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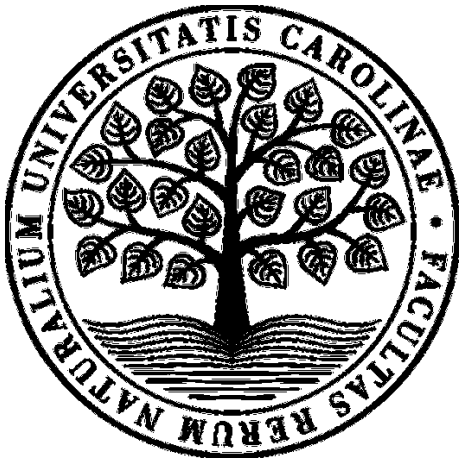

Nicole Aemilia Urban

Vliv psychofarmak na cirkadiánní hodiny v mozku

Effect of psychopharmacological drugs on circadian clocks in brain

Bakalářská práce

Vedoucí závěrečné práce:
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Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval/a samostatně a že jsem uvedl/a všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, ……

Poděkování

Chtěla bych poděkovat především své školitelce doc. PharmDr. Aleně Sumové, CSc., DSc., za trpělivost a cenné rady.

Anotace

Tato bakalářská práce poskytuje přehled poznatků ohledně vlivu dopaminergních substancí na vnitřní hodiny mozku. Cirkadiánní rytmy jsou endogenní povahy a probíhají periodicky v circa 24hodinových cyklech. Tyto rytmy ovládají mnoho procesů, zejména cyklus bdělosti a spánku, změny v teplotě těla či hladině určitých hormonů. První znaky cirkadiánní rytmicity mohou být pozorovány již během embryonálního vývoje a v raných postnatálních stádiích, kdy jsou synchronizovány s hodinami matky. Cirkadiánní systém savců podléhá hlavním hodinám, které se nachází v suprachiasmatickém jádru v hypotalamu (SCN). Dopamin jakožto neurotransmiter přenáší informace v dopaminergních drahách, které slouží v mozku mimo jiné v systému odměn. Metamfetamin je stimulant spadající mezi amfetaminy. Amfetaminy zvyšují hladinu dopaminu a také částečně blokují jeho vstřebávání. Probíhající výzkumy nalezly propojení mezi dopaminergním systémem a cirkadiánním systémem. Léze SCN způsobuje ztrátu behaviorálních rytmů a zvíře zůstává arytmické. Suplementace metamfetaminem se pojí s návratem rytmicity s dlouhou periodou. Metamfetamin-senzitivní oscilátor by mohl být jednou z příčin, avšak jeho povaha zůstává stale neobjasněná.

Klíčová slova: metamfetamin, cirkadiánní hodiny, SCN, hodinové geny, dopaminergní látky

Annotation

This bachelor's thesis summarizes what is known about the effect of dopaminergic substances on circadian clocks in the brain. Circadian rhythms are of endogenous nature and run periodically in circa 24-hour cycles. The rhythms control many processes, namely the sleep/wake cycle, the changes in body's temperature or the levels of certain hormones. The first rhythmicity can be detected during the embryonal development and early postnatal stages when the clocks are synchronized with the mother's clock. The circadian system of mammals is governed by the master clock located in the suprachiasmatic nuclei of the hypothalamus (SCN). Dopamine as a neurotransmitter transfers information in the dopaminergic tracts which work, apart from other functions, as a part of reward center of the brain. Methamphetamine is a stimulant categorized under amphetamines. Amphetamines increase the levels of dopamine as well as block some of its reuptake. Ongoing research found a connection between the dopaminergic system and the circadian system. Lesion of the SCN causes loss of the behavioral rhythms leaving the animal arrhythmic. Supplementation with methamphetamine has been shown to rescue the behavioral rhythmicity running with a long period. Methamphetamine-sensitive oscillator could be one of the causes, although its nature remains to be elucidated. This bachelor's thesis will provide overview of the up-to-day knowledge on the issue.

Keywords: methamphetamine, circadian clock, SCN, clock genes, dopaminergic drugs

List of abbreviations

BMAL1	*brain and muscle ARNT-Like 1*
CR	circadian rhythms
CRY	*cryptochrome*
DA	dopamine
GABA	Gamma-aminoburyric acid
GRP	gastrin-releasing peptide
LD	light-dark cycle
MAO	monoamine oxidase
MAP	methamphetamine
MASCO	methamphetamine sensitive oscillator
PER	*Period gene family*
RF	restricted feeding
SCN	suprachiasmatic nucleus
SS	somatostatin
VIP	vasoactive intestinal peptide
VP	vasopressin

Contents

1. Introduction to circadian clocks

Patterns of cycles can be found in each living organism on the Earth. In general, there are three levels of biological rhythms – infradian rhythms with a period longer than one day, circadian rhythms with a period length approximately of one day, and ultradian rhythms with a period shorter than one day. This bachelor thesis will focus on circadian rhythms (CR).

CR control the sleep/wake cycle, changes in body temperature, changes in hormone production during the day (e.g. melatonin), nutrient uptake etc. About 650 genes are dependent on the circadian cycles of the SCN and liver (Panda et al., 2002). The amount of protein coding genes that follow CR is about 43%, being different among tissues and organs (R. Zhang, Lahens, Ballance, Hughes, & Hogenesch, 2014).

CR are set by autonomous transcriptional and translational feedback loops of clock genes (see chapter 2). They can be entrained by external conditions, e.g. by keeping the organism in various light or dark conditions, restricting the feeding to a certain temporal window during the day, or, as will be further developed, by drugs.

CR are controlled by clocks with various levels of autonomy. The principal pacemaker is called the suprachiasmatic nucleus (SCN). More information on the SCN can be found in chapter 3.

