake pattern were affected particularly during the night when the SCN network and single cell characteristics were mainly altered.

It is shown in **chapter 3** that old animals were unable to have a long consolidated waking episodes and displayed more NREM sleep in the night, which is their active phase. The activity duration shortened and rest duration lengthened progressively in senescence and behavioral activity pattern was increasingly fragmented as mice were aged. These activity-rest duration changes initiated when animals were approximately 700 days. The total activity levels decreased and the period increased much earlier in mice life span, in adulthood ~ 300 days.

The light-induced phase-shifting capacity, which is a hallmark feature of the circadian clock depending on SCN network connectivity (Vanderleest et al., 2009), was reduced dramatically in old mice. The reduced amplitude of electrical activity rhythms in old mice seen in **chapter 3** and previous studies (Satinoff et al., 1993; Watanabe et al., 1995; Nakamura et al., 2011) was mainly caused by significant number of active subpopulations clustered around mid-night.

Many of the membrane properties and ionic channel functions were affected by aging in the SCN in different phases of the cycle:

During the day electrical firing frequency and the magnitude of the transient A-type K^+ current, I_A, of aged SCN neurons were decreased as compared to the young SCN. Consequently, the circadian regulations of both electrical activity and I_A currents were lost in aged SCN neurons (**chapter 3**).

During the night two types of the K^+ currents essential for action potential repolarization and afterhyperpolarization were modified in aged SCN neurons and their circadian regulation was blunted: FDR and BK currents (**chapter 3 and 4**). On the other hand, rhythmic regulation of resting membrane potential and input resistance deteriorated (**chapter 3**), and daily rhythm of intracellular Ca^{2+} concentration was inversed in aged SCN neurons at night (**chapter 4**).

Both in the day and night the amplitude of GABAergic currents and cell capacitance were decreased in aged SCN neurons (**chapter 3**).

There were also some cellular properties which were **unaffected** by age in the SCN neurons such as the magnitude of the SDR current and the frequency of post synaptic GABAergic currents. [**chapter 3**; The later however was shown to be reduced in a previous study in aged SCN (Nygard et al., 2005)]. The data show that aging affects the circadian clock mechanism selectively, not due to a general deterioration of tissue or membrane function by age.

Role of potassium channels in aging

FDR current passes through Kv3.1b and Kv3.2 channels and Kv3.4 underlies I_A current in the SCN and other brain regions. Kv3 channels cause a rapid repolarization of the action potential and enable the cell to spike with high frequency (Rudy and McBain, 2001). Moreover, these channels are important for the modulation of synaptic interactions (Ishikawa et al., 2003; Goldberg et al., 2005), memory formation (Boda et al., 2012), cognitive functions (WTCCC, 2007; Yanagi et al., 2014), processing of auditory information (Zettel et al., 2007) and regulation of sleep-wake duration (Espinosa et al., 2004). Both FDR and I_A currents are affected by aging in the SCN. This is an indication of possible modification in Kv3 protein expression or function within the SCN during aging, which may also affect the sleep-wake regulation and intercellular communications in elderly. Sleep-wake changes reported in **chapter 3** in the course of aging such as increased NREM sleep and decreased waking could therefore be a result of changes at the cellular level within the SCN network which has interactions with sleep centers in the brain. Aging influences also the expression of Kv3 channels in other brain regions. Expression of Kv3.1 and Kv3.2 are increased in olfactory bulb (Boda et al., 2012), Kv3.1b protein is decreased in medial olivocochlear efferent system (Zettel et al., 2007) and Kv3.4 is less expressed in neocortex and

septum during aging process (Boda et al., 2012). These modifications cause different age-dependent disorders depending on the affected brain area.

