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The influence of lidocaine on the permeability of the blood--cerebrospinal fluid barrier in experimental acute hypercapnia in the rabbit

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Abstract. In a previous study we have provided evidence, that acute experimental hypercapnia due to hypoventilation in the rabbit alters blood-cerebrospinal fluid barrier function in the brain (Pakulski et al. 1998). The purpose of this study therefore was to determine if lidocaine would prevent the observed alterations in the blood-cerebrospinal fluid barrier function. The experiments were conducted in 16 adult Chinchilla rabbits submitted to acute hypercapnia due to mechanical hypoventilation ($PaCO_2$ between 8 - 9.5 kPa over 180 minutes) under pentobarbital anaesthesia. The studied group (n = 8) was treated by lidocaine infusion 10 mg kg^{-1} h^{-1}. After 180 minutes of hypercapnia the value of cerebrospinal fluid-blood index of gentamycin concentration, indicating the permeability of the blood--cerebrospinal fluid barrier, was significantly lower in animals treated with lidocaine (4.03 ± 2.32 vs. 19.05 ± 5.49; P< 0.01). We conclude that lidocaine may attenuate the increase of blood-cerebrospinal fluid barrier permeability under conditions of experimental acute hypercapnia lasting 180 minutes in the mechanically ventilated rabbit.

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INTRODUCTION

Hypercapnia, an abnormal elevation of carbon dioxide tension in blood, may be encountered in many clinical situations. Acute hypercapnia may occur in patients submitted to regional anaesthesia due to respiratory depression associated with premedication and sedation or be a sequele of laparoscopic procedures (Smith et al. 1996, Pakulski et al. 1997). In view of evidence that mechanical ventilation *per se* can alter lung homeostasis and initiate inflammatory response, current approaches for preventing ventilator--induced lung injury involve manipulating ventilator parameters to limit lung stretch (Tremblay et al. 1997). Hypoventilation results in turn in "permissive hypercapnia" which is an accepted strategy in the critically ill (Dries 1995).

It has been well documented that hypercapnia may alter the permeability of brain barriers. In a previous study we have provided evidence, that acute experimental hypercapnia in the rabbit alters barrier function in the brain, i.e., results in a significant increase of blood-cerebrospinal fluid barrier permeability (Pakulski et al. 1998). Brain barrier permeability alterations, as seen in a number of pathological situations, lead to oedema and impairment of brain function (Tommasino 1998). Effective brain protection remains one of the most elusive goals of contemporary medicine. Modern management recommendations include sodium channel blockers, i.e., lidocaine, which seems to be an effective cell protective drug (Oldfield et al. 1990). The purpose of this study therefore was to determine if lidocaine would prevent alterations in the blood--cerebrospinal fluid barrier function due to experimental acute hypercapnia.

METHODS

The experiments were conducted in 16 adult Chinchilla rabbits (an average body weight 3.0 ±0.4 kg, either sex), randomized into two groups, eight animals each, both submitted to acute hypercapnia. Group I constituted the control group and was treated by saline infusion and group II by lidocaine 10 mg $kg^{-1}h^{-1}$.

Care of rabbits conformed to the recommendations of Helsinki Declaration and the study was performed in accordance with the regulations of Ethics University Commission and Polish Animal Protection Law.

Experimental protocol

After inserting a cannula (19G Venflon, Ohmeda, Sweden) into a left ear margin vein the animals were anaesthetized intravenously by pentobarbital (Vetbutal, Biowet), a loading dose given in small increments to a total of 40 mg kg^{-1}, with a subsequent continuous infusion at a rate of 25 mg kg^{-1} h^{-1}. Then the rabbits were intubated with a cuffed endotracheal tube (Ch .-B., I.D. 3.5mm, Ruesch, Germany). Muscle paralysis was obtained by intravenous pipecuronium (Arduan, Richter; 0.1 mg kg^{-1}) supplemented every 40-50 minutes.

Rabbits were mechanically ventilated with an air-oxygen mixture, F_iO_2 - 0.35, by using Zimmerman pump (WGL, Germany); tidal volume [TV] was 10 mL kg^{-1} and ventilation frequency [f] was adjusted to achieve a F_e CO_2 of 4.7 - 6 kPa (35 - 45 mmHg). After a period of stabilization (30 minutes), ventilator parameters were set down to provide hypoventilation: TV was reduced to 5 mL kg^{-1}, and a frequency was adjusted to maintain F_e CO_2 between 8 - 9.5 kPa (60-70 mm Hg).