The SCN, located in the hypothalamus, governs peripheral clocks by synchronizing their outputs. The regulation is mediated via several different paths depending on the tissue (Guo, Brewer, Champhekar, Harris, & Bittman, 2005). The adjustment of CR in behavioral activity happens via SCN-derived humoral signals rather than via neuronal connections (Silver, LeSauter, Tresco, & Lehman, 1996).

The SCN drives rhythms in peripheral tissues via autonomous nervous system formed by the sympathetic and parasympathetic pathways. The sympathetic path also controls production of melatonin (Perreau-Lenz et al., 2003) or contributes to the secretion of adrenal corticosteroids (Engeland & Arnhold, 2005). The multiple pathways which synchronize the peripheral clocks are summarized in Figure 1.

The peripheral clocks can be found in most of the tissues, e. g. lung, fat (both white and brown), kidney and many more (R. Zhang et al., 2014), including immune cells, like macrophages (Kurepa, Rabatić, & Dekaris, 1992). A self-sustained CR was found in the mouse retina culture (Ruan, Allen, Yamazaki, & McMahon, 2008).

The input to the SCN pacemaker is not conditional for the rhythm generation. However, oscillatory cells of most extra-SCN tissues need to receive rhythmic stimuli, otherwise they become mutually desynchronized, and gradually lose coherent rhythmicity (Moore-Ede, Schmelzer, Kass, & Herd, 1976). However, the synchronization does not mean that all extra-SCN clocks are running in the same phase. In nocturnal species, some of them are delayed relative to the SCN clock, and some may run even in antiphase to each other (Oishi, Sakamoto, Okada, Nagase, & Ishida, 1998).

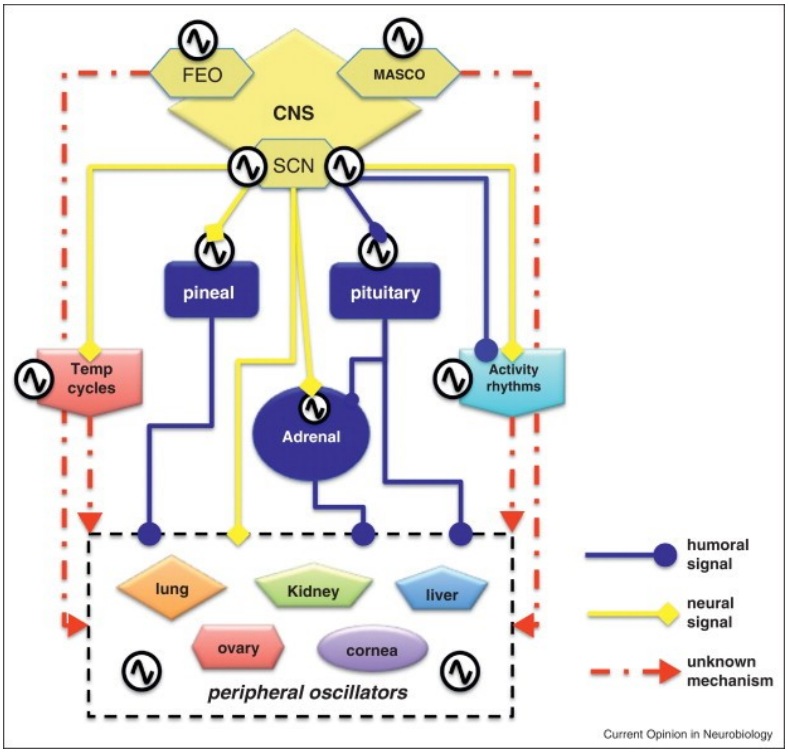

Figure 1: Scheme of various pathways the circadian clock in the SCN uses to control the rest of the body rhythms. While some mechanisms use humoral and neuronal signals, others have yet to be discovered (taken from Menaker, Murphy, & Sellix, 2013)

Having a properly running CR is crucial for humans, and their disruption is linked to a variety of mental health issues such as depression for review see (Germain & Kupfer, 2008) or schizophrenia (Wulff, Dijk, Middleton, Foster, & Joyce, 2018), physical issues such as obesity (for review see Broussard & Van Cauter, 2016), and even complex problems including addiction (for review see Barko, Shelton, Seggio, & Logan, 2019; Falcón & McClung, 2009; Logan et al., 2018; Webb, 2017).

2. Circadian transcription-translation feedback loop in mammals

The whole concept of circadian clock starts in the cell itself with a biochemical basis. The conservation of the genes involved in circadian rhythmicity has been going for millions of years, many of them are orthologues among the invertebrate and the vertebrata (Young & Kay, 2001). There have been found several clock genes involved in the CR of mammals.

The *Period (Per)* family consists of three paralogues *mPer1, mPer2 and mPer3,* each carrying a specific function, *mPer1* and *mPer2* being homologically closer than *mPer3* (Zylka, Shearman, Weaver, & Reppert, 1998). Both *mPer1* and *mPer2* share a PAS domain and both are light-inducible (Albrecht, Sun, Eichele, & Lee, 1997). The levels of *PERs* differ throughout the subjective day with *mPer1* levels rising first, followed by *mPer3* and later *mPer2,* each peaking at different times (Gekakis et al., 1998).

The *Cryptochrome (Cry)* genes, namely *Cry1* and *Cry2* are necessary for keeping the CR and their disruption leads to arrhythmicity. Mutants in *Cry1* run with a significantly shorter period, whereas the period of *Cry2* mutants lengthens (Horst et al., 1999). However, the *Cry* mechanisms may work independently of light conditions (Lucas & Foster, 1999).