K^+ currents and excitability in aged SCN

In aging, a reduction in the peak and an elevation of the trough of the circadian rhythm in multi-unit electrical activity of the SCN leads to a decline in the amplitude of the central clock output (Satinoff et al., 1993; Watanabe et al., 1995; Nakamura et al., 2011; Farajnia et al., 2012). Correspondingly, patch-clamp recordings have demonstrated that on the cellular level the frequency of electrical activity is reduced in aged SCN during the day compared to young controls (**chapter 3 and 4**). The I_A K^+ current which is diminished in the day in aged SCN, can be a possible cause of the reduced firing frequency (**chapter 3**). In young mice, application of an I_A channel blocker (4-AP, 5mM) reduced the amplitude of the SCN multi-unit electrical activity during the day (**Fig. 1**).

In the night firing frequency of aged SCN neurons measured with patch-clamp recordings shows a small, but not significant increase (**chapter 3**). The proportion of silent cells also decreased in aged group at night (but not significantly considering the small samples; **Fig. 2**). However, multi-unit recordings in vitro (**chapter 3**) and in vivo (Nakamura et al., 2011) revealed a significant increase of neuronal activity in the night. The night-time increase in neuronal activity is caused by a subpopulation of SCN neurons which generate action potentials in anti-phase to the main group of neurons active during mid-day (**Fig. 3** of **chapter 3**). FDR current promotes the repolarization

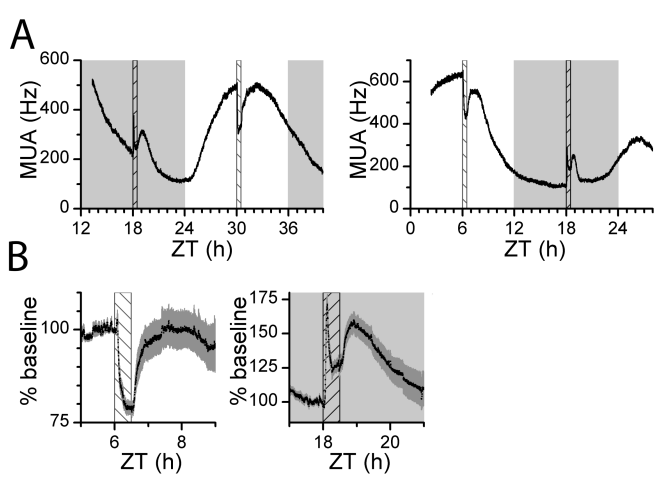

Figure 1. I_A channel blocker has a bidirectional effect on firing rate. (**A**) Different examples of multi-unit electrical activity with different time of slice preparation show similar results. During the day application of I_A channel blocker, 4-AP (5 mM, 30 min) reduced the SCN electrical activity. At night electrical activity was increased during the blocker application. (**B**) A zoom in the application time during the day (left) and at night (right). The vertical frame indicates the application time for day and night respectively at ZT6 and ZT18. The white and gray backgrounds represent the subjective day and night respectively.

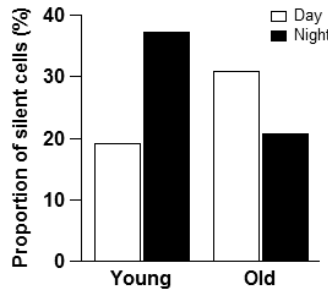

Figure 2. There is more electrical activity in the aged SCN at night. Bar graph of percentage of silent cells reveals that there are more silent cells in the day and less at night in aged group as compared with young group.

followed by an action potential in concert with I_A and BK currents (Bouskila and Dudek, 1995; Itri et al., 2005; Vandael et al., 2010) and therefore is considered to be a modulator of firing rate in the SCN (see **chapter 1**). It is also shown that genetic deletion of BK or FDR channels dramatically affects the output of the circadian system by disturbing the rhythms in behavior and SCN physiology (Meredith et al., 2006; Kudo et al., 2011). In aging, up-regulation of FDR current together with down-regulation of BK current -both during the night- could explain the subpopulation of SCN neurons which are active in anti-phase. Nevertheless, it seems that there are still a subpopulation of cells which function normally (**Fig. 3**). These normal subpopulations contribute to the compromised but still functional rhythm of the SCN network.