End-tidal CO_2, inspiratory O_2 fraction (Anaesthetic Gas Monitor Type 1304, Brueel & Kijaer, Denmark) and ECG were monitored continuously. Saturation was measured by means of a pulsoxymetric finger transducer placed on a middle finger of a left paw and maintained between 95 - 99%.

An arterial access in femoral artery was established allowing continuous recording of mean arterial blood pressure (MAP) via Statham transducer and drawing blood samples for gentamycin concentration. A central venous catheter through a femoral vein was placed in pulmonary artery, to continuously measure the mean pulmonary arterial pressure (MPAP). Skin on the neck was incised under local infiltration anaesthesia and muscles were prepared. Then a pediatric cannula (22G Venflon, Ohmeda, Sweden) was inserted suboccipitally into a *cisterna cerebellomedullaris* in order to measure intracranial pressure (ICP) continuously and to obtain cerebrospinal fluid (CSF).

Cerebral perfusion pressure (CPP) was calculated according to the equation:

CPP = MAP - ICP

and expressed in mm Hg.

Measurement of the blood-cerebrospinal fluid barrier permeability

Gentamycin was used as marker of the blood--cerebrospinal fluid barrier permeability (Spector 1975,

Pakulski et al. 1998). The drug was given intravenously at the beginning of the experiment as a bolus of 3 mg kg^{-1} and was subsequently continued at an infusion rate of 4.54 mg $kg^{-1}h^{-1}$ - this regimen allowed a relatively stable blood concentration of the drug, i.e., steady-state concentration, to be obtained.

The permeability was assessed by means of gentamycin permeability index QG, defined as gentamycin concentration in the cerebrospinal fluid-to-serum gentamycin concentration at the given moment of investigation. Gentamycin concentrations in serum (C_B) and in cerebrospinal fluid (C_{csf}) were estimated by means of high performance liquid chromatography method (HPLC) at the end of the stabilization period and again at the end of the experiment. The blood-cerebrospinal concentration ratio was calculated by means of the equation:

$$QG_{[\%]} = (C_{csf} / C_B) \times 100$$

Statistical analysis

Data of blood and cerebrospinal fluid gentamycin concentrations are shown as mean ± SD.

Statistical analysis was performed by means of Mann--Whitney non-parametric test (blood and cerebrospinal fluid gentamycin concentrations) and Student's *t*-test (hemodynamic data). Significance at the 95% confidence level ($P<0.05$) is indicated by an asterisk.

RESULTS

Haemodynamic monitoring

Results of haemodynamic monitoring after 180 minutes of hypercapnia are presented in Table I. No significant differences were noted between both groups considering heart rate (HR), MAP, ICP and CCP. MPAP was found to be significantly lower in rabbits treated with lidocaine.

Gentamycin concentrations in serum and in the cerebrospinal fluid

Serum gentamycin levels shown in Table II did not significantly change after 180 minutes of lidocaine infusion in both groups. However, there was a slight, but still significant difference between gentamycin concentration at the timepoint of stabilization (T_0), which was lower in the lidocaine group. The concentrations of the tracer in the cerebrospinal fluid appeared to be significantly lower at the end of the experiment in the lidocaine group as compared to control group (Table III). In the rabbits treated with lidocaine the cerebrospinal fluid concentrations of the tracer were significantly lower after 180 minutes of acute hypercapnia ($P<0.01$).

Table I

Results of haemodynamic monitoring in control and lidocaine treated rabbits after 180 minutes of acute hypercapnia

	Group I (control)	Group II (lidocaine infusion)
HR (min^{-1})	199.0 ± 6.0	191.0 ± 4.0
MAP (mm Hg)	86.8 ± 3.6	79.6 ± 2.9
ICP (mm Hg)	3.0 ± 0.15	2.9 ± 0.1
CPP (mm Hg)	83.8 ± 3.6	76.9 ± 3.2
MPAP (mm Hg)	7.5 ± 0.1	7.3 ± 0.0*

Mean ± SD; HR, heart rate; MAP, mean arterial pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MPAP, mean pulmonary artery pressure; * denotes $P<0.05$.

Cerebrospinal fluid-blood ratio of gentamycin concentration

Calculated cerebrospinal fluid-blood ratio of the gentamycin concentrations after three hours was strikingly lower in the lidocaine group (4.03 ± 2.32 vs. 19.05 ± 5.49; $P=0.001$), as shown in Fig. 1.