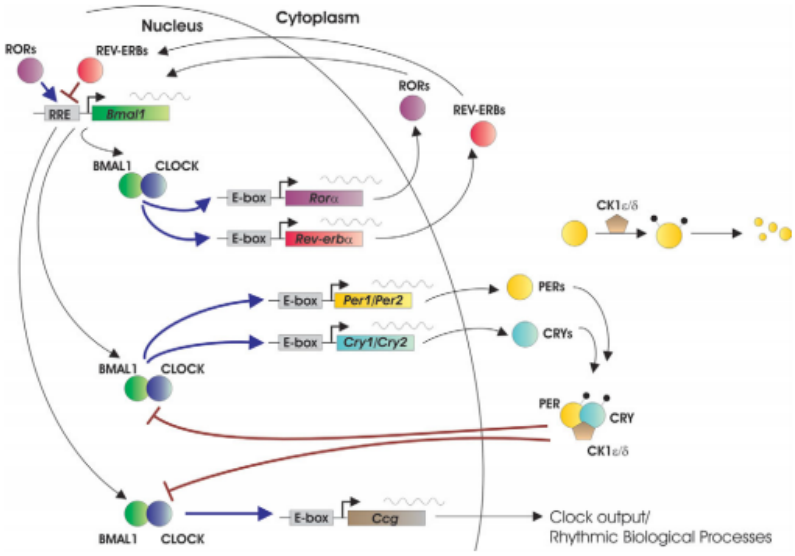

Figure 2: Scheme of the transcription-translation feedback loop done by (Ko & Takahashi, 2006). Various genes and their products are shown to influence each other in a cycle (explained in the text)

The rhythm in *Per* and *Cry* transcription is driven by the transcription-translation feedback loop as described in Figure 2. In this mechanism, the *Circadian locomotor output cycles kaput (CLOCK)* gene functions as a positive element by binding with *Brain and Muscle ARNT-Like 1* (*Bmal1),* inducing the activation of E-box in promotors of *Per1/Per2/Per3* and *Cry1/Cry2* genes. PERs and CRYs form heterodimers. The proteins are phosphorylated (Sangoram et al., 1998) by protein kinases CK1δ and CK1ε and are translocated into the nucleus where they inhibit their own transcription by blocking the transcription process on the BMAL1-CLOCK heterodimer. Since the rhythmic expression of the genes is dependent on their own products, the process is called negative feedback loop.

The additional loops involved in the mechanism involve activation of E-boxes (by the BMAL1/Clock heterodimer) of nuclear receptors *Rev-Erbαβ* and *Rorα/β.* These transcriptional factors are capable of blocking and activating the transcription of *Bmal1*, respectively (for review see Trott & Menet, 2018).

3. Suprachiasmatic nucleus

Suprachiasmatic nucleus (SCN) is a heterogeneous structure in the brain located in the anterior hypothalamus above the optic chiasm. The SCN is a circadian pacemaker responsible for generating the rhythmic signal and its synchronization with external environmental cycles. Without the synchronization, the rhythm would run with an endogenous period of approximately 24 h (Moore & Eichler, 1972; Stephan & Zucker, 1972).

The history of research leading to discovery of the SCN as the self-autonomous pacemaker is reviewed in the paper The Suprachiasmatic Nucleus: A 25-Year retrospective by David R. Weaver published in April 1998 (Weaver, 1998).

The SCN rhythm is synchronized with external factors called “zeitgebers” – the most important ones for mammals being light/dark conditions. However, there is a possibility of other factors which will be further developed later in this thesis.

The SCN is composed of cells which are capable of producing rhythms on their own, however, they need to be inter-connected to produce a coherent rhythm at the cell population level. When the neuronal paths in vitro are blocked, the cells become desynchronized (Welsh, Logothetis, Meister, & Reppert, 1995). The rhythm is directed by several of loci in different parts of the SCN

(Yamaguchi et al., 2003), that are shown in Figure 3. For example, *Per1* peaks in clusters at different times (Quintero, Kuhlman, & McMahon, 2003).

The bilateral SCN is divided into two parts: the ventral part and the dorsal part (Figure 3). These parts differ in the cell type and their distribution, the cells in the dorsal part being smaller and less spread (van den Pol, 1980). They also differ in function and the neurotransmitters expressed.

The ventral part (core) receives information from the retinal ganglion cells containing a special photopigment melanopsin. The connection is monosynaptic and is called the retinohypothalamic tract (Moore & Lenn, 1972). This part of the SCN produces two neuropeptides responsible for synchronization of neuronal activity within the SCN – vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) (Aioun, Chambille, Peytevin, & Martinet, 1998).

The dorsal part (shell) does not have a direct connection with retina and produces vasopressin (VP) and somatostatin (SS) (Abrahamson & Moore, 2001).

Gamma-aminoburyric acid (GABA) plays a role in connecting the ventral and dorsal SCN by providing the phase information between the two oscillators (Albus, Vansteensel, Michel, Block, & Meijer, 2005).

