(MINI REVIEW)

Neurotransmitters and nitric oxide are released in various brain areas according to ultradian and infradian rhythms

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Abstract

The push-pull superfusion technique was used to investigate release of endogenous neurotransmitters and nitric oxide in various brain regions. The transmitters catecholamines, histamine, GABA, glutamate, as well and nitric oxide are released according to ultradian rhythms which generate fluctuations of vegetative functions such as blood pressure and arousal. More frequent infradian oscillations of neurotransmitter and nitric oxide release fates are implicated in mutual interneural control.

Keywords: Push-pull superfusion; Ultradian and infradian oscillations; Neurotransmitter release; Nitric oxide; Blood pressure; arousal

1. Introduction

As determined by chronobiology, ultradian rhythms are periodicities repeated throughout a 24-hour day, whereas infradian rhythms last less than one hour. Meanwhile, several brain functions that control peripheral systems have been described which vary according to ultradian fluctuations. However, to get an insight into the mechanisms involved in the processing of these brain functions, more than their mere description is necessary. The knowledge of the neurons and their transmitters involved in these processes is indispensable for understanding how brain is working, but experimental approach is demanding.

An outstanding time resolution and very sensitive methods are needed to record rapid changes in the release rates of endogenous neurotransmitters from their neurons in very short time periods as is the case in ultradian and infradian rhythms. Because of these prerequisites, the push-pull superfusion technique (PPST) has been used in almost all investigations. In cats, the time resolution of PPST is as low as 10 s, in small animals like rats less than 2 min (for technical details see 1-4). Moreover, recoveries must be constant up to 20 h. In fact, no other approach fulfils these prerequisites for the quantitative determination of neurotransmitters released in the synaptic cleft. Other approaches such as microdialysis are not suitable, because glial cells around the probe modify after few hours the recovery of released transmitters and other compounds. Moreover, larger molecules do not permeate easily through the semipermeable membrane of the probe [5, 6]

Using the PPST it has been shown that in the cat posterior hypothalamus the release rates of the catecholamines dopamine, noradrenaline and adrenaline are not constant over time but they vary according a bimodal pattern, since peaks of high release rates are separated from each other by peaks of low amine concentrations pointing to phasic changes in the release rates of all three catecholamines. In six hours, five peaks of increased release rates appear. Thus, the time interval between two adjacent peaks is about 70 min showing that, in the cat hypothalamus, the three catecholamines are released according to an ultradian rhythm [7].

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In other brain areas of cats and rats, catecholamines are also released according to ultradian rhythms. When perfusates are continuously collected in time periods of 10 min, in the nucleus of the solitary tract (NTS) of cats the release of catecholamines oscillates with a frequency of approximately one cycle per hour. Moreover, when superfusates are collected every 2.5 min instead of 10 min an additional ultradian rhythm appears with a frequency of one cycle per 10 min [8]. In the locus coeruleus, dopamine, noradrenaline and adrenaline are liberated according ultradian rhythms of 37±2, 52±4 and 36±2 min, respectively [9]. Similarly, in the posterior hypothalamus of conscious, freely moving rats, the three catecholamines are released according to an ultradian rhythm of 92-99 min [10].

These fluctuations of catecholamine concentrations in the synaptic cleft are the reason for ultradian alterations of brain activity and consequently of neurovegetative functions such as central blood pressure control and arousal. Fluctuations of peripheral catecholamine levels are due to the abovementioned fluctuations in the catecholamine release in the brain [11]. It has also been shown that the catecholaminergic neurons of hypothalamus, nucleus of the solitary tract, locus coeruleus are strongly involved in central regulation of blood pressure [12, 13]. Moreover, striatal dopamine levels fluctuate in synchrony with ultradian activity cycles [14], while the dopaminergic neuromodulation of the monkey visual cortex greatly influences both spontaneous and visually-evoked neural activity [15]. Very likely, the fluctuating transmitter concentrations in the synaptic cleft lead to fluctuating stimulation of postsynaptically located auto-receptors and hetero-receptors, thus changing periodically the activity of peripheral sympathetic system and suprarenals [12, 13] and the levels of peripheral catecholamines fluctuate rhythmically. The release of other neurotransmitters, such as GABA [16], glutamate [17], histamine [18-20] and nitric oxide [3, 22, 22] also fluctuates according to similar ultradian rhythms. Findings are recapitulated in Table 1.

In the hypothalamus, the similar periodicities of transmitter release with those of autonomic, cardiovascular, and neuroendocrine rhythms provide evidence for their physical coupling within this brain region (Shannahoff-Khalsa and Philippu, to be published).

Besides ultradian rhythms, infradian oscillations [10, 20] have also been described in experiments, in which samples were continuously collected every 2.5 min. Obviously, they reflect interneural signals related to stimulation of autoreceptors and herewith are associated with mutual regulations of neuronal activity (Table 1).

Interestingly, ultradian and infradian oscillation have been found in conscious and anaesthetized animals as well (Table 1).

Please the following four lines should appear below the Table!Ultradian rhythms in min. Samples were collected in time periods of 10 min or *2.5 min. NAc nucleus accumbens, PH posterior hypothalamus, AH anterior hypothalamus, NTS nucleus of the solitary tract, LC locus coeruleus, MAN medial amygdaloid nucleus, MB mammillary body, DA dopamine, NA noradrenaline. A adrenaline, HI histamine. GLU glutamate, an. anaesthetized, co. conscious (modified from Philippu, 2016).

Table 1 Ultradian and infradian rhythms of neurotransmitters and nitric oxide released in various brain regions

	Animal Species	NAc	PH	AH	NTS	LC	MAN	MB
NO	an. rat	24						
DA	an. cat		70	70	60 10*	37		
NA	an. cat		70	70	60 10*	52		
A	an. cat		70	70	60 10*	36		
HI	an. cat	60					135 19*	90 19*
HI	an. rat		115					
HI	co. rabbit	70	70					
GABA	co. rat		65					
GABA	an.cat	70	70					
GLU	co. rat		45					

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2. Conclusion

Several neurotransmitters and the neuromodulator nitric oxide are released according to ultradian and infradian rhythms in various brain regions, which reflect oscillating neuronal activity. These rhythmic changes are the reason for the ultradian alterations of the peripheral neurovegetative system.

Compliance with ethical standards

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