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CORTICAL SPREADING DEPRESSION MODULATES THE CAUDATE NUCLEUS ACTIVITY

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Abstract—Cortical spreading depression (CSD) plays an important role in migraine with aura. The caudate nucleus has crucial functional interactions with brain regions likely to be important in migraine. The aim of the present *in vitro* study was to investigate the effect of CSD on the neuronal activity of the caudate. Intracellular recording was performed in the head of the caudate nucleus alongside of extracellular recording in Wistar rat somatosensory cortex. CSD was induced by local KCl injection. Changes in the membrane potentials of the caudate neurons began 1.2 ± 0.2 min after CSD. The neurons of the caudate nucleus depolarized first gradually and slightly then it depolarized abruptly at nearly the same point of time of the recovery of the cortical DC potential. Action potentials (APs) reappeared after the cortical DC shift returned to the baseline. Forty-five minutes after CSD, the caudate neurons showed lower frequency of APs and larger amplitude of depolarization prior to APs. The firing pattern of the caudate neurons evoked by injection of intracellular current pulses changed from slow adapting to fast adapting after CSD. Reduced neuronal activity in the caudate after CSD may be assumed to contribute to pain as well as changes in cognition and behavior in patients with migraine.

Key words: spreading depolarization, striatum, aura, dopamine, inhibition.

INTRODUCTION

Cortical spreading depression (CSD) is a pronounced depolarization of neurons and glia that spreads slowly across the brain tissue followed by dramatic changes in the distribution of micromilieu ions between intracellular and extracellular compartments (Leao, 1944; Somjen, 2001). There is unequivocal evidence that CSD occurs in the brain of patients suffering from migraine with aura, ischemic as well as hemorrhagic brain diseases and traumatic brain injury (Lauritzen et al., 2011; Dreier et al., 2012). It has been shown that CSD trigger epileptiform burst discharges in the human brain (Dreier et al., 2012; Eickhoff et al., 2014). The causative role of CSD in the generation of aura symptoms of migraine attacks is well established (Goadsby, 2007). An area of controversy surrounds whether CSD triggers the rest of the attack, including pain and postdrome. There is some evidence to suggest that CSD is also implicated in migraine pain (Gorji et al., 2004; Lambert et al., 2011; Bhaskar et al., 2013) as well as other premonitory and postdrome symptoms (Gorji, 2001). The potential interrelation of CSD and migraine has usually involved neocortical tissues and the possible roles in other brain regions, including the caudate nucleus were not fully investigated.

The caudate, originally thought to primarily be involved with the control of voluntary movement, is now known to be also an important part of cognitive and behavioral functions. The caudate nucleus has crucial functional interactions with brain regions likely to be important to migraine, such as areas associated with vision, the auditory and neighboring associative cortex, the thalamus and the amygdala (Oleshko and Maisky, 1993). The caudate nucleus plays a central role in cognitive processes, particularly executive functions, emotion and behavior (Grahn et al., 2008). Furthermore, the caudate nucleus seems to play an important role in both the sensory processing and suppression of pain (Wunderlich et al., 2011). The caudate nucleus stimulation modulated both sensory and motor components of the trigeminal system (Harper et al., 1979).

Characteristic features of spreading depression (SD) in the caudate nucleus were first described by Leao and Martines-Ferreira (Bures et al., 1974). Classical animal studies investigated the pattern of CSD propagation in the caudate and its neighboring structures. It has been shown that CSD propagates mostly to the caudate. Similarly, the wave of caudate SD penetrates to the

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Abbreviations: ACSF, artificial cerebrospinal fluid; AHP, after-hyperpolarization; APs, action potentials; CSD, cortical spreading depression; DAPs, depolarization prior to APs; RMP, resting membrane potentials; SD, spreading depression.

