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Ultradian and hyperdian rhythms determine the output of transmitters from brain neurons

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Abstract

Using the push-pull superfusion technique for determining the in vivo release the neurotransmitters catecholamines, histamine, GABA and the neuromodulator nitric oxide in distinct brain areas revealed that they are released according to ultradian rhythms with frequencies of 135-36 min per cycle and hyperdian rhythms with frequencies of less than 30 min (24 -10 min) per cycle. The electrical activity of EEG delta and theta waves also varies rhythmically. The pacemaker of the EEG and histamine rhythm is located in the hypothalamus. Simultaneous recordings of EEG and histamine release revealed that high neuronal activity of EEG coincides with low histamine release rates and vice versa. The significance of these rhythms for brain function and modulation of the activity of peripheral organs by the brain is discussed.

Keywords: Brain; Push-pull superfusion; Neurotransmitters; Neuromodulators; Nitric oxide; EEG; Ultradian rhythms; Hyperdian rhythms

1. Introduction

Use of the push-pull superfusion technique (PPST) makes it possible to determine in the synapse continuously for several hours and in short time periods minute concentrations of neurotransmitter and neuromodulators released in distinct brain areas from their neurons. EEG waves may be simultaneously recorded [1-4]. Our studies revealed that in all brain areas investigated the spontaneous release rates of neurotransmitters and nitric oxide are not constant but vary according to ultradian rhythms and rhythms shorter that the ultradians, the hyperdian rhythms observed under particular experimental conditions.

2. Results and discussion

2.1. Ultradian rhythms

2.1.1. Catecholamines

Superfusion of the posterior hypothalamus of anaesthetized cats through the PPS over 6 hours and collection of the superfusates in time periods of 15 min revealed that the release rates of the catecholamines dopamine, noradrenaline and adrenaline varied from sample to sample. When the peak release rates of each experiment were synchronized, 5 peaks with high release rates in 6 hours appeared (Fig. 1). Thus, in this region of the cat brain the release rates of all three catecholamines are not constant but fluctuate according to an ultradian rhythm with a frequency of 70 min per cycle. Similar frequencies were observed in the anterior rat hypothalamus [5, 6]. Findings are summarized in Table 1.

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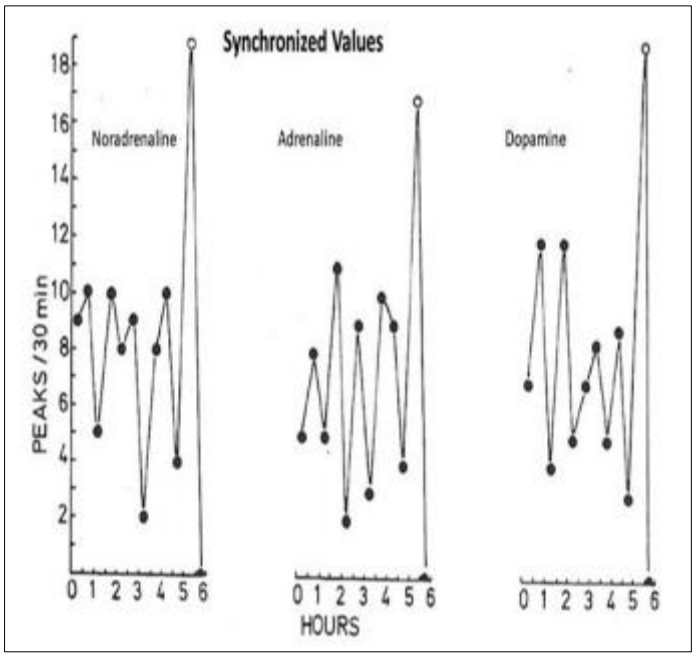

Figure 1 Spontaneous release of endogenous catecholamines in the cat posterior hypothalamus after synchronization of values shown in Fig. 1. Samples were continuously collected in 15 min periods. The last peak of high rate of release was taken as the antepenultimate sample (5.5 h) and the other samples were re-arranged accordingly. After this synchronization five peaks of high release became visible in each experiment. For differences between phases of high rate of release (5 phases, number of observations 85–95 for each catecholamine) and phases of low rates of release (5 phases, number of observations 85–95 for each catecholamine): noradrenaline, adrenaline, dopamine $P < 0.001$ (Philippu et al. 1979). Reproduced with kind permission of Springer-Verlag

