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Effects of Electroconvulsive Shock on Catecholamine Release in the Corpus Striatum of the Rat: A Voltammetric Study

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Summary

A voltammetric technique was used (differential pulse voltammetry with a carbon fibre microelectrode) to investigate dynamics of the changes of catecholamine overflow in the corpus striatum following electroconvulsive stimulation (ECS) of chloral hydrate-anaesthetized rats. Application of "maximal" ECS (50 Hz, AC, sine wave, approximately 150 mA, 0.2 s) caused large enhancement of catechol-oxidative current (CA.OC): In the first minute after its arrest, the CA.OC peak raised to 1032±405 % (n=5, mean±S.D.) of the controls ($P \leq 0.001$, Student's t-test). This large elevation of the extracellular catecholamine content ceased rapidly – the baseline level was attained in the second minute. CA.OC changes evoked by a "minimal" ECS (50 Hz, AC, sine wave, approximately 30 mA, 0.2 s) were equivocal in the first minute (increase, decrease: 145±56 %, $P > 0.05$, n=6). Possible mechanisms of the ECS therapeutic effect are discussed.

Key words

Catecholamines – Striatum – Electroconvulsive stimulation – Voltammetry – Rat

Introduction

The fact that electrical stimulation of the brain can cause seizure activity (electroconvulsive stimulation – ECS) has been known for over a century (Fritsch and Hitzig 1870, Albertoni 1882). Electroconvulsive therapy had been partially neglected during the past few decades, but a report of the American Psychiatric Association (Task Force on Electroconvulsive Therapy, Report N.14, Washington DC, 1978) emphasizing its curative potency and minimal side effects rehabilitated this method to a great extent.

Electroconvulsive therapy can fully substitute or alternate with the use of antidepressive and neuroleptic drugs in the treatment of a variety of psychiatric syndromes (Black *et al.* 1982, Rudorfer and Linnoilla 1986).

Though important steps in the elucidation of beneficial effect of the electroconvulsive therapy have been made (Pfersmann and Karazman 1991), current information does not offer any conclusive theory. The behavioural symptoms in schizophrenic patients may be caused by dysfunction in both the noradrenergic limbic and basal ganglia dopaminergic systems (Hornykiewicz 1986). Chronic ECS has been shown to induce behavioural supersensitivity to dopamine agonists (Modigh 1975, Grahame-Smith 1984). The *in vivo* microdialysis studies focused on the effects of ECS on the extracellular concentration of dopamine in the basal ganglia provided controversial results: large increase (Nomikos *et al.* 1991) as well as no effect (Glue *et al.* 1989) were reported.

We have therefore examined the influence of ECS by a voltammetric method which is a valuable tool for the monitoring of dopamine and its derivates with high temporal and spatial resolution (Adams 1990).

Methods

Animals and surgery

Male Wistar rats (body weight 300 g) were anaesthetized with chloral hydrate (Lachema, Brno, 4 % solution in physiological saline, 40 mg/100 g b.w., i.p.) and 20 min later fixed in a stereotaxic apparatus. A hole was drilled in the skull with stereotaxic

coordinates (Fifková and Maršala 1960) enabling insertion of the working electrode into the corpus striatum (AP 1.0 mm, L 2.3 mm, V 4.0 mm); the dura and the pia mater were pierced in this opening. Two other appertures served for reference and auxiliary electrode (Fig. 1A).

Recording electrodes

A glass micropipette with five to eight carbon fibres (Serofim, Gennevilliers, France, diameter of each fibre was approximately 8 μm) served as the voltammetric working electrode; their contact with a connecting wire was established by means of Hg-Pt bridge. The length of exposed carbon filaments protruding from the tip (diameter 100–150 μm, filled with paraffin wax in order to prevent liquid seeping into the micropipette) was approximately 150 μm; their surface was treated electrochemically (Gonon *et al.* 1981). The auxiliary electrode (a stainless-steel watchmaker's screw) and the reference electrode (Ag/AgCl wire) were in contact with the dura.