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lateral nucleus of the amygdala and from there to the neocortex (Fifkova, 1964; Fifkova and Syka, 1964; Vinogradova et al., 1991, 2005). Because altered neural circuit function can be seen remote from the CSD initiation and propagation sites (Obrenovitch, 1999; Wernsmann et al., 2006; Dehbandi et al., 2008), using *in vitro* brain models, the effects of CSD on the neuronal activity of the caudate tissues were tested.

EXPERIMENTAL PROCEDURES

Slice preparation

Twenty adult Wistar rats (250–300 g) were decapitated under deep isofluran anesthesia and the brains were quickly transferred to ice-cold (4 °C) artificial cerebrospinal fluid (ACSF). The cerebellum was removed and a cut was made to divide the two cerebral hemispheres. Combined striatum–hippocampus–cortex slices containing the temporal cortex, the entorhinal cortex, the subiculum, the hippocampus as well as the striatum (500 μm) were cut in a nearly horizontal plane. The slices that were preincubated in ACSF contained (in mmol/l): NaCl 124, KCl 4, $CaCl_2$ 1.0, NaH_2PO_4 1.24, $MgSO_4$ 1.3, $NaHCO_3$ 26, and glucose 10 at 28 °C for 60 min. The ACSF was continuously equilibrated with 5% CO_2 in O_2, stabilizing pH at 7.35–7.4. After 30 min preincubation, $CaCl_2$ was elevated to 2.0 mmol/l. The slices were transferred to an interface recording chamber and perfused with ACSF at 32 °C. To assure oxygen supply, a warmed and humidified gas mixture of 95% O_2 and 5% CO_2 was conducted over the surface of the slices. During the experiments, the pH, the bath temperature, and the flow rate (1.5–2 ml/min; Schurr et al., 1985) remained constant.

Electrophysiological recordings

Intracellular recordings were performed in the head of the caudate nucleus using sharp micropipettes filled with 2 mol/l potassium methylsulfate (pH 7.4). The micropipette tips were merged for a long-time in ACSF. Two hundred ms square positive and negative current pulses were injected into the neurons, intending to determine the neuronal input resistance and discharge patterns. A constant positive or negative current was injected to the cells and the membrane potentials were elevated to −40 mV and decreased to −80 mV, respectively. The reference electrode and the connection to the microelectrode were symmetric Ag–Ag–KCl bridges. The microelectrodes were selected to have a resistance in the range between 80 and 160 MΩ. Simultaneous extracellular field potentials along with intracellular recordings were recorded with glass microelectrode (150 mmol/l NaCl; 2–10 MΩ) in the fifth layer of the somatosensory neocortex and I the head of caudate. The distance between intra- and extracellular recording microelectrodes in the caudate was approximately 0.5 mm and the distance between extracellular recording electrodes in the neocortex and caudate was approximately 5–6 mm. Neuron impalement was performed with a conventional high-performance, motor-driven microdrive. The potential of the intracellular electrode was referred to an extracellular micropipette electrode to ensure control of the true membrane potential during large shifts of extracellular potential. Extracellular recordings were obtained using a custom-made differential amplifier (with band-pass filters at 0.5–30 kHz, sampling rate 10 kHz, and 0.3–100 Hz) and the membrane potential fluctuations were obtained using a home-made active bridge mode amplifier (Jafarian et al., 2010; Gorji et al., 2011; filter 10 kHz). Traces were digitized by a Digidata 1200 (Axon Instruments, CA, USA) and the data were collected and analyzed by Axoscope 10 (Axon Instruments, CA, USA).

For each minute of experiments 20 action potentials (APs) were randomly selected for measurements. The amplitude of the APs was measured peak to nadir of the after-hyperpolarization (AHP) and the duration was measured by half-amplitude width duration. Intracellular recording data acceptable for inclusion in the study met the following criteria: recording stability without any sign of injury discharges, membrane potential more negative than −50 mV with a deviation of less than 5% during the first 15 min of recording.