K^+ currents and membrane potential in aged SCN

In the young SCN cells an unidentified TEA-sensitive K^+ conductance was shown to be responsible for the night-time membrane hyperpolarization (Kuhlman and McMahon, 2004). As this K^+ conductance increases in the night the input resistance of SCN cells decreases at night compared to the day. There is a positive correlation between RMP and R_{input} in SCN neurons (Kuhlman and McMahon, 2004). In both **chapters 3** and **4** a more depolarized membrane potential of aged neurons as well as increased R_{input} was reported in the night. The responsible K^+ conductance for regulation of RMP may therefore be impaired or closed in aging at night. Changes of the FDR currents are in the opposite direction as they increase in the night. However, an age related reduction of the BK current occurs in the night. Blocking of the BK channels in young SCN neurons at night depolarizes the membrane potential significantly. BK current reduction in aging thus, is partly responsible for the depolarized membrane potential at night. Albeit, the role of other membrane potential modulators, such as K2P K^+ channels, cannot be excluded and needs to be investigated.

In summary, circadian controlled K^+ currents involved in excitability modulation, seem to be important players in the process of aging. During aging, oxidation of

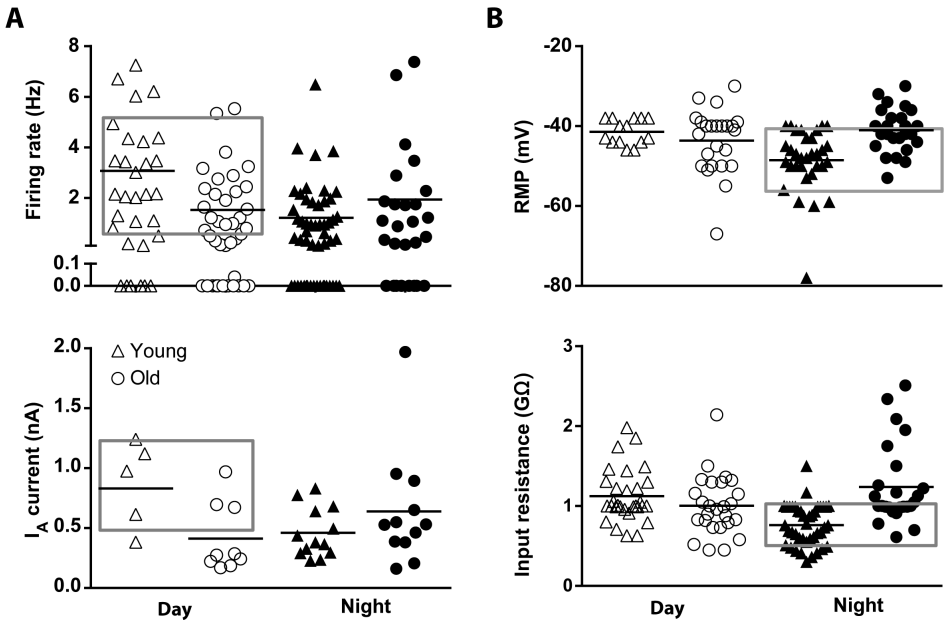

Figure 3. A group of aged cells function normally. (**A**) Scatter graphs for firing rate (top) and I_A current (bottom). Note that in old group there are more silent cells during the day and less at night compared to the young group. The frame is mean ± standard deviation of young cells in the day, when the significant changes occur in firing rate and I_A current in aged cells (**B**) Scatter graphs for resting membrane potential (RMP, top) and input resistance (bottom). The frame is mean ± standard deviation of young cells at night, when the significant changes occur in RMP and input resistance in aged neurons. Horizontal lines demonstrate the mean value for each experimental group.

potassium channels by reactive oxygen species is a major mechanism underlying the loss of neuronal function (Sesti et al., 2010). Restoring the normal rhythm of K^+ currents may help to preserve the functionality of the circadian system.

