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BRAIN RESEARCH

Research Report

Mechanically-induced cortical spreading depression associated regional cerebral blood flow changes are blocked by Na^+ ion channel blockade

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ABSTRACT

Migraine with aura occurs in up to 20–30% of all migraineurs. The regional cerebral blood flow (rCBF) changes that occur during cortical spreading depression (CSD) are considered to be an experimental correlate of aura. CSD is synchronous with a failure in brain ion homeostasis and efflux of excitatory amino acids from nerve cells. Therefore studying the mechanisms that underlie CSD, such as ion channel manipulation, and observing rCBF changes may help our understanding of migraine aura. In this study we used mechanical stimulation to induce oligemia and hyperemia, in surgically prepared cats and rats, using laser Doppler probes to measure the cerebral blood flow and single cell cortical recording to measure the spike/neuronal burst, both generated as a consequence of CSD. We looked at the response of ion channel blockers directed at sodium, voltage-dependent calcium and ATP-activated potassium ion channels. The sodium ion channel blocker was able to inhibit rCBF changes in both the cat and rats. Voltage-dependent calcium channel blockers had little effect on the initiation or propagation of the spread, as did the ATP-activated potassium channel blocker. The data are consistent with what is known of human aura in that sodium ion channels are those predominantly involved in mechanical stimulation-induced rCBF changes and thus may represent therapeutic targets for the aura response in migraine.

1. Introduction

Migraine is a common (Lipton et al., 2001) and disabling (Menken et al., 2000) neurological disorder involving activation, or the perception of activation, of trigeminal neurons (Goadsby et al., 2002). It has been estimated to be the most costly neurological disorder in the European Community at more than €27 billion per year, affecting 14% of the population (Andlin-Sobocki et al., 2005). Up to 30% of sufferers report focal neurological disturbances: the 'aura' (Rasmussen and Olesen, 1992). The aura symptoms develop over 5–20 min and usually last less than an hour, taking the form of visual, sensory and motor disturbances. Aura is thought to be a wave of oligemia (Lauritzen, 1994), or deficiency in blood flow preceded by a brief hyperemia, that spreads across the cortex at 2–6 mm min^{-1} (Headache Classification Committee of The International Headache Society, 2004). Indeed the aura phase has been shown to be accompanied by a slowly spreading

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Abbreviations: ANOVA, analysis of variance; AU, arbitrary units; AUC, area under curve; CSD, cortical spreading depression; FHM, familial hemiplegic migraine; HR, hyperemic response; rCBF, regional cerebral blood flow; SP, speed of propagation; TTX, tetrodotoxin; VDCC, voltage-dependent calcium channel

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reduction in regional cerebral blood flow (rCBF) (Olesen, 1991; Olesen et al., 1981).

The hyperemia followed by oligemia occurring during the migraine aura is similar to the changes that take place during the cortical spreading depression (CSD) of Leao (Leao, 1944, 1944). CSD is believed, primarily, to be an electrophysiological phenomenon involving a wave of depolarisation followed by a short-lasting depression that spreads across the cortex at a similar rate to aura, and is also associated with regional cerebral blood flow changes and a sustained hypoperfusion in the same brain region as the depolarisation. The vascular changes are largely (Lauritzen, 1994), but not exclusively due to vasoneuronal coupling (Brennan et al., 2007). It is the blood flow changes that have been observed in migraine aura (Lauritzen, 1994). The changes are synchronous with a failure in brain ion homeostasis and efflux of excitatory amino acids from nerve cells (Kraig and Nicholson, 1978; Lauritzen, 1994, 2001); (Martins-Ferreira et al., 2000; Somjen, 2001). This similarity helps provide important support for the theory that the mechanism of CSD may underlie migraine aura. Studying the mechanisms involved in CSD, such as ion homeostasis and excitatory amino acid efflux, using the observation of vascular and neuronal changes in animals may help in our understanding of the migraine aura.