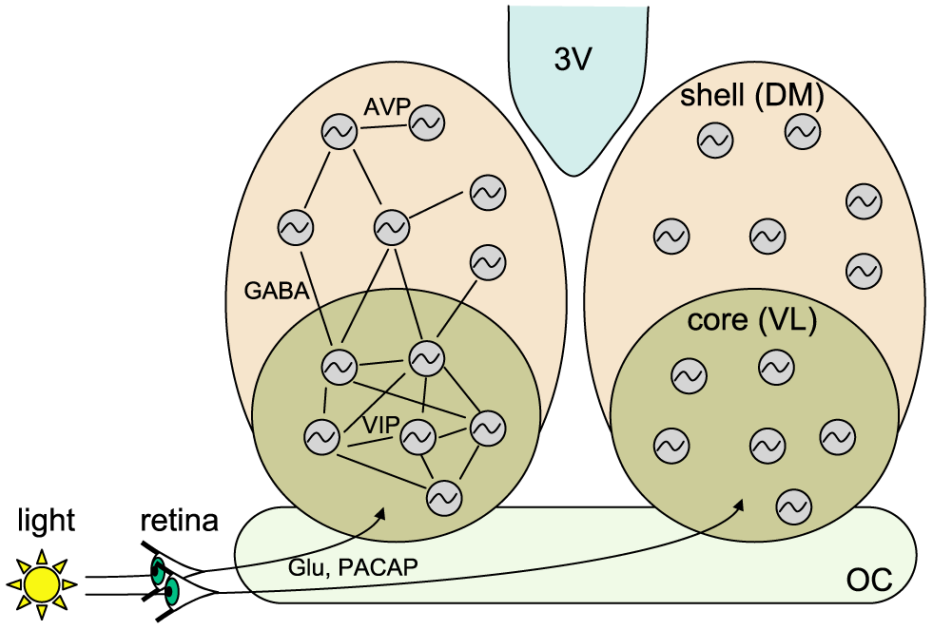

Figure 3: Schematic drawing of the SCN, its subpopulations and neurotransmitters (from Hafner, Koeppl, & Gonze, 2012).

When the SCN is surgically lesioned, the animal becomes behaviorally arrhythmic. However, the total amount of sleep did not differ between the SCN lesioned animals and animals with fully functional SCN (Liu, Zhang, Xu, Huang, & Qu, 2012).

The SCN develops during fetal stage. In rats, the neurogenesis takes place on embryonic days 12-18 of the embryonal development, peaking on day 16 (Ifft, 1972) and the SCN becomes fully recognizable as a structure on embryonic day 17 (Altman & Bayer, 1978).

In mice, the neurogenesis takes place on days 12-14.5 of the embryonal development, being heterochronous rostrocaudally and mediolaterally (Kabrita & Davis, 2008).

4. Extra-suprachiastmatic oscillators

Apart from the SCN, almost all peripheral tissues in the body have been found to keep their own oscillations, although without the SCN they would quickly get desynchronized. Setting their phases occurs for example by rhythmic release of hormones from the adrenal glands (Buijs et al., 1999). Other pathways are summarized in Figure 1.

In the brain itself, extra-SCN oscillations are found, often running in a different phase than the SCN (Harbour, Weigl, Robinson, & Amir, 2014) or even in an opposite phase (Lamont, Robinson, Stewart, & Amir, 2005).

Harbour and colleagues (Harbour, Weigl, Robinson, & Amir, 2013) studied patterns of expression of PER2 protein in 20 brain regions in rats entrained to four different light-dark (LD) cycles – each taking 12 hours of light and 12 hours of dark, starting with 6-hour shifts (the first one taking place at 3:00). The shifts did not differ and were only to prevent potential differences between the groups and to collect well distributed zeitgeber-affected samples. To characterize the expression of PER2 throughout the brain, samples were collected every 30 minutes and analyzed with an immunohistochemistry method, using a PER2 antibody.

Rhythmic patterns emerged in most of the brain regions, namely in the amygdala region, hippocampus, dorsal striatum, and nucleus accumbens. However, two regions came out as arrhythmic – medial amygdala and the nucleus accumbens shell. The question remains, whether the whole areas are arrhythmic or whether the cells are rhythmic but fail to synchronize with each other. The study suggests that the expression of *Per2* in the nucleus accumbens shell should be examined under drug administration.

The expression of *Per2* in most regions peaked in the last quarter of the dark phase. The expression of modified *Per* carrying the luciferase gene in brain tissue cultures done in vitro has shown a rhythm independent of the SCN in 14 of the 27 examined areas, including the olfactory bulb (Abe et al., 2002). The longest lasting rhythm was found in the pineal and pituitary glands.

4.1.Food-entrainable oscillator

One of the extra-SCN oscillators is the food-entrainable oscillator (FEO) which is entrained by a restricted feeding schedule (Mistlberger, 1994). The FEO can be measured by food anticipation during which locomotor activity increases. Lesion of the SCN does not affect the anticipatory activity (Stephan, Swann, & Sisk, 1979). However, location of FEO remains unknown. While connection with the digestive tract may seem intuitive, this logic has been proven faulty. Rather it seems that the amount of calories acts as a signal (Stephan, 1997).

No difference was found in animals kept under glucose and chow restriction regime and chow restriction – in both groups food anticipatory activity increased (Carneiro, Fernandes, Medeiros, Diniz, & Araujo, 2012), suggesting that sole glucose levels are not responsible for the entrainment of FEO, but glucose itself is capable of producing an anticipatory activity.

Some experiments speak for the FEO location in the brain, rather than in the peripheral tissue – e.g. one study suggested that lesioning the dorsomedial hypothalamic nucleus repressed the entrainment (Gooley, Schomer, & Saper, 2006), however, later studies did not confirm it.

Whether or not FEO is interacting with the other extra-SCN oscillator called methamphetamine sensitive oscillator (MASCO) (see below) is yet to be discovered (see 5.2.1. MASCO versus FEO).

5. Dopamine and its biosynthesis

Dopamine (DA) is a hormone and a neurotransmitter. The liver is necessary for synthesis of its precursor since it forms tyrosine from phenylalanine – an essential amino acid that need to be consumed in dietary sources. Tyrosine itself may also be consumed.

A facilitated diffusion carrier for tyrosine can be found in the blood-brain barrier which would otherwise restrict the passage of large molecules in and from the brain. The biosynthesis is catalyzed by the enzyme tyrosine hydroxylase.