Table II

Serum concentrations of gentamycin [mg mL^{-1}] at two studied timepoints: T_0: a baseline point and T_1: after 180 minutes of acute hypercapnia due to hypoventilation in the mechanically ventilated rabbit under pentobarbital anaesthesia

	T_0	T_1
Group I (control)	10.26 ± 0.52	8.41 ± 1.61
Group II (lidocaine infusion)	9.07 ± 0.74*	9.35 ± 0.64

Mean ± SD; * denotes $P<0.05$.

Table III

Cerebrospinal fluid concentrations of gentamycin [mg mL^{-1}] at two studied timepoints: T_0: a baseline point and T_1: after 180 minutes of acute hypercapnia due to hypoventilation in the mechanically ventilated rabbit under pentobarbital anaesthesia

	T_0	T_1
Group I (control)	0.32 ± 0.18	1.57 ± 0.44
Group II (lidocaine infusion)	0.27 ± 0.11	0.38 ± 0.21*

Mean ± SD; * denotes $P<0.05$.

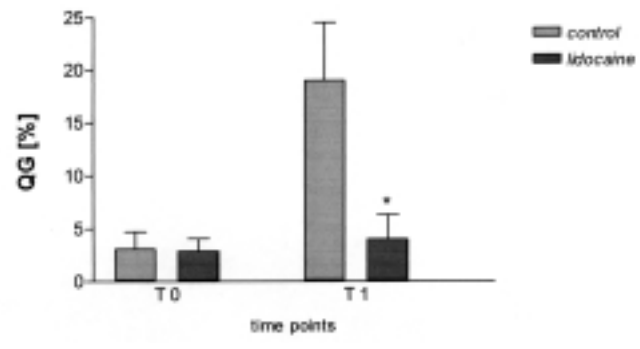

Fig. 1. Cerebrospinal fluid-blood index of gentamycin concentration, indicating permeability of the blood-cerebrospinal fluid barrier. Mean ± SD; * denotes $P<0.01$.

DISCUSSION

In this study we have shown that lidocaine may attenuate the increase of blood-cerebrospinal fluid barrier permeability, under conditions of experimental acute hypercapnia lasting 180 minutes, in the mechanically ventilated rabbit under pentobarbital anaesthesia.

Brain barrier systems sequester the brain and cerebrospinal fluid from the extracranial environment, and play a pivotal role in maintaining brain homeostasis. The unique morphology of the central nervous system microvascular endothelium with tight intercellular junctions of high electrical resistance and lack of fenestrations serve relative impermeability to proteins and other solutes from the blood to the brain extracellular compartment (Crone et al. 1982, Paradige 1987). The unique epithelium of the choroid plexus also results in a blood-cerebrospinal fluid diffusion barrier, which constitutes part of blood-brain barrier.

A rabbit experimental model proved to be a very useful tool for studying the properties of brain barriers or/and the effects of hypercapnia (Dybkowska 1997, Pakulski et al. 1998). In our study hypercapnia was achieved by controlled hypoventilation, which mimics an often encountered clinical situation.

In a series of experiments conducted previously in our laboratory we were able to demonstrate that acute hypercapnia alters brain barriers' permeability and thus may influence brain homeostasis (Pakulski et al. 1998). This observation was also made by other investigators, suggesting for example that hypercapnia allowed the passage of bilirubin-albumin macrocomplexes across blood-brain barrier (Dominguez-Ortega et al. 1997). Findling et al. (1994) observed a significant increase in tracer extravasation over the blood-brain barrier, as studied by intravital fluorescence microscopy under condition of hypercapnia. In newborn and adult rats it has been shown that hypercapnia resulted in the increased steady-state cerebrospinal fluid/plasma ratios for a wide range of permeability markers. However, it has been also suggested that this effect may be due, partly at least, to reduction in the rate of cerebrospinal fluid secretion induced by CO_2 (Habgood 1995).

An anaesthetic used in our study, pentobarbital, has been shown to be able to increase blood-brain barrier permeability (Stewart et al. 1988) and could possibly contribute to the observed increase of barriers permeability.

To assess the brain-cerebrospinal fluid permeability we have chosen gentamycin as a permeability marker. Under normal conditions this well-known aminoglicoside does not cross brain barriers and does not undergo biotransformation, which makes it a suitable tool to detect alterations in the brain-cerebrospinal fluid barrier integrity (Neuwelt et al. 1990, Pakulski et al. 1998). Recent studies indicate that gentamycin, acting also as a mechanogated ion channel blocker, may itself decrease brain endothelium permeability in certain pathologic conditions (Vaz et al. 1998). Gentamycin levels in cerebrospinal fluid depend on a function of the endothelium of choroid plexus vessels, but also may be influenced by the amount of cerebrospinal fluid produced.