Table 1 Ultradian and hyperdian rhythms of NO, neurotransmitter and EEG in various brain regions

	Animal Species	NAc	PH	AH	NTS	LC	MAN	MB
NO	an .rat	24*						
EEG	an. rat		100					
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	60				135 9.5*	90 18*
HI	an. Rat co. Rat		115 90					
HI	co. rabbit	70	70	70				
GABA	co. rat		65					
GABA	an.cat	70	70					

Ultradian and hyperdian rhythms in min. Samples were collected in time periods of 10 min or less than 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, NO nitric oxide, DA dopamine, NA noradrenaline. A adrenaline, HI histamine. GLU glutamate, ARG arginine, Tau taurine, an. anaesthetized, co. conscious. For references see text. Modified from [7}.

Most of the noradrenergic and adrenergic neurons ending in the hypothalamus arrive from the locus coeruleus [8, 9], which also contains catecholaminergic nerve endings [9, 10]. Investigation of the catecholamine release in the locus coeruleus using the PPST showed that in this area the release of dopamine, noradrenaline and adrenaline also oscillates with a frequency of 37, 52 and 36 min per cycle, respectively [11]. The dissimilar ultradian rhythms of noradrenaline from those of dopamine and adrenaline point to the releaseof the amines from different neuronal sites (Table 1).

Similar ultradian rhythms were found in the nucleus of the solitary tract [12].

2.1.2. Amino acids

Similar to catecholamines, the inhibitory amino acid GABA is released in the posterior hypothalamus of conscious and anaesthetized rats according to an ultradian rhythm with a frequency of 65 min and 70 min per cycle, respectively [13]. Hypothalamic GABA originates to a great part from GABAergic neurons, because its release is enhanced on superfusion with potassium rich artificial cerebrospinal fluid and greatly reduced on hypothalamic superfusion with the neurotoxin tetrodotoxin [14].

2.1.3. Histamine

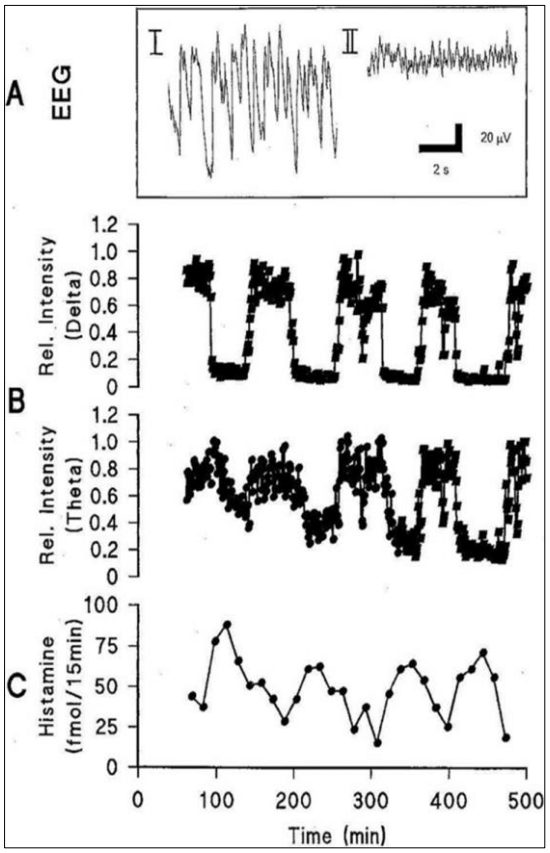

Figure 2 Two states of electrical activity in the posterior hypothalamus of the anesthetized rat. I Period of highelectrical activity, II period of low electrical activity. Calibrations are indicated by the bars. Representative experiment showing the relative power the EEG 1-minmean power values in the delta (1.25–4.50 Hz) and theta (4.75–6.75 Hz) frequency waves and the release rates of histamine. Ordinates: B Relative power intensities of the delta and theta frequency waves, C Release of histamine as fmol/15 min, abscissa: time in min. Histamine: means of 7 experiments ± S.E.M. Correlation coefficients: histamine versus delta frequency wave R = −0.5797 (P <0.001), histamine versus theta frequency wave R = 0.5106 (P < 0.01). Reproduced from Prast et al. 1997 with kind permission of Springer-Verlag

The cell bodies of histaminergic neurons ending in the posterior hypothalamus are located in the tuberomammillary nucleus [15]. In the cat posterior hypothalamus the release of histamine oscillates with a frequency of one cycle per 60 min. In the hypothalamus of conscious and anaesthetized rats the frequency is 90 and 115 min, respectively, while in the posterior and anterior hypothalamus of the conscious rabbit (Table 1), the frequency amounts to is 70 min [16].