K^+ channels and Ca^{2+} signaling in aged SCN

Intracellular calcium concentration ($[Ca^{2+}]_i$) in the SCN is regulated by membrane voltage-gated or intracellular ligand-gated Ca^{2+} channels such as ryanodine or IP_3 channels (Diaz-Munoz et al., 1999; Pennartz et al., 2002). It is well known that Ca^{2+} channels are co-localized with BK channels in the cell membrane in many brain areas (Muller et al., 2007). Increased $[Ca^{2+}]_i$ is as effective as voltage to activate the BK channels in neurons (Faber and Sah, 2003). BK currents are crucial to regulate the action potential waveform as they are involved in membrane repolarization and afterhyperpolarization following an action potential (Shao et al., 1999; Faber and Sah, 2002; Womack and Khodakhah, 2002; Cloues and Sather, 2003; Lin et al., 2014). The shape of the action potential determines the amount of Ca^{2+} ions which enter the cell during spontaneous firing (Miranda et al., 2003; Womack et al., 2009; Lin et

al., 2014). When an action potential is prolonged and the repolarization is delayed, voltage-gated Ca^{2+} channels remain open for a longer time and allow elevated Ca^{2+} influx. In contrast a rapid repolarization and/or a fast afterhyperpolarization bring the membrane potential to the rest values more quickly, result in the closure of voltage-gated Ca^{2+} channels and less Ca^{2+} entry. The night-time impairment of BK current in aged SCN neurons is correlated with reduced AP amplitude, declined AHP peak and prolonged repolarization (**chapter 4**). Application of IbTX, the specific BK channel blocker to young SCN neurons caused attenuated AHP and prolonged repolarization in young SCN neurons and thereby emulates the aged phenotype. The decline in amplitude and the increase in duration of the AP however were reversed in aged neurons after experimental restoration of the membrane potential to values recorded in young SCN neurons (**chapter 4**). This demonstrate that reduced spike amplitude and prolonged repolarization are indirect consequences of depolarization of V_m by altered BK current and/or changes in other ion channels affecting resting membrane potential. In any case, depolarization of V_m will lead to a decline in the number of active fast Na^+ channels and delayed rectifier channels that contribute to amplitude and repolarization of the AP respectively. AHP amplitude however, was decreased directly by closure or impairment of the BK channels in aging. Therefore BK channel impairment alters the accurate shape of action potential at night and it may affect the $[Ca^{2+}]_i$ in the aged SCN. Ca^{2+} imaging experiments revealed that $[Ca^{2+}]_i$ increases in the aged SCN at night, when the BK currents and AP waveform are changed, but not in the day (**chapter 4**). Treating the young SCN neurons to the BK-channel blocker IbTX confirms the BK-dependent increase in $[Ca^{2+}]_i$ in the majority of cells in the night. BK channels therefore, are considered to be a functional link between membrane electrical activity and Ca^{2+} signaling and declined BK current in aged SCN contribute to disturbed rhythm in $[Ca^{2+}]_i$ and pathologically high concentrations at night.

In the process of aging, $[Ca^{2+}]_i$ increases not only in the SCN but also in many other brain regions, e.g. hippocampus and prefrontal cortex (Toescu and Vreugdenhil, 2010). Ca^{2+} ion is a ubiquitous intracellular messenger controlling a diverse range of cellular processes (Berridge, 2012). It has become clear that altered Ca^{2+} signaling affects viability and function of neurons in aging and neurodegenerative diseases (Muller et al., 1996; Hermes et al., 2010; Duncan et al., 2010b). Increased $[Ca^{2+}]_i$ in aged SCN neurons can trigger many intracellular pathways involved in gene transcription, neurotransmitter release and relaying light information. A rise in $[Ca^{2+}]_i$ at night could cause the decreased light-induced phase shifts in aging since, a low baseline $[Ca^{2+}]_i$ contributes to generating phase shifts in response to glutamatergic RHT transmission (Irwin and Allen, 2007). Thereby, increased $[Ca^{2+}]_i$ in aged SCN neurons may alter the function of SCN cells and finally the SCN output.