Once synthetized in the brain, DA is transported into synaptic vesicles where it is sheltered from catabolic processes. After being released into the cytosol it is metabolized by monoamine oxidase (MAO) (Cumming, 2009).

Cells responsible for DA release are neurons located in the brain, namely in the basal nuclei – in the upper brain stem and diencephalon. The DA neurons are concentrated in the substantia nigra pars compacta (part of the basal nuclei) which releases the dopamine into the ventral striatum. These neurons also innervate the dorsal striatum.

High concentrations of DA were found in the striatum by Swedish researchers Bertler and Rosengren in the year 1959 (Marsden, 2006). The pathways between substantia nigra and the striatum and the ventral tegmental area were discovered by Andén and colleagues in 1966 (Andén et al., 1966).

High levels of DA were also measured in the median eminence of the diencephalon and the ventral tegmental area of the mesencephalon (Versteeg, Van der Gugten, De Jong, & Palkovits, 1976).

Levels of DA increase in the striatum after the use of stimulants, e.g. cocaine or methamphetamine. The prolonged use of drugs may lead into sensitization of the dopamine system (Nestler, 2005). The effects of methamphetamine will be further developed in chapter 6. Methamphetamine.

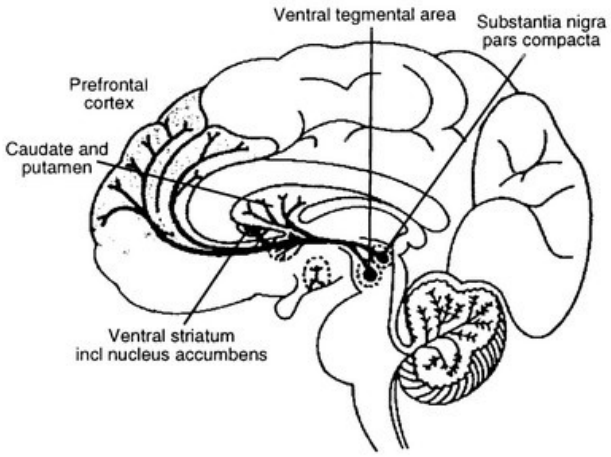

Figure 4: Scheme of the dopaminergic innervation in a brain of a primate (taken fromSchultz, 1999).

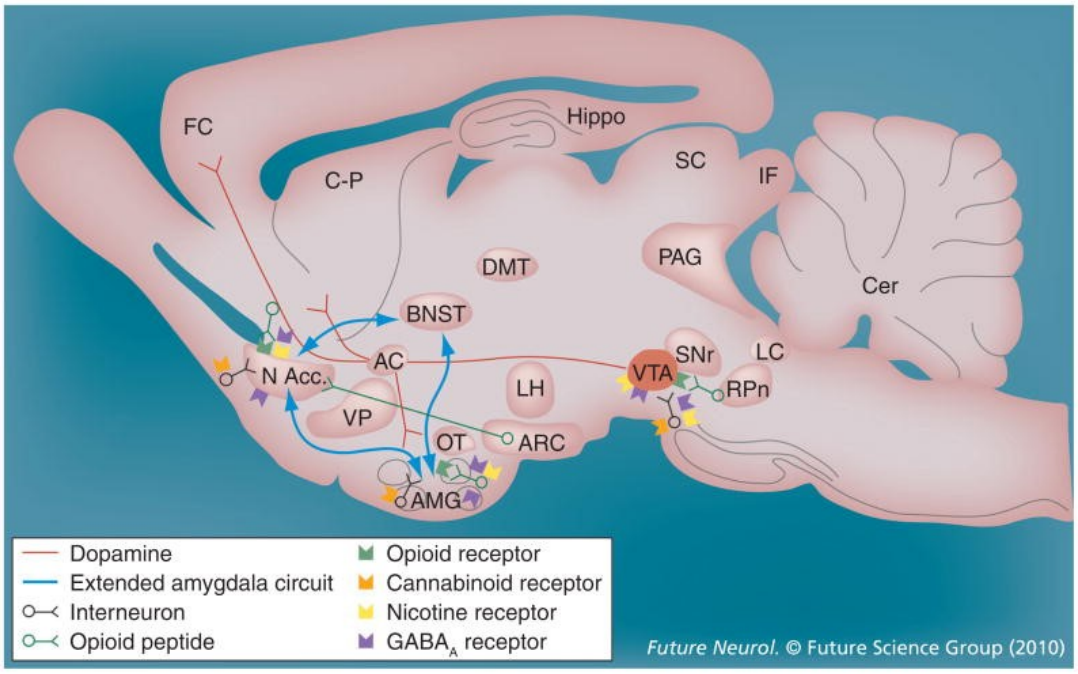

Figure 5: Scheme of neurotransmitter pathways in the rat brain (taken fromEdwards & Koob, 2010).

5.1.Dopamine receptors

Historically, there were two classes of dopamine receptors called D1 and D2, with D1 being excitatory and D2 inhibitory. D1 is now further divided to D1-like receptors D1 and D5. D2 is now divided into D2-like receptors D2, D3, and D4. D2 allows for expression of two splicing variants resulting in a short form (D2S) and a long form (D2L). Both classes are coupled to GTP-binding proteins (Cumming, 2009).

D2 receptors have been linked to drug addiction (Barnes, 1988). It has been proposed that cocaine increases the expression of D3 receptor mRNA in rodents (Le Foll, Francès, Diaz, Schwartz, & Sokoloff, 2002). Morphine has been shown to increase D3 receptor RNA but decrease D2 receptor RNA (Spangler, Goddard, Avena, Hoebel, & Leibowitz, 2003).