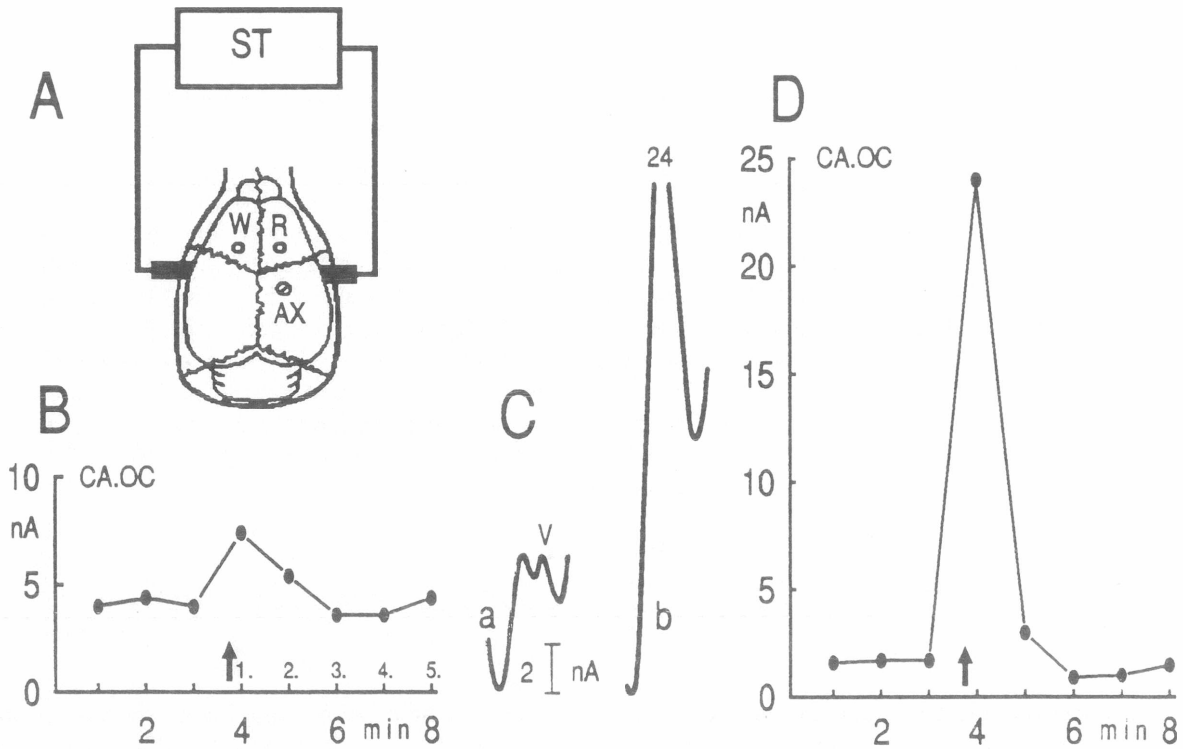

Fig. 1
The influence of electroconvulsive stimulation (ECS) on catecholamine overflow (catechol-oxidative current – CA.OC) in the rat striatum as determined by voltammetry. A. Experimental arrangement: ST – stimulating device, W – working electrode, R – reference electrode, AX – auxiliary electrode. B. Changes of the CA.OC (ordinate, nA) after application of the "minimal" ECS (arrow, scale on abscissa in minutes; serial numbers above abscissa indicate measurements after execution of the ECS); results from one experiment. C. Voltammetric recordings: a – control, v denotes CA.OC peak; b – about twenty seconds after "maximal" ECS, number above recording informs about the amplitude (nA) of the peak. D. Changes of the CA.OC after application of the "maximal" ECS; the result of the experiment which is documented in part C.

Voltammetric measurements

A polarographic analyzer (PA 4, Laboratory Equipment, Prague) connected with three-electrode system in a differential pulse voltammetry (DPV) mode with the following parameters: scan rate of the polarization voltage 100 $mV.s^{-1}$, pulse amplitude 100 mV, pulse on duty 60 ms, pulse period 0.2 s; the voltage supplied to the working electrode ranged from −150 mV to +800 mV. The voltammetric signal was drawn with an x–y plotter (XY 4106, Laboratory Equipment, Prague).