Induction of CSD

A glass electrode filled with 3 M KCl or ACSF (control) was fixed in a special holder connected with plastic tube to a pressure injector and the tip inserted into the somatosensory neocortical slices (layer I–II). A high-pressure pulse was applied to inject in the tissue an amount of K^+ sufficient to induce CSD (tip diameter, 2 μm; injection pressure, 0.5–1.0 bar applied for 200–300 ms, two separate injections, 1–3 nl per pulse, 2–5 mm apart from nearby recording electrodes). The same amount of ACSF was applied in the slices in control experiments to exclude that the fluid injection per se may trigger CSD. CSD were evaluated with respect to their amplitudes, duration and velocity rates. Duration of DC potential fluctuation width was measured at its half-maximal amplitude. In each slice, only one SD was induced.

Experimental protocol

Intracellular recording was performed in the head of the caudate nucleus alongside of extracellular recording in the somatosensory neocortex (layer V). CSD was induced after at least 15 min of continuous intracellular recordings of the membrane potential in the caudate. Intracellular recordings were continued for at least 60 min after CSD initiation.

All data are given as mean ± SEM. The data were statistically processed and compared using Mann–Whitney Rank Sum test. Significance was established when the probability values were less than 0.05. The experiments were carried out in accordance with the EU Directive 2010/63/EU on the protection of animals used for scientific purposes and were approved by the local ethics committee (Bezirksregierung Münster, AZ: 50.0835.1.0, G79/2002).

RESULTS AND STATISTICAL ANALYSES

Induction of CSD

After local pressure application of KCl, extracellular potential recordings of the neocortex showed a transient slight positive DC shift, sometimes followed by a brief burst of high-frequency EEG spikes that heralded the appearance of the negative DC potential wave with the amplitudes of 18.5 ± 1.2 mV and durations of 120 ± 3 s (Fig. 1). Application of ACSF in the same cortical layer of the neocortex did not elicit any negative DC deflection.

The effect of CSD on intracellular activity of the caudate

Intracellular recordings were obtained from 24 cells in the head of the caudate nucleus (from 19 rats). The intracellular activities were recorded for periods of 76–132 (92.5 ± 4.7) minutes. The mean resting membrane potentials (RMP), the mean amplitude of depolarization prior to APs (DAPs), the mean duration as well as amplitude of APs, the amplitude and duration of AHP, input resistance and the burst frequency before induction of CSD (control period) are presented in Table 1.

CSD propagated to the caudate nucleus in 22 of 24 recorded neurons. Negative DC deflections (with the amplitudes of 10.5 ± 1.2 mV and durations of 120 ± 3 s) were recorded in the caudate nucleus (Fig. 1). Changes in the field potentials as well as the membrane potentials of the caudate neurons began 1.4 ± 0.2 min after application of KCl in layer I–II of the neocortex (propagation velocity of 3.6 ± 0.1 mm/min). These changes started usually with a short and small hyperpolarization followed by depolarization. The neurons of the caudate nucleus depolarized first gradually and slightly then it depolarized abruptly at nearly the same point of time of the recovery of the negative DC potential shift in the caudate. The mean RMP of the caudate cells reached −12 ± 3.2 mV before gradual repolarization of the membrane potentials at the height of CSD. APs reappeared after the cortical negative DC shift returned to the baseline (recovery to baseline). Forty-five minutes after induction of CSD,