Restoring the decayed SIRT1 molecular pathway, involved in clock gene transcription, alleviates the aged-related decline in re-entrainment to environmental light/dark cycles (Chang and Guarente, 2013). Readjustment of $[Ca^{2+}]_i$ in aged SCN

thus, may help to ameliorate the aged phenotype reflected in physiology and behavior. Finding ways to restoring $[Ca^{2+}]_i$ balance could be a breakthrough in the improving clock function in the aged SCN.

PHOTOPERIODIC ADAPTATION

Many organisms must adapt their physiology and behavior to environmental daily and seasonal cycles to be able to survive. The SCN plays a key role in seasonal adaptation by adjusting its electrical output to the day length of the changing photoperiod. Intercellular communications are assumed to readjust the phase relationship between SCN neurons in different photoperiods. However, the precise mechanisms underlying the photoperiodic phase readjustment are not known. In **chapters 5** and **6** neuronal properties and GABAergic transmission in the SCN were investigated in different photoperiods simulating long summer days or short winter days. In the following part the results of these chapters will be discussed.

Impact of photoperiod on SCN single cell properties

The SCN encodes the day length by readjustment of neuronal phase distribution without changing the single cell profile in electrical activity which showed similar duration and amplitude after adaptation to long-day or short-day photoperiod (Vanderleest et al., 2007; Naito et al., 2008; Brown and Piggins, 2009). In **chapter 5**, intracellular electrical activity recordings of the SCN neurons confirmed this finding as the firing rate both in long-day (LD16:8) and short-day (LD8:16) photoperiods is comparable with those observed under equinoctial photoperiod (LD12:12): the firing frequency shows a rhythmic variation with a higher rate during the day and a lower rate at night in all photoperiods. Passive membrane properties such as resting membrane potential and input resistance are unaffected in different photoperiods. Therefore, consistent with molecular and electrophysiological studies (Hazlerigg et al., 2005; Inagaki et al., 2007; Vanderleest et al., 2007; Naito et al., 2008; Brown and Piggins, 2009), the output and characteristics of single cells do not change in the process of photoperiodic adaptation. Photoperiodic phase adjustment thus is not a result of altered cellular circadian profile but is more likely to be caused by a modified intercellular communications.

Recording of three kinds of K^+ currents involved in action potential generation within the SCN revealed that I_A and SDR currents are not affected by photoperiod. However the FDR current was higher in the night in long-day photoperiod as compared to short-day and equinoctial photoperiods. Increased FDR current in long photoperiod is comparable with enhanced FDR current in aging during the night. Although, with aging the rhythmic regulation of the FDR current is deteriorated while in long photoperiod clock-regulated FDR rhythm is sustained but inversed in phase.

Surprisingly in both aging and long photoperiod, the elevated FDR current at night did not change the spontaneous electrical firing frequency. Next to its traditional

role of modulating spike frequency (Rudy and McBain, 2001), FDR current has other important roles in the brain; such as regulation of neurotransmitter release in brainstem and neocortical neurons (Ishikawa et al., 2003; Goldberg et al., 2005) and controlling long-range synchronization in pyramidal neurons (Harvey et al., 2012). FDR current in the SCN modulates circadian rhythm in spike frequency (Itri et al., 2005). In addition, FDR current is known to be important for synchronization of the SCN to photic information received from environment and is necessary for photic regulation of gene expression within the SCN (Kudo et al., 2011). Moreover, the magnitude of the FDR current is increased by light pulses or light-mediated stimuli such as GRP and VIP, received at night (Gamble et al., 2011; Kudo et al., 2013). Similarly light in *Drosophila's* photoreceptors rapidly up-regulates the *shab* family of delayed rectifier K^+ channels (Krause et al., 2008). This kind of quick reactions of Kv3 channels to environmental cues has also been reported in auditory brainstem neurons (Leao et al., 2010). It is therefore probable that light input to the SCN is modulating FDR current properties/ activity in a short time frame. Prolonged light duration in long-day photoperiod may thus modulate the FDR current. Altogether it is conceivable that the relation between FDR current and photic information is a two way road: FDR current relays the photic information in the SCN (Kudo et al., 2011), but light also can modulate the FDR current activity (Gamble et al., 2011; Kudo et al., 2013).