Mapping and comparing mRNA of D2 and D3 receptor has shown lower levels for the D3 receptor mRNA to the D2 receptor mRNA (Bouthenet et al., 1991). Moreover, their homology in the third cytoplasmatic loop is about 26%.

D2 receptors also play a role in the circadian system, enhancing the expression of CLOCK:BMAL1 dimer (Yujnovsky, Hirayama, Doi, Borrelli, & Sassone-Corsi, 2006). However,

the effect did not take place in nonneuronal cell lines. D2 receptors also helped alleviate the repression of CLOCK:BMAL1 caused by *mCry1*.

5.2.Dopamine and circadian system

Dopamine levels have been found to fluctuate in changing light/dark conditions. The transition from dark to light decreases dopamine levels as opposed to transition from light to dark mode, which increases dopamine levels in the extracellular matter (Castaneda, de Prado, Prieto, & Mora, 2004).

High levels of D1 receptor gene expression were found in the rat SCN in embryonic days 18 and 20. The mRNA levels were higher than those in the adult SCN, suggesting that a dopaminergic regulation may be important for the synchronization of the fetus' biological clock (Strother, Norman, & Lehman, 1998; Weaver, Rivkees, & Reppert, 1992). Stimulation of the D1 receptors induces expression of gene *c-fos* gene in fetal SCN, but not in adult rats (Weaver & Reppert, 1995). In adult hamster SCN, *c-fos* expression is inducted by exposure to light during night (Kornhauser, Nelson, Mayo, & Takahashi, 1990).

However, the DA receptor expression in the SCN lasts until adulthood. The dopaminergic input to the SCN has been proven necessary in hamsters, causing metabolic disruption (Luo, Luo, Meier, & Cincotta, 1997). The expression of D1 receptors in the SCN causes a prolonged entrainment period in mice (Grippo, Purohit, Zhang, Zweifel, & Güler, 2017). Introducing the expression of D1 receptors restores the entrainment to wild type.

DA receptors were found to affect responses to light stimulus called "positive masking". Masking is by definition *"the attenuation (negative) or enhancement (positive) of a measure of the circadian master clock by an exogenous stimulus or factor"* (Lamont & Amir, 2009). It is when a behavioral change occurs without the change in the endogenous cycle.

When the D2 receptor is missing in mice, they exhibit a normal light entrainment (Doi et al., 2006). The D2 receptor deficient mice also exhibit a reduced overall locomotor activity (Baik et al., 1995) during the dark period but not in the light period (Doi et al., 2006). To test the sensitivity of D2 receptors to light, the LD cycle was inverted. While in the wild type mice light exposure caused masking effect on their wheel running activity, the D2 receptor deficient mice stayed active on light during the inverted light/dark phase.

To confirm the effect, the mice were subjected to a light pulse test during the subjective night. Again, in wild type mice light inhibited the activity, whereas in the D2 receptor deficient mice it did not.

To further analyze the mechanism, the authors found that whereas in wild type mice light induced expression of gene *Per1*, in the mutant mice the induction was defective (Doi et al., 2006).

6. Methamphetamine

Methamphetamine (chemically *N*-methyl-1-phenylpropan-2-amine) as a drug falls into the category of stimulants and is classified as a Schedule II drug. Its chemical structure makes it related to phenylethylamine, amphetamine, and dopamine (*Neurobiology of Methamphetamine*, 2013).

There are two optical isomers – L-methamphetamine and D-methamphetamine, which is the one with stimulant effect (Lurie, Bozenko Jr., Li, Miller, & Greenfield, 2011).

6.1. Methamphetamine sensitive oscillator

As already mentioned, while SCN is the master clock in the body, there have been found other SCN-independent clocks in the brain, which also drive behavior. These clocks are sensitive to non-photic cues, such as food for FEO (as described in the chapter 4.1.). Another SCN-independent clock is sensitive to dopaminergic drugs, such as methamphetamine, and is called methamphetamine-sensitive (MASCO).

Experiments performed in rodents have shown significantly higher effect of methamphetamine in entraining rhythms with chronic usage (K.-I. Honma, Honma, & Hiroshige, 1986, 1987).

In 1986, Honma and colleagues applied methamphetamine to drinking water of Wistar rats (concentration 0.01 % and 0.005 %). The rats were placed on a LD cycle and treated with methamphetamine solution for consecutive period of 3-6 months. After the period passed, the methamphetamine solution was changed to tap water. The control group expressed locomotor activity during the dark part of the LD cycle, but the methamphetamine-treated male rats' activity cycle was delayed. The phase delay progressed until the middle of the light period, then changed and started phase advancing, until it reached its starting point.

In female rats, the process started immediately after the beginning of the methamphetamine treatment, and their rhythm free-ran, returning to norm 3-4 days after the end of methamphetamine treatment.

The researchers concluded that there were 3 possible explanations for the effect – (1) reduction of the sensitivity to light, (2) methamphetamine prolongs the period or (3) a new oscillator driving

the behavior is present. Reducing the sensitivity to light is not probable since the changes appeared the same after switching to DD cycle. There has been found a connection between period length and methamphetamine (Tataroglu, Davidson, Benvenuto, & Menaker, 2006).

In the follow up study in 1987, the same authors removed the SCN from rats completely, resulting in a complete absence of locomotor activity rhythm, then they proceeded with lacing water with methamphetamine – at a concentration of 0.005 %, same as in the previous study – which resulted in formation of a rhythm with a 26.4 h period. The lower the dose, the shorter the period became. However, the rhythm did not last after the withdrawal of methamphetamine.