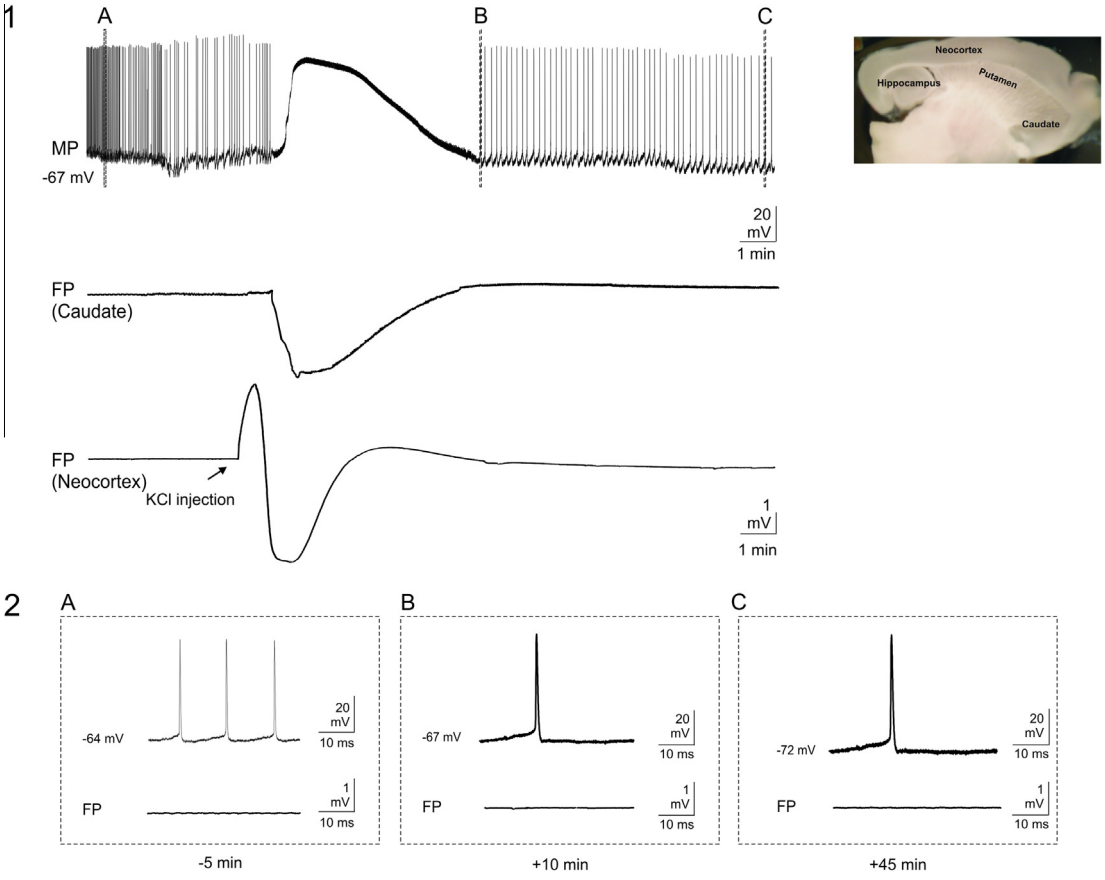

Fig. 1. Membrane potential changes (MP) of a caudate neuron (the head of caudate nucleus; rat) during and after a cortical spreading depression (CSD) induced by application of KCl in layer I–II of the neocortex. Extracellular potential recordings (FP) of the neocortex and the caudate nucleus showed occurrence of the negative DC potential waves after injection of KCl in the neocortex. Changes in the MP of the caudate neurons began 1.2 ± 0.2 min after CSD. The neurons of the caudate nucleus depolarized first gradually and slightly then it depolarized abruptly at nearly the same point of time of the recovery of the negative DC-potential shift in the caudate. APs reappeared after the negative DC shift returned to the baseline (recovery to baseline). Representative traces of intracellular recordings 5 min before (A), 10 min (B) and 45 min (C) after initiation of SD are shown. *Note:* the reduction of the mean resting membrane potentials and the frequency of action potentials after CSD. Negative voltage is represented by a downward deflection in extracellular FP recording.