The role of the FDR current in photoperiodic adaptation is not clear. In neocortical neurons, FDR current has a crucial role in long-range synchronization (Harvey et al., 2012). In the SCN long-range synchronization between dorsal and ventral regions is affected by different photoperiods (Bodenstein et al., 2012). A rare cell-to-cell connection in long-day photoperiod enables the network to readjust to a broad activity phase. The FDR current may determine the degree of intercellular synchronization in the SCN network as it does in neocortex (Harvey et al., 2012). Illumination of the exact role of FDR currents in photoperiodic adaptation needs further investigations.

Environmental day-light and GABAergic signaling in the SCN

If the individual cellular output profile remains unchanged in different photoperiods, intercellular connections must be involved in photoperiodic phase adjustment within the SCN network. As GABA is the major neurotransmitter in the SCN and is implicated in phase synchronization, GABAergic synaptic transmission was studied in different photoperiods in **chapter 6**.

The frequency of the GABAergic spontaneous post-synaptic currents (sPSCs) during the day was decreased in short-day as compared to long-day photoperiod. These data suggest that GABAergic inputs to the SCN are modulated presynaptically by the day length.

Postsynaptically, GABA can act on the $GABA_A$ receptors within the SCN either with an excitatory or inhibitory function depending on the intracellular Cl^- concentration ($[Cl^-]_i$; see **chapter 1;** Wagner et al., 1997; De Jeu and Pennartz, 2002; Choi et al., 2008; Irwin

and Allen, 2009). $GABA_A$ receptor is coupled to a Cl^- channel therefore, E_{Cl} and E_{GABA} are about equal (Kaila, 1994). When Cl^- concentration is increased inside the cell, the E_{Cl} is shifted to more positive values. In this condition, stimulating the $GABA_A$ receptors results in Cl^- efflux and a depolarization of the membrane potential (Cherubini et al., 1991). NKCC1 and KCC2 are two important Cl^- co-transporters, which determine the cytosolic Cl^- concentration in the SCN (Belenky et al., 2008). NKCC1 transports the Cl^- ion into the cell and increases the $[Cl^-]_i$. Consequently, opening the Cl^- channel under this circumstance results in Cl^- efflux and membrane depolarization (**Fig. 3** of **chapter 1**).

In the SCN, GABA-mediated excitation has been reported particularly in the dorsal SCN at night (De Jeu and Pennartz, 2002; Albus et al., 2005; Choi et al., 2008). Experiments described in **chapter 6** show that adaptation to long-day photoperiod (16h light) significantly enhances the excitatory responses to the GABA in the SCN when compared to short (8 h light) or equinoctial (12 h light) photoperiod. Patch-clamp experiments revealed that this excitatory function of GABA is due to a depolarizing shift in E_{GABA}. Pharmacological experiments suggest that NKCC1 cotransporter is involved in the GABAergic functional switch during long-day photoperiod. E_{GABA} was shown to be modulated in the SCN depending on the region and time of the day (De Jeu and Pennartz, 2002). The NKCC1 co-transporter was recently shown to be involved in E_{GABA} modulation within the SCN (Alamilla et al., 2014). In long-day photoperiod the switch in the function of GABA from inhibition to excitation is a key pathway to transfer the external information to the SCN and whole body. Therefore, environmental cues are able to change the SCN function at the cellular and molecular level.