In the median amygdaloid nucleus and the mamillary body histamine release rates fluctuate with frequencies of one cycle every 135 min and 90 min, respectively (Table 1). The bilateral electrocoagulation of the suprachiasmatic nucleus decreased the release of histamine in the mamillary body without influencing it in the amygdaloid nucleus. indicating that in the mamillary body the release of histamine is regulated by excitatory neurons arising in the suprachiasmatic nucleus [17].

Interestingly, the long frequencies of histamine release are similar to those of EEG power (Table 1). The simultaneous determination of histamine release rates and EEG recordings has shown that the low histamine release rates coincide timely with high neuronal activity of EEG (Figure 2) and vice versa [18]. The close relationship between the fluctuations of histamine release and EEG power is underlined through the observation that agonists ad antagonists of histamine receptors influence the EEG rhythm (19).

The pacemaker for the EEF power oscillations is obviously in the rostral arcuate nucleus and median eminence, because the oscillations disappear after electrocoagulation of these areas[7, 20, 21]. Possibly this pacemaker is also responsible for the oscillations of histamine release rates in the hypothalamus [14, 18, 20, 22, 23].

2.2. Hyperdian rhythms

As already mentioned, in all investigations described above the superfusates of the various brain regions were collected in time periods of 10 or 15 min. To be able to collect them in time periods down to 10 s, the speed of superfusion was slightly increased so as to increase the volume per sample necessary for the biochemical analyses. This is only possible when PPST is used and makes it feasible to investigate whether rhythms exist which are more rapid than the described ultradian rhythms. These very rapid rhythms are named hyperdian rhythms.

2.2.1. Catecholamines

In the cat nucleus of the solitary tract collection of the samples in short time periods of 2.5 min or less revealed that all three catecholamines [24] are additionally released according to a rapid hyperdian rhythm with the frequency of 10 min per cycle (Table **1**).

2.2.2. Histamine

Continuous collection of the superfusate in time periods of 2 min instead of 20 min as above disclosed that in the amygdala and mamillary body of the anaesthetized cat [25] histamine is additionally released according hyperdian rhythms with frequencies of 19.5 and 18 min, respectively (Table 1).

2.2.3. Nitric Oxide

Nitric oxide is considered to be the universal modulator of brain function [26 - 28]. To determine the release of nitric oxide under real-time conditions, a sensitive and specific amperometric sensor was inserted into the PPC. In the nucleus accumbens of rats (Table **1**) the values of nitric oxide also oscillate with a frequency of one cycle per 24 min [28, 29]. This finding seems to be of particular interest is one considers the modulation of brain activity by nitric oxide [27,28]. Surprisingly is the similarity of the duration of the hyperdian rhythm in the release of nitric oxide and the duration of the hyperdian rhythm that modulates the release of histamine (see above).

3. Conclusion

Neurotransmitters and neuromodulators like nitric oxide are released in the brain according to ultradian and hyperdian rhythms. The rhythmic changes of the transmitter concentrations in the synaptic cleft influence the activity of peripheral systems, such as the cardiovascular system. Further investigations will clarify the importance of these biorhythms for the activity of central and peripheral neurons and their mutual interferences. A pacemaker located in the rostral arcuate nucleus and median eminence is responsible for the EEF power oscillations in the hypothalamus because they disappear after electrocoagulation of these areas. Possibly this pacemaker also generates the oscillations of histamine release rates in the hypothalamus.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of ethical approval

All animal care and experimental protocols were approved by the Commission for Animal Experiments, Federal Ministry of Science, Research and Art, Austria. All procedures used were as humane as possible. The ARRIVE guidelines for reporting experiments involving animals have been followed (Kilkenny et al., 2010; McGrath et al., 2010).

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