In our study no significant changes were noted between serum gentamycin concentration after 180 minutes of hypercapnia in both groups, whereas cerebrospinal fluid concentration of the tracer and the calculated blood--cerebrospinal fluid concentration index proved to be significantly lower in rabbits treated with lidocaine in

continuous intravenous infusion at a rate of 10 $mgkg^{-1}h^{-1}$, indicating a possible protecting effect of the drug against the barrier dysfunction under conditions of acute hypercapnia. Serum concentrations of the drug were similar to the results reported by Strausbaugh (Strausbaugh et al. 1983). The discrete difference between gentamycin serum concentrations in both groups at the baseline point, which however appeared to be significant (Table II) might be attributed to relatively small study groups and did not influence final conclusions.

Lidocaine, a well known regional analgesic and antiarrhythmic drug with membrane stabilizing properties, has been used in brain protection, blocking the open state of brain Na^+ channels, both slow- and fast-inactivated ones with an comparable affinity (Balser et al. 1996). The agent readily passes from blood into cerebrospinal fluid. The isolated rabbit choroid plexus has been shown to accumulate [14C] lidocaine by both active saturable and non-saturable processes; non-specific binding and metabolism of the drug within or on the choroid plexus have been excluded (Spector 1980). More recent studies provided evidence that lidocaine is transported across the blood-brain barrier by a carrier-mediated transport system, common to lipophilic basic drugs and H1 antagonists (Yamazaki et al. 1994). It does also influence endothelial function, modulating vessel tone and blood flow *via* a NO- and PGI_2 - dependent mechanism and exerting an antiinflammatory effect being a free radical scavenger (Az-ma et al. 1995). However, it should be mentioned that high $PaCO_2$ and low pH increase the cationic form of local anaesthetic, decrease its protein binding capacity and also the convulsive threshold. The uptake of a local anaesthetic may be also increased because of existing vasodilation in a course of hypercapnia (Datta, 1993).

In our experiments lidocaine tended to lower such hemodynamic parameters as heart rate and mean arterial pressure, and resulted in a statistically significant decrease of mean pulmonary arterial pressure at 180 minutes of hypercapnia. These effects might be attributed to the sympathetic blocking activity of systemically administered lidocaine (Birch et al. 1987). Additionally the agent was shown to decrease tension in airway smooth muscle *via* an effect on intracellular Ca^{+2} stores (Kai et al. 1993) and thus, acting decreasingly on airway pressures, could also lower mean pulmonary arterial pressure.

Cerebral perfusion pressure at 180 minutes of hypercapnia was also slightly lower in lidocaine group, but this difference did not prove statistically significant.

We are prompted to speculate that the mechanisms underlying the observed protective effect of lidocaine against the brain-cerebrospinal fluid barrier dysfunction due to hypercapnia might involve: a modulation of the cerebrospinal fluid formation, an antiinflammatory influence on vascular endothelium and an interference with the neuropeptide metabolism.

Concerning the first possibility; CSF formation is connected with an active transport of Na^+ from blood to CSF and also depends on blood flow to choroid plexus.

It has been demonstrated that amiloride treatment and also acidosis, inhibit Na^+/H^+ exchange, and Na^+ uptake into CSF, suggesting a decreased CSF production (Murphy et al. 1989). It could be also expected that lidocaine as a sodium channel blocker would act decreasingly on CSF production. Indeed, Artru et al. (1997) were able to confirm in anaesthetized rabbits that lidocaine decreased the rate of cerebrospinal fluid formation. The authors suggested that this phenomenon might result from decreased secretory activity at the choroid plexus epithelium and/or alterations in blood flow: decreased choroid plexus blood flow and constriction of the general cerebral vasculature (Artru et al. 1997). Under condition of hypercapnia lidocaine could potentiate inhibitory effect of acidosis on Na^+/H^+ exchange. As to the influence on blood flow, it has been also demonstrated in umbilical vessel preparations that hypercarbia does not influence direct vascular response to lidocaine (Halevy et al. 1995). Choroid plexus blood flow in hypercapnia depends on the level of sympathetic activity, and it has been postulated that increased catecholamine blood levels, due to carbon dioxide retention, might prevent increases in choroidal blood flow (Williams et al. 1991). Decreasing sympathetic activity by lidocaine could eventually increase blood flow to choroid plexus, partly counteracting its direct vasoconstrictory action. Lidocaine was also shown to be able to inhibit nitric oxide release from endothelial cells (Az-ma et al. 1995). However, as hypercapnic cerebral vasodilation and increased blood flow are mainly due to NO of neuronal origin, the agent is probably not involved in attenuation of vasodilatation due to NO mechanisms (Wang Q et al. 1994).