Table 1. Characteristic features of membrane potential changes in the striatum slices 5 min before and 45 min after induction of cortical spreading depression (CSD) at the resting membrane potentials (RMP) and after injection of constant positive or negative current to depolarize or hyperpolarize the membrane. APs, action potentials; AHP, after-hyperpolarization; DAPs, depolarization prior to action potentials. Values represent mean ± SEM

	RMP (mV)	DAPs (mV)	Amplitude of APs (mV)	Duration of APs (ms)	Amplitude of AHP (mV)	Frequency of APs (per min)	Input resistance (MΩ)
Before CSD	−68.1 ± 1.3	4.7 ± 0.1	61.8 ± 1.3	0.53 ± 0.06	4.3 ± 0.2	43.2 ± 4.3	28.6 ± 0.7
After CSD	−73.2 ± 1.7*	6.3 ± 0.2**	64.1 ± 1.9	0.56 ± 0.05	4.5 ± 0.4	8.6 ± 2.2*	25.2 ± 0.6
Depolarization (−40 mV)							
Before CSD	–	6.5 ± 0.33	59.9 ± 1.7	0.49 ± 0.05	5.1 ± 0.3	67.5 ± 8.3	–
After CSD	–	5.2 ± 0.2	62.9 ± 2.1	0.45 ± 0.03#	4.7 ± 0.2#	48.4 ± 6.3	–
Hyperpolarization (−80 mV)							
Before CSD	–	4.5 ± 0.3	72.8 ± 3.1	0.49 ± 0.03	4.8 ± 0.8	10.6 ± 0.9	–
After CSD	–	7.2 ± 0.2*	75.6 ± 2.7	0.61 ± 0.04	3.1 ± 0.2	4.7 ± 0.5*	–

* $p < 0.001$.
** $p < 0.001$.
\# $p < 0.05$

RMP, DAPs, the mean duration as well as the amplitude and frequency of APs, input resistance, the duration and amplitude of AHP were analyzed (Table 1). After CSD, the caudate neurons showed a significant reduction of the mean RMP and the frequency of APs ($P < 0.001$) as well as an enhancement of the mean amplitude of DAPs ($P = 0.004$; Figs. 1 and 2, Table 1). Depolarization of the membranes of these cells to −40 mV significantly decreased the duration of APs ($P < 0.05$) and decreased the AHP amplitude ($P < 0.05$). Hyperpolarizing of the membrane to −80 mV significantly increased the mean amplitude of DAPs and decreased the frequency of APs ($P < 0.001$; Fig. 2). In two slices which CSD did not travel to the caudate (from two rats) as well as in control experiments ($n = 4$ form four rats), there were no changes observed in the characteristic features of the neurons (data not shown).

The response to intracellular current pulses injected through the microelectrode (200 ms; 400 pA) was recorded before (5 min) and after (45 min) of CSD induction. After CSD, the evoked firing pattern of caudate cells changed from slow adapting (a sustained discharge or a discharge interrupted by hyperpolarization periods) to fast adapting (an initial spike followed by a depolarizing plateau; Moddel et al., 2003). The caudate neurons after induction of CSD displayed a lower frequency of APs evoked by depolarizing current injection pulses ($p < 0.001$). In addition, these neurons also exhibited a larger depolarization step after current injection ($p < 0.001$; Fig. 3). All above-mentioned parameters were analyzed 90 min after induction of CSD ($n = 15$); there were no changes observed in these parameters compared with those recorded 45 min after CSD induction. The pattern of neuronal activities was not changed in control experiments during at least 45 min of continuous recordings.

DISCUSSION

The present study revealed that CSD exerts an inhibitory effect on the neurons of the caudate nucleus. CSD hyperpolarized the caudate nucleus neurons and decreased the neuronal burst activities. Furthermore, the evoked firing pattern of the neurons in the caudate was changed after CSD.