To answer the question whether dopamine is involved in the MASCO mechanism, a non-selective dopamine receptor antagonist, Haloperidol, was injected into methamphetamine treated SCN lesioned rats. A phase dependent shift occurred, suppressing the locomotor activity for a prolonged period of time (S. Honma & Honma, 1995).

The results of Honma et al., 1987 suggested the existence of a methamphetamine sensitive oscillator which works independently on the SCN and is capable of driving behavioral rhythm in animals in which the SCN was lesioned.

Tataroglu and colleagues (Tataroglu et al., 2006) replicated the Honma experiment, which has been mentioned earlier, using mice. The lesion of the SCN was done via electrolytic method and the methamphetamine was given chronically with first effects showing in 7-14 days.

Their results were consistent between the rodent species; however, a couple of differences were discovered. While the rats expressed differences between male and female (K.-I. Honma et al., 1987), no such phenomenon was observed in mice (Tataroglu et al., 2006).

The MASCO cooperates with the SCN in non-lesioned rats (K.-I. Honma et al., 1986) and non-lesioned mice. The mice expressed deeper connection than rats (Tataroglu et al., 2006).

Both the mechanism and location of MASCO are yet to be discovered.

6.2.MASCO and FEO clock genes interaction

The interaction of MASCO and FEO is still in question.

Methamphetamine has a short-term effect on fasting blood glucose, slightly increasing it when injected chronically (4 weeks). The levels decrease after its discontinuation, finally returning to normal levels after several weeks (Y. Zhang et al., 2018).

In mice in which all three *Per* paralogues were knocked-out, the period determined by MASCO was present, however, it was shorter than in wild type mice (Pendergast, Oda, Niswender, &

Yamazaki, 2012). The rhythm, consistently with previous findings, was somehow cooperating with the SCN.

The same conditions were applied to mice to test the FEO. In mutant mice kept in constant darkness the FEO was not entrained to the restricted feeding with food supplied in a 24-hour cycle. It was however able to entrain to a 21-hour cycle, similar to the MASCO (running approximately at 21-hour cycles). In conclusion, the interaction between MASCO, FEO and canonical clock genes is more than probable.

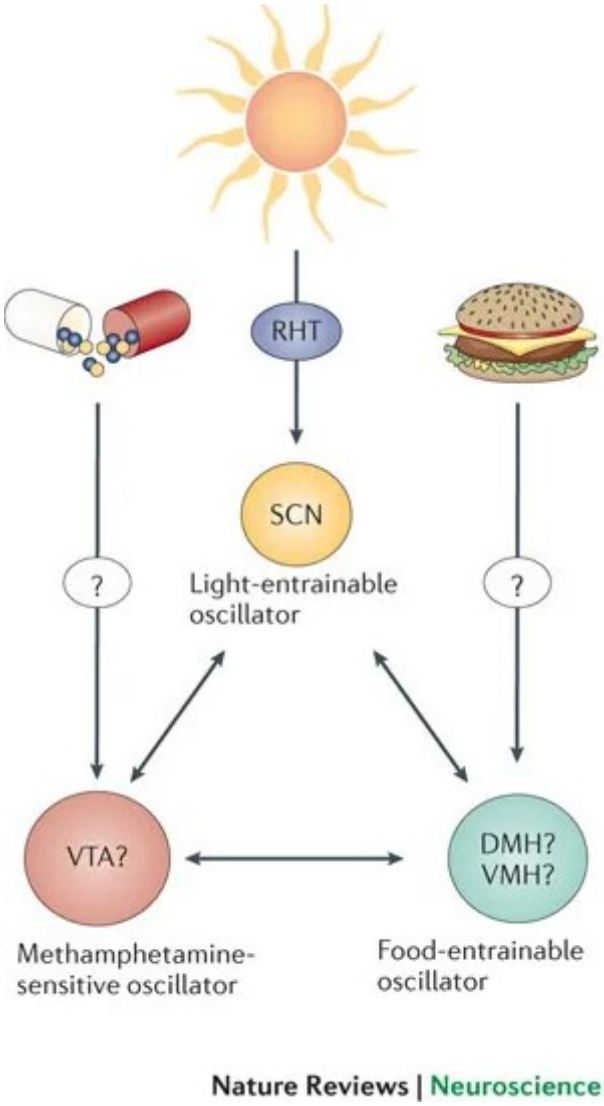

Figure 6: Scheme of the putative interaction between Food-entrainable oscillator (FEO) and Methamphetamine-sensitive oscillator (MASCO) (Masri & Sassone-Corsi, 2013)

6.3.Methamphetamine and canonical clock genes

Canonical clock genes are not employed by MASCO (Mohawk, Baer, & Menaker, 2009). There was a cohort of mice with various circadian clock genes defected (*Per1, Per2, Cry1, Cry2, Bmal1, Npas2, Clock* and *Ck1*ε) by either mutation or knockout. Some had SCN lesion. All the mice showed methamphetamine-induced changes.

The period of mutants lengthened, and a rhythm appeared in SCN-lesioned arrhythmic animals. The response to methamphetamine withdrawal differed among animals with various mutations. Both homozygous and heterozygous *Clock* mutants exhibited a rhythm for days and even weeks with the heterozygotes keeping the effects for a longer time.

There were cases of SCN-lesioned mice expressing a rhythm for a few cycles, supporting MASCO as an endogenous oscillator. The rest of the mice converted back to their original free-running cycles quickly (Mohawk et al., 2009). On methamphetamine, the period of intact mice is shorter than that of SCN-lesioned mice (Tataroglu et al., 2006), suggesting that MASCO cooperates with the SCN.