Electroconvulsive stimulation (ECS)

Two stainless-steel screws (2 mm in diameter) were fixed to the temporal side of the skull (about 3 mm below the edges of the temporal bones at the level of the bregma). These were connected to a stimulation device (made in the Institute of

Experimental Endocrinology, Bratislava) – Fig. 1A. Two different intensities of electrical stimuli were used: 1) "Minimal" electroshock (50 Hz AC, sine wave, intensity about 30 mA for 0.2 s). 2) "Maximal" electroshock (50 Hz AC, sine wave, intensity about 150 mA for 0.2 s). The current used as "minimal" ECS was just below the intensity required to produce facial and forelimbs clonus in the anaesthetized rat. Parameters of "maximal" ECS used in our study corresponded to the seizure test (Browning 1987) behaviourally consisting of about 3 s of tonic ventroflection of the body followed by hindleg extension lasting around 10 s terminated with a short hindleg clonus resembling bicycle type kicking. Only results obtained in animals surviving ECS were included in the statistics.

Protocol of the experiment

The voltammetric signals were recorded at regular 60 s intervals. The arithmetic mean of the last three voltammetric signals at the end of the time period (10–15 min), when they had become stabilized, served as the control value (100 %) for subsequent recordings. After ECS five recordings were taken (Figs 1B and 1D). Only one ECS was applied in each experiment.

Evaluation of results

Voltammetric recordings consisted of two peaks (Fig. 1C,a). The first one was identified with oxidation of ascorbic acid, the second peak (v) occurring in the range from +320 mV to +360 mV of the polarizing voltage at the working electrode corresponded to an oxidation current of catecholamine and their derivates (CA.OC) – Lane *et al.* (1976), Pavlásek *et al.* (1992). Only this second peak (CA.OC) was measured (arithmetic mean±S.D.) and evaluated statistically by means of Student's t-test.

Results

The influence of the "minimal" ECS was equivocal: in the first minute – about twenty seconds following ECS application (the first measurement after ECS) there was an increase of the CA.OC (Fig. 1B) in four experiments while a CA.OC decrease was observed in the remaining two; values ranged from 85 to 214 % with the arithmetic mean differing only insignificantly from the control (145±56 %, $P>0.05$). Changes of the CA.OC amplitudes in the 2nd, 3rd, 4th and 5th min were not significant in comparison with the control – Table 1.

In the first minute – about twenty seconds after the "maximal" ECS a large increase of the CA.OC (Fig. 1C,b,D) to 1032±405 % (Table 1) of the control was observed. Its recovery to the initial values was rapid (Fig. 1D): in the second measurement after ECS application the CA.OC peak was 148±80 % (n=5, $P>0.05$) above the baseline and all values afterwards (in the 3rd, 4th and 5th min) did not exceed the control level significantly (CA.OC value in the third minute was significantly lower) – Table 1.

Table 1
Changes of the catechol-oxidative current (CA.OC) in the rat striatum evoked by electroconvulsive stimulation (ECS). Values recorded from the first up to the fifth measurement after application of the "minimal" or "maximal" ECS are expressed as the percentage of the control

Time (min)	"Minimal" ECS		
1	145±56	NS	(6)
2	110±40	NS	(6)
3	85±16	NS	(6)
4	88±15	NS	(5)
5	104±22	NS	(5)
	"Maximal" ECS		
1	1032±405	$p<0.001$	(5)
2	148±80	NS	(5)
3	74±18	$p<0.02$	(5)
4	88±21	NS	(5)
5	110±32	NS	(4)

Data are Means ± S.D.. Number of experiments is given in parenthesis. NS – non significant