Inhibitory effect of CSD on the caudate nucleus

Several investigations point to direct and indirect inhibitory effects of CSD on the caudate nucleus activity. In keeping with our data, CSD decreased the spontaneous activity of 80–90% of neurons in the ipsilateral caudate nucleus to or below 20% of the pre-CSD frequency (Bures et al., 1974). It has been shown that the amplitude of the spontaneous activity of the head of the caudate nucleus was decreased from 80 to 30 mV during CSD-induced depression of the electroencephalogram activities in the frontal cortex (Giammanco and Paderni, 1967). Propagation of CSD in the somatosensory cortex produced a decrease in evoked potentials in the caudate responses to sciatic nerve stimulation (Giammanco and Paderni, 1967). In spontaneously active cells of the rat caudate, CSD induced a transient and reversible arrest of spontaneous activity lasting few minutes (Trachtenberg et al., 1970; Kasser et al., 1988; Albe-Fessard et al., 1990). Investigation of SD propagation in the caudate revealed that SD wave moving in a rostrocaudal direction first blocks the pyramidal pathway, then the somatosensory radiation, and finally slightly alters the auditory radiation, while leaving the visual projection unimpaired (Bures and Fifková, 1968). A few seconds after induction of CSD as well as SD in the head of the caudate nucleus, the rats developed considerable locomotor activity, including gnawing, sniffing and searching; an effect that coincided with suppression of caudate EEG activity (Stille, 1971). The close temporal association between locomotor activity and SD in the striatum suggests that the neurochemical changes that underlie this behavior are most likely short-lasting processes related to the active depolarization that occurs during SD (Jakobartl and Huston, 1977). It has been shown that CSD upregulated $GABA_A$, serotonergic 5-HT and dopaminergic D_1 receptor binding sites in the striatum (Haghir et al., 2009); the receptors that are crucial in the