To test whether the clock genes *Cry1* and *Cry2* have a connection to MASCO, methamphetamine was administered to *Cry1/Cry2* double deficient mice in their drinking water in concentration 0.0025%. Most of the mice exhibited a rhythm with longer period than common in wild-type animals, varying from 23.8 to 32.3 h. Although one mouse failed to exhibit a CR, a circabidian rhythm of about 48 h was present. Just like in the experiment run by Mohawk and colleagues, the rhythms persisted after the withdrawal of methamphetamine from drinking water, indicating that *Cry1* and *Cry2* are not necessary for methamphetamine-induced activity (S. Honma, Yasuda, Yasui, van der Horst, & Honma, 2008).

When exploring the effect on the clock gene *Per2* (Natsubori, Honma, & Honma, 2014), methamphetamine was added to drinking water of rats for 14 days with the access to it for a restricted time of a day. After 14 days, the access was changed to ad libitum. For this experiment, only female rats with a *Period2-dLuciferase* gene were chosen.

The SCN of rats was lesioned and the rhythm was set by MASCO. In the brain slices cultures (SCN, olfactory bulb, caudate-putamen, parietal cortex and substantia nigra), CR were observed in the expression of Per2-driven bioluminesce. The rhythm diminished within several cycles in the OB as well as the rhythms in CPU and PC.

Phase-shift occurred in the expression of *Per2* in the extra SCN areas, being greater in SCN lesioned rats, which mean that the SCN still influenced the extra-SCN oscillators even when methamphetamine was present.

The result suggested that MASCO may be a complex of oscillators, rather than oscillator located in one brain region.

7. Cocaine

Cocaine, similar to methamphetamine, has been classified as a stimulant and a Schedule II drug. Both interact with the dopamine pathway, although the mechanism differs (for review see Lazzaretti, Mandolini, Altamura, & Brambilla, 2018).

7.1.Cocaine and circadian rhythm

Abarca and colleagues (Abarca, Albrecht, & Spanagel, 2002) administered cocaine intravenously to mice, searching for similar influence on homologous genes *mPer1* and *mPer2*. The first part of the experiment studied short-time sensibility.

The mice were separated to three groups – *mPer1* and *mPer2* mutants and wild-type. All groups responded similarly to initial injection. This reaction has not changed in mPer1 mutant mice after repeated administration followed with a 3-day withdrawal. Wild-type mice showed sensitized response and *mPer2* mutants responded hyper-sensitively. The test was then repeated with a lowered dose of cocaine 10 mg/kg to 5 mg/kg. The results remained consistent.

In the second part of the study, the test was repeated with a long-term sensitization, exposing the mice to cocaine for 3 consecutive weeks. Again, *mPer1* mutant mice showed no sensitization and *mPer2* mutant mice reacted hyper-sensitively.

These results represent a link between circadian clock genes and cocaine. Since the acute single administration showed no difference between the mice phenotypes but the chronic administration did, the mechanism responsible for acute and chronic effects lies under different genes (Abarca et al., 2002).

A different study (Wang et al., 2019) focuses not only on the genes *Per1* and *Per2*, but also the other clock genes *Per3*, *Cry*, *Bmal1* and *Clock*. The study was done on male Sprague-Dawley rats, which cocaine were injected intraperitoneally with cocaine at a dose 20 mg/kg at Zeitgeber time 4 for 21 days (Zeitgeber time 0 corresponds to lights on). The control group was administered saline solution.

Collecting of the tissue samples began 24 hours after last injection and was performed every four hours, starting at zeitgeber time 0 to zeitgeber time 20.

Cocaine treated rats expressed a shift in phase, and expressed a regular CR in expression of *rPer1*, *rClock* and *Bmal1* in the SCN. Decrease in *rPer2*, *rPer3* and *rCry* was observed (Wang et al., 2019) in the SCN. In the prefrontal cortex a diurnal rhythm emerged for *rPer1, rPer2, rPer3, rCry* and *rBmal1.* Their expression also increased with the exception of *rCry.*

8. Conclusion

Disrupted CR in humans have been linked to a variety of mental health issues including susceptibility to addiction and substance abuse. Addictive substances influence CR and vice versa. In past years, new pathways for regulating CR have been discovered. Apart from the SCN, two extra-SCN oscillators have been discovered – FEO, an oscillator sensitive to food, and MASCO, an oscillator sensitive to methamphetamine, a highly addictive substance falling under the Schedule II drug category. Details about MASCO have been developed in chapter 6. So far, the knowledge on MASCO is only sparse. Further research could lead to the discovery of its location and pathways used in interaction with FEO and SCN. MASCO runs independently of the SCN, however, a cooperation between MASCO and SCN has been explored for the wildtype animals which react differently to those with SCN lesion.

Methamphetamine is capable of restoring the rhythm in arrhythmic animals, albeit the effects last only for a limited number of cycles and differ dramatically between wildtype animals and clock mutant mice. Various clock genes are involved in the response to methamphetamine and levels of their expression alter the changes in behavior after ingesting methamphetamine, especially the duration of CR period. By knocking out the clock genes one by one, including well known *Per1, Per2, Cry1, Cry2, Bmal1* and *Clock*, none of them have been proved necessary for MASCO entrainment, although each mutation brought its own specification of the CR period. Circabidian rhythm emerged in one subject double deficient in *Cry1/Cry2* and period of the rest of the cohort appeared longer than of wildtype.

The effects differ among species, too. While the response in mice does not change among sexes, the opposite has been observed in rats.

Further research could also bring new information regarding other functions of MASCO, as rodents did not evolve alongside stimulants, thus raising questions about the structure's existence.

New evidence is needed to assess the cooperation and other links between MASCO and FEO, similar responses to both have been found and the oscillators probably interact with canonical clock genes.

The outcomes have been fairly consistent among studies, providing a grounding area for the exploration of the fascinating subject of MASCO.

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