Discussion

Membrane defects affecting the function of the membrane-bound sodium pump (Naylor and Smith 1981, El-Mullakh 1983), with a consequent increase of intracellular sodium concentration (Naylor *et al.* 1971, Goodwin and Jamison 1990) and resulting in abnormalities of neurotransmitter release, were suggested to be responsible for affective misconduct (e.g. maniac-depressive illness). Disorders concerning noradrenergic transmission related to locus coeruleus (Leckman and Maas 1984) and the nigrostriatal dopaminergic system (Iverson 1978, Depue and Iacono 1989) are considered to be the underlying mechanisms. Actually, the catecholamine hypothesis still provides the theoretical basis for treatment of depression (Depue and Spoont 1986), although disorders in other neurotransmitters such as 5-hydroxytryptamine (Depue and Spoont 1986), gamma-aminobutyric acid (Bernasconi 1982) and neuroendocrine dysregulations (Fink and Ottosson 1980) have also been reported.

Experiments attempting to elucidate the mechanisms by which a series of ECS achieves its therapeutic effect have revealed that catecholamine-regulated behavioural activities are preferentially modified. Related mechanisms for these effects are changes in function of receptor systems and second messengers are related (Deakin *et al.* 1981, Kellar and Bergström 1983).

Our voltammetric study confirmed that "maximal" ECS produced a large elevation of catecholamine concentrations in the extracellular space of the striatum (1032 % of the baseline). According to the results obtained with microdialysis (Nomikos *et al.* 1991) this change corresponded to the increase of dopamine concentration. Rapid CA.OC enhancement, comparable with that which we observed after ECS, was recorded in several other experimental situations: after a microinjection of 3 μl 0.5 mol.l^{-1} KCl into the vicinity of the tip of the working electrode (Murgaš *et al.* 1991, Pavlásek *et al.* 1992), or the same amount of detergent Triton X-100 (unpublished result), and in the course of an anoxic/ischaemic insult of the brain during terminal states (Murgaš and Pavlásek 1990). Reserpinization of the experimental animal prevents the postmortal surge of dopamine in the extracellular space of the brain (Wong 1992); this indicates that released dopamine is of neuronal origin. With all probability the same mechanism underlies the dopamine increase in the case of ECS, though participation of the changes in the blood-brain barrier which are associated with ECS (Petito *et al.* 1977) cannot be completely excluded.

The dopamine concentration increase in the microenvironment of the striatum evokes various and probably even contrary effects. It is supposed that down-regulation (up-regulation) of receptor functions can reflect the brain's adaptive reaction to the increase in transmitter "tonus" given by its overflow into extracellular microenvironment (Gleiter and Nutt 1989). Terminals of dopamine neurones of the nigrostriatal pathway possess extrasynaptic autoreceptors which are of the D_2 type. These can inhibit synaptic transmission in the striatum by decreasing neurotransmitter release at the synaptic sites (Palij *et al.* 1990). If presynaptic receptors are affected chronically, disuse hypersensitivity of postsynaptic membrane receptors can occur (Grahame-Smith 1984) on the basis of protracted suppression of transmitter liberation. By an increase of mediator concentration in the extracellular space a further mechanism regulating receptor functions can be activated, i.e. various forms of desensitization: receptor uncoupling, receptor affinity changes, down-regulation of receptor number (Sibley and Lefkowitz 1985). In spite of the diversity of the mentioned effects to which many other factors can make a substantial contribution – e.g. activity changes of voltage-controlled ion channels by a direct transmitter influence (Nicoll 1982), or by modulatory interactions of different neurotransmitters in the striatum, concomitantly released by ECS, a series of ECS has a number of reproducible actions on brain neurotransmitters and their receptors. Many of these changes (specific in action and characterized by clear regional differences) can plausibly be linked to positive behavioural alterations in psychopathic patients (Gleiter and Nutt 1989).

Some clinical studies considered convulsions, occurring in the course of seizure activity, crucial for the ECS therapeutic effect (Frankel 1988). The present report provides evidence that massive neurotransmitter release into the extraneuronal space does not occur when a subthreshold intensity for evoking tonic-clonic seizures is applied ("minimal" ECS). Thus the lesser therapeutic effect in patients treated with near above threshold ECS can be due to this fact.

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