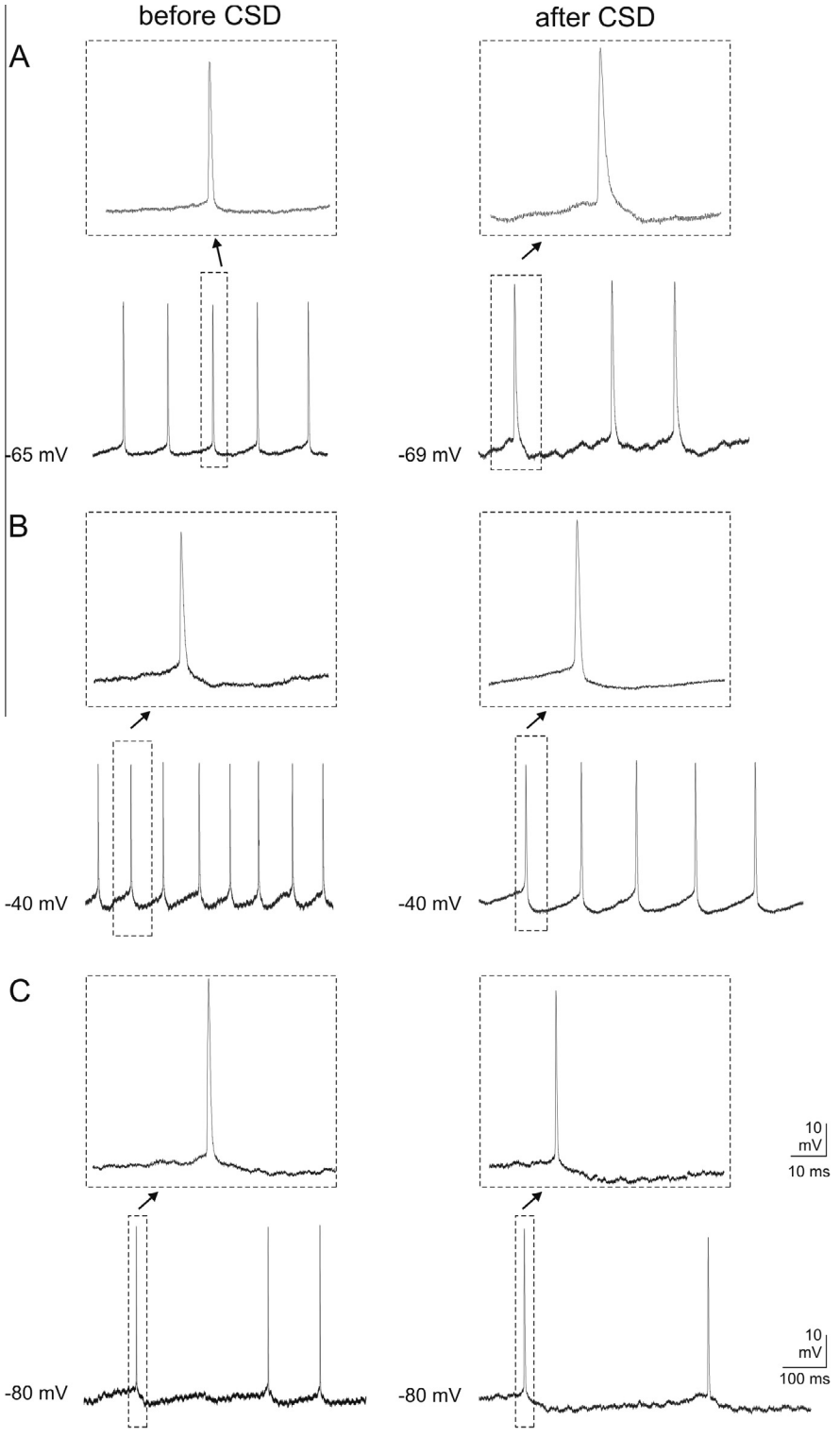

Fig. 2. The membrane potential fluctuations recorded from head of the caudate nucleus before and after induction of cortical spreading depression (CSD). Intracellular injection of a constant positive or negative current was used to investigate how burst characteristics and after-potentials change at depolarized (−40 mV; B) and hyperpolarized (−80 mV; C) states of the membrane and were compared with the values observed at the resting membrane potential (A). CSD was elicited by KCl injection in layer I–II of the neocortex. Traces were selected from intracellular activities 5 min before (left) and 45 min after (right) induction of CSD. *Note:* (i) the significant enhancement and reduction in neuronal burst firing after constant injection of positive and negative currents, respectively, (ii) the reduction in the duration of action potentials and the amplitude of the afterhyperpolarization after induction of CSD at the membrane potentials of −40 mV, and (iii) enhancement of depolarization after potentials after CSD at the membrane potentials of −80 mV.

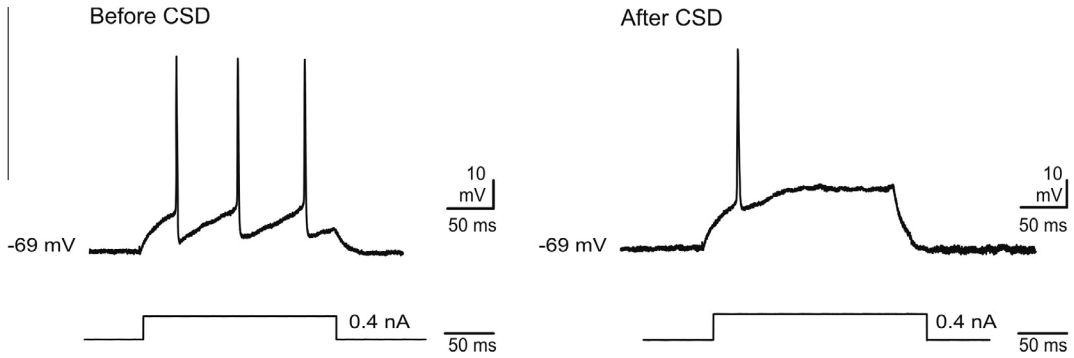

Fig. 3. Typical discharge patterns of the caudate neurons induced by intracellular injection of square positive current pulses (200 ms; 400 pA). Current injection was performed before (A) and after (B) induction of cortical spreading depression (CSD). *Note:* (i) the lower frequency of action potentials and (ii) the larger depolarization step after current injection 45 min after induction of CSD.