Cortical hyperemia can be triggered by electrical, mechanical and chemical stimuli in vivo (Ebersberger et al., 2001, Kaube and Goadsby, 1994, Kaube et al., 1999, Lauritzen et al., 1988; Nellgard and Wieloch, 1992, Richter et al., 2002, Somjen, 2001, van den Maagdenberg et al., 2004). Many experiments have used compounds that interfere with the ion homeostasis and excitatory amino acid efflux and measured the blood flow response in order to understand its mechanism more fully. At present only MK801, an NMDA glutamate receptor blocker, halothane and topiramate have been shown to block mechanically induced vascular changes and the neuronal burst of firing coincident with CSD (Akerman and Goadsby, 2005, Kaube and Goadsby, 1994, Zhang et al., 1990). While it has recently been shown that some migraine preventives may have actions in inhibiting CSD with longer term administration (Ayata et al., 2006).

In the present study we used whole animal in vivo techniques to study vascular changes, and used mechanical stimulation of the cortex to induce the wave of spreading depression, a correlate of the blood flow changes that occur during aura. We sought to investigate the underlying mechanism of the rCBF changes that occur by targeting potential specific ion changes that may take place in CSD. Studies looking at these targets have been done previously using electrical stimulation and KCl induced CSD in rodents (Fabricius et al., 1995, Kow and van Harreveld, 1972, Lauritzen and Hansen, 1992, Lauritzen et al., 1988, Marrannes et al., 1988, Nellgard and Wieloch, 1992; Richter et al., 2002; Shimazawa and Hara, 1996; Shimizu et al., 2000; Sugaya et al., 1975; van den Maagdenberg et al., 2004; Wu et al., 2003). We used Na^+, ATP-activated K^+ and voltage dependent Ca^{2+} ion channel blockers, and carefully observed the rCBF changes. If the rCBF changes were significantly affected by the addition of the test compound we proceeded to observe the single unit electrical changes as well, to confirm that the compound is affecting the electrical activity and not just blood flow. The work has been presented in preliminary form at the XIth International Headache Congress [Kyoto, October 2005 (Akerman et al., 2005)].

2. Results

In all cats the respiratory parameters were maintained at physiological levels throughout the experiments: pH 7.43±0.01, pCO_2 2.72±0.1 kPa and O_2 33.5±1.2 kPa. To avoid hypovolemia in the rat experiments arterial samples were

Table 1 – Summary of raw data for the ion channel modulators that highlights whether cerebral blood flow changes have occurred

Experimental plunge	Did rCBF change occur?	Statistical significance	
		Probe 1	Probe 2
Saline control	✓	*(t_7=6.22, n=8)	*(t_9=7.75, n=10)
Post ω-conotoxin-GVIa (20 μg kg^{-1})	✓	*(t_{10}=4.1, n=11)	*(t_{10}=3.48, n=11)
Saline control	✓	*(t_6=3.78, n=7)	*(t_6=8.02, n=7)
Post ω-agatoxin-IVa (20 μg kg^{-1})	✓	*(t_6=2.90, n=7)	*(t_6=5.44, n=7)
Saline control	✓	*(t_5=4.51, n=6)	*(t_5=4.09, n=6)
Post calciseptine (20 μg kg^{-1})	✓	*(t_5=2.74, n=6)	*(t_5=2.83, n=6)
Saline control	✓	*(t_5=3.31, n=6)	*(t_5=4.71, n=6)
Post TTX (60 μg kg^{-1}, cat)	×	(t_5=1.55, n=6, p=0.18)	(t_5=1.55, n=6, p=0.18)
60 min post TTX	✓	*(t_4=, n=5)	*(t_3=3.3, n=4)
Saline	✓	*(t_7=−6.46, n=8)	–
Post TTX (10 μg kg^{-1}, in rat)	×	(t_7=−1.35, p=0.22, n=8)	–
45 min post TTX	✓	*(t_7=−6.77, n=8)	–
Control plunge	✓	*(t_4=3.81, n=5)	*(t_4=3.29, n=5)
Post cadmium chloride (20 μg kg^{-1})	✓	*(t_4=3.62, n=5)	*(t_4=3.33, n=5)
Saline control	✓	*(t_6=4.02, n=7)	*(t_6=11.79, n=7)
Post glibenclamide (30 mg kg^{-1}, ip)	✓	*(t_5=3.22, n=6)	*(t_5=3.23, n=6)

✓ — CSD occurred, × — CSD did not occur (or inhibited).
TTX — tetrodotoxin.
* $p<0.05$ significance compared to the baseline in that series of experiments, indicating significant blood flow change.