In reference to second possibility; functional state of the central nervous system capillary endothelium is crucial for the permeability of blood-brain barriers. The Na^+/H^+ exchange depression by lidocaine should be responsible, partly at least, for the effect of nitric oxide and prostacyclin release inhibition from endothelial cells

with subsequent platelet aggregation, as previously mentioned (Dembinska-Kiec et al. 1990, Az-ma et al. 1995). The influence of lidocaine on endothelium also involves the decrease of the reactive oxygen intermediates production. The agent was shown to be able to attenuate endothelial changes due to oxidative stress (Schmidt et al. 1997) and also in the brain its scavenging properties were well documented (Lantos et al. 1996). It is well known that blood-brain barrier permeability corresponds with the degree of oxidative stress (Noseworthy et al. 1998), however it is perhaps worth mentioning that the oxidative stress in some conditions may be beneficial to a certain degree, confining the postischaemic hyperemia (Tasdemiroglu et al. 1994). Whether and to what degree the mechanism of an increased permeability of blood-cerebrospinal fluid barrier in course of hypercapnia involves oxidative stress is not well documented, but it could not be excluded that, partly at least, lidocaine protects the cerebrospinal fluid-blood barrier, reducing the oxidative stress. Hypercarbia also alters the integrity of brain barriers by promoting pinocytosis in CNS capillary endothelial cells (Lange et al. 1991). As lidocaine has been shown to block pinocytosis, acting on microfilaments (Dean 1979), it may be also another possible explanation of its protecting effect on blood--cerebrospinal fluid permeability under conditions of hypercapnia.

The third possibility is, that brain barrier permeability may be also modulated by certain neuropeptides (Goldman et al. 1993) and lidocaine, decreasing the aminopeptidase activity in some brain areas is also able to influence the neuropeptide metabolism (de Gandarias et al. 1997). Therefore, it could not be excluded that this mechanism may contribute to the protecting effect of the agent under the conditions of hypercapnia.

Under conditions of hypercapnia and pentobarbital anaesthesia two important factors which may modulate a protective effect of lidocaine should be considered: acidosis and the barbiturate used. In our previous study it has been shown that acute experimental hypercapnia in the rabbit is connected with acidosis of moderate degree (arterial blood pH decreases to 7.1 at the 3rd hour of hypercapnia; Pakulski et al. 1998). The promoting influence of carbon dioxide retention on brain barriers permeability may be partly due to coexisting acidosis, i.e., the enhanced brain permeability to lactate is possibly a consequence of the decrease in pH (Knudsen et al. 1991). This effect may result from alterations in ion channels functional state; hypercapnic acidosis promotes an influx of external Ca^{2+} through voltage-gated Ca^{2+} channels, altering intracellular calcium concentration $[Ca^{2+}]i$ (Sato 1994) but also results in Na^+/H^+ exchange inhibition (Kaplan et al. 1995). Acidosis due to hypercapnia has been shown to be an important protective factor against cell injury by the mechanism of decreased activity of xantine oxidase - this phenomenon is known as the concept of the "pH paradox" (Kaplan et al. 1995, Shibata et al. 1998).

As previously mentioned, lidocaine as a sodium channel blocker might potentiate the effects of acidosis on Na^+/H^+ exchange. It is well known that acidosis enhances effects of the drug, which as a weak base have pH-dependent electrophysiologic effects (Hille 1977); probably it is also the case concerning endothelial protection. However, it has been reported that lidocaine treatment of dogs with *Escherichia coli septicemia* causes itself metabolic acidosis (Hardie et al. 1988).

Another important point may be the possible interaction between pentobarbital and lidocaine in the observed protective effect on blood-cerebrospinal fluid barrier permeability. Pentobarbital possesses sodium channel stabilizing properties, so a synergism between these two agents can not be excluded (Wartenberg et al. 1993).

Taken together, the observed protecting effect of lidocaine on the blood-cerebrospinal fluid barrier permeability increase in course of acute hypercapnia is probably a complex phenomenon. The detailed mechanism of its action in this particular experimental setting would need further elucidation. We suggest that lidocaine may be a useful tool stabilizing the blood--cerebrospinal fluid barrier permeability in acute hypercapnia.

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