For several years it has been known that GABA acts as an excitatory neurotransmitter within the SCN. However the role of GABAergic excitation was elusive. An electrophysiological study from our laboratory indicated that GABAergic excitation is involved in inter-regional communications within the SCN (Albus et al., 2005). In **chapter 6**, a possible role for GABAergic excitation/inhibition ratio is suggested in photoperiodic adaptation. Interestingly, the role of inhibition in synchronization has been demonstrated previously in other neuronal networks and is now widely accepted (Bartos et al., 2002). Whether inhibition would also induce synchrony in the SCN remains to be established. In **chapter 6** I report a relatively high percentage of GABAergic inhibition in short-day when compared to long-day photoperiod, which could contribute to the phase synchrony seen in short days. However, Freeman *et al.* (2013) showed that GABA could be a desynchronizer and destabilizer in the SCN, but the degree of GABAergic excitation or inhibition was not evaluated in this study. We suggest that GABAergic excitation could be related to desynchronization due to the relative increase in excitation seen in the widely phase distributed condition (long-day photoperiod). Therefore, the polarity of GABAergic activity may shift the synchronous state of the network. The key mechanisms that contribute to the phase readjustment within the SCN may depend on the ratio of excitatory to inhibitory GABAergic activity within the SCN, rather than an overall increase in GABAergic tone.

Long-day photoperiod changes a neurotransmitter function not only in the SCN, but also can switch the expression of dopamine to somatostatin within single cells in other hypothalamic nuclei (Dulcis et al., 2013). The paraventricular nucleus is one of these nuclei which receives the light information indirectly from the SCN. There is clear evidence that altered environmental lighting causes stable changes in DNA structure within the SCN (Azzi et al., 2014). Plastic DNA methylation results in altered gene expression and behavioral adaptation in the SCN. DNA methylation alters the period of the circadian behavior and seasonal reproductive phenotype (Stevenson and Prendergast, 2013; Azzi et al., 2014). A prolonged light duration in summer days or in modern life society using artificial lights, affects at least some brain circuits. While neuronal adjustments to environmental cues in natural situation such as long summer days can be beneficial for the organisms, artificial environmental changes may affect our brains in an undesired way. GABAergic signaling is a common pharmacological target to cure or ameliorate many neurological disorders such as sleep problems (Passarella and Duong, 2008; Gajcy et al., 2010). GABA function is affected by length of the day in the SCN, but may also be influenced in other brain regions by similar or other external cues. Exposure to artificial evening light in the 24/7 society may therefore affect our physiology and behavior with negative effects on health and well-being.

CONCLUDING REMARKS AND FUTURE DIRECTION

Neuroscientist believed for many decades that adult brain specially neurotransmitter system is stable and static throughout the life. This view is now slowly changing and we start to realize that the brain is more plastic than foreseen even in adults. This thesis evidenced that mammals possess very adaptable clock circuits. The plasticity within the clock results from changes in intra and intercellular communications and helps the organism to adjust to environmental signals such as gradual natural changes in photoperiod throughout a year. In contrast, cellular properties are adjusted in response to physiological perturbations, such as aging, perhaps to preserve the functionality of the system.

Aging of the SCN occurs in all level of organization from molecular level towards the entire network. It is not certain whether the defective cells and interrupted intercellular communication found in aging in the SCN are caused by or are a causal factor of aging. What is certain is that the modified aged SCN output is reflected in the altered behavioral activity and sleep-wake pattern. However, the ensemble output of the SCN neuronal network is more robust than individual cells' output suggesting a compensatory role of the network in aging. Voluntary exercise improves the amplitude of the SCN's electrical and molecular rhythms in aged mice (Leise et al., 2013) confirming that other systems, *in vivo*, could compensate partially for the cellular deficiencies in the SCN and ameliorate the aged network function. The mechanisms by which the network corrects for cellular deficiencies are not known however, the intact system seems to be needed for such restoration.

A functional well-preserved clock will help a healthy aging. Potassium ion channels are one of the key players in the SCN aging process and can be new targets for therapeutic manipulation to mitigate the age-related disorders.

Hypothalamic nuclei coordinate complex neuroendocrine outputs and homeostatic mechanisms by integrating different internal and external signals. The network of the SCN directly receives the light information from the environment and being the main circadian pacemaker, it entrains many peripheral oscillators both within and outside the brain. The individual SCN cells compose a network that exhibits more properties than its solitary components. A better understanding of the network function and cellular properties of the SCN helps us to control or prevent modern life-related diseases caused by circadian disturbances and aging.

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