regulation of caudate neuronal excitability as well as mood and behavior (Suzuki et al., 2011). SD induced a large electrochemical signal which corresponded with the increase of dopamine release in the caudate nucleus and may have a general impact on redistribution of oxygen supply in these subcortical areas and on behavior associated with migraine (Yavich and Ylinen, 2005). Dopamine hyperpolarized RMP and reduced APs firing rate in the animal and human caudate neurons (Herrling and Hull, 1980; Cepeda et al., 1994; Yavich and Ylinen, 2005). The evoked firing pattern of caudate cells changed from slow adapting to fast adapting after CSD. In line with our results, it has been shown that depolarizing stimuli elicited repetitive discharges with little adaptation of firing rate in the caudate. Hyperpolarization of RMP and application of dopamine reduced the firing frequency and produced spike prolongation effects in the caudate cells (Sugimori et al., 1978). SD is accompanied by a transient rise in intracellular Ca^{2+} concentrations (Aitken et al., 1991). An intracellular increase in Ca^{2+} could serve as an intracellular signal triggering the opening and modulation of certain channels, such as Ca^{2+}-mediated K^+ channels, via second messengers (Parekh, 2008). Activation of these channels could critically contribute to the shaping of APs, firing rates and AHP (Friel and Chiel, 2008).

CSD, the caudate nucleus and migraine pain

The caudate nucleus has been demonstrated to possess anti-nociceptive function in both animal experiments and clinical observations (Wunderlich et al., 2011). The pain modulation effect of the caudate is found to be related to the periaqueductal gray matter. Stimulation of the caudate activates the periaqueductal gray matter to release opioid peptides onto their receptors to produce an inhibition of inhibitory interneurons and a subsequent disinhibition of the output neurons, resulting in the activation of a pain modulating system (Dong and He, 1982). The caudate activation is interpreted as a feature of the task to suppress the feeling of pain. In contrast, a lack of caudate activation is suggested to be associated with pain (Wunderlich et al., 2011). Reduced activation in response to pain, as measured in the interictal period, was observed in the caudate nucleus in migraine patients. In response to external pain, compared to patients whose migraine episodes did not progress (mean of two migraine attacks/month), the patients whose migraine episodes progressed (mean of nine migraine attacks/month) showed lower activations in the caudate nucleus (Maleki et al., 2011). CSD may hyperpolarize the caudate neurons, inhibit their activities and change the sensory processing as well as feeling of pain.

Direct inputs from trigeminovascular neurons in the thalamus to the caudate nucleus suggest direct effects of migraine on basal ganglia function (Noseda et al., 2011). The caudate nucleus receives a prominent sensory input, possibly nociceptive, from the trigeminal system (Stankewitz et al., 2011). Some neurons in the marginal zone of the caudal spinal trigeminal nucleus (lamina I) sent their axons to the ventrolateral part of the caudate nucleus (Yasui et al., 1987). Trigeminal-evoked caudate responses were observed when stimulation was suprathreshold for both Aβ and Aδ fibers of afferents from jaw elevator stretch receptors and dental and periodontal receptors (Harper et al., 1979). CSD induced a transient suppression of spontaneous burst discharges followed by a significant enhancement of the neuronal activity in trigeminal nucleus (Gorji et al., 2004). The complex interactions between the trigeminal nucleus and the caudate nucleus after occurrence of CSD need to be investigated. Our *in vitro* investigation is not capable of replacing *in vivo* studies because they do not reflect *in vivo* nervous system complexity nor assess the full range of neurobiological functioning *in vivo*.

CONCLUSION

The caudate nucleus receives inputs from many brain regions including the neocortex, hippocampus, amygdala and thalamus. Changes in cortical and subcortical neuronal activities induced by CSD may contribute to affect excitability of the brain in patients suffering from migraine (Ghadiri et al., 2012). Reduced neuronal activity in the caudate after CSD may be

assumed to contribute to pain as well as changes in cognition and behavior in patients suffering from migraine with aura.

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The Authors declare that there is no conflict of interest.

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