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ORIGINAL ARTICLE

Cytotoxic brain edema induced by water intoxication and vasogenic brain edema induced by osmotic BBB disruption lead to distinct pattern of ICP elevation during telemetric monitoring in freely moving rats

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Abstract

OBJECTIVES: A novel method of long-term telemetric monitoring of mean arterial pressure (MAP) and intracranial pressure (ICP) for the determination of current cerebral perfusion pressure (CPP) and the time course of ICP in freely moving rats under physiological conditions and with increased ICP due to the induced cerebral edema were studied.

METHODS: The brain edema, that caused volume enlargement and ICP elevation was achieved in entirely experimental conditions without any parallel pathological process. Vasogenic/extracellular edema was induced by osmotic blood-brain barrier disruption (BBBd) and for induction of cytotoxic/intracellular edema the water intoxication model (WI) was used.

RESULTS: The results showed significantly elevated values of ICP both in conditions of osmotic blood-brain barrier disruption (BBBd model) and cytotoxic/intracellular edema (WI model) compared to intact rats. The average values of ICP were significantly higher in WI model compared to osmotic BBBd model. Distinct pattern of elevated ICP, related to the selected way of experimental brain edema induction, was found. In the experimental model of osmotic BBB disruption, the elevation of ICP started earlier but was of very short duration. In WI model the elevation of ICP was present during the whole period of monitoring.

CONCLUSION: Our results indicate that purely experimental models of brain edema (WI, BBBd) without any parallel pathological process can compromise the basic brain homeostatic activity.

Abbreviations and units:

ICP	- intracranial pressure	BBB	- blood-brain barrier
MAP	- mean arterial pressure	BBBd	- blood-brain barrier disruption
CPP	- cerebral perfusion pressure	WI	- water intoxication
CBF	- cerebral blood flow	CG	- control group

WI group	- water intoxication group
MA group	- Manitol group
CNS	- central nervous system
SEM	- standard error of mean
CCA	- common carotid artery
ICA	- internal carotid artery
ROI	- regions of interest
MV HU	- mean values of Hounsfield Units
Na^+	- sodium
i.e.	- id est/that is
g	- gram
ml	- millilitre
mm	- millimetre
Fig.	- figure
mmHg	- millimetre of Mercury

INTRODUCTION

Brain edema is a fatal pathological state in which brain volume increases as a result of abnormal accumulation of fluid within the cerebral parenchyma. The abnormal accumulation of fluid causes an increase of brain volume together with elevation of intracranial pressure (ICP) because of an enclosed rigid skull. The increase in brain volume is observed prior to elevation of ICP. Brain edema is usually classified into vasogenic edema and cytotoxic edema. Vasogenic edema is characterized by extravasation and extracellular accumulation of fluid into the cerebral parenchyma caused by disruption of the blood-brain barrier (BBB). In contrast, cytotoxic edema is characterized by intracellular accumulation of fluid and Na^+ resulting in cell swelling (Kimlberg, 1995; Klatzo, 1967; Liang *et al.* 2007; Michinaga & Koyama, 2015). The most frequently used animal experimental model of BBB disruption is the cold injury model.

The freezing and thawing of central nerve tissues by cold injury directly impairs the integrity of vascular endothelial cells and enhances extravasation of intravascular proteins through the disrupted BBB (Michinaga & Koyama, 2015, Murakami *et al.* 1999; Nag, 1996; Oury *et al.* 1993).

In our experimental model annother method of BBB disruption was used – intracarotid injection of hyperosmolar solution (Kozler & Pokorný, 2003). The idea of disruption the BBB by an osmotic insult was first accomplished by Rapoport (1970). By means of intracarotid administration of a hyperosmolar solution, shrinkage of endothelial cells is achieved, causing tight junctions to expand up to an average of 20 times their normal diameter. Owing to the distension of the tight junctions, BBB becomes permeable to high-molecular substances, which should be followed by water in the direction of osmotic gradient (Rapoport, 2000). In a slight modification of this method implemented by Kroll&Neuwelt (1998) and Rapoport (2000) we use solution of 20% Mannitol to achieve the osmotic BBB disruption.

The mostly used experimental model of cytotoxic edema is the water intoxication model. The intra-extracellular water balance depends on Na^+ concentration, and the fluctuation of intra-extracellular Na^+ concentration leads to water inflow into cells or water outflow from cells. Disturbance of the Na^+ balance as seen in hyponatremia induces disruption of the water balance. Hyponatremia causes a decrease of extracellular Na^+ contents and relative increase of intracellular Na^+ contents. Subsequently, water flow into cells is accelerated. In experimental animal models, the water intoxication model best reflects simulation of hyponatremia because it induces a relative decrease of extracellular Na^+ concentration. The water intoxication model is produced by intraperitoneal loading of excessive amount of distilled water corresponding to 10%–40% of the body weight of experimental animals. The high water load induces an increase of water content in central nervous tissue and an excessive influx of water into astrocytes, resulting in astrocytic swelling (Kozler *et al.* 2013; Manley *et al.* 2000; Yamaguchi *et al.* 1994; Yang *et al.* 2008; Yeung *et al.* 2009). In our experiments to induce the cytotoxic – intracelllular edema, we have been using the water intoxication model for a long time (Kozler *et al.* 2018).

In this study ICP, MAP and CCP were telemetrically monitored (Guild *et al.* 2015; Hiploylee & Colbourne, 2014) for 72 hours in freely moving intact animals (controls), in rats with cytotoxic /intracellular edema induced by water intoxication (WI) and in rats with vasogenic/ extracellular edema induced by osmotic BBB disruption (BBBd). The aim of the present study was to find out the differences of the pressure levels over an extended time period after induction of distinct types of brain edema in conditions of purely experimental models (WI, BBBd) without the occurrence of any pathological process.

MATERIAL AND METHODS

All experiments were approved by the Ethical Committee of the First Faculty of Medicine (Charles University in Prague) and were in agreement with the Guidelines of the Animal Protection Law of the Czech Republic and Guidelines for the treatment of laboratory animals EU Guidelines 86/609 / EEC. For experiments, male rats of the Wistar strain weighing 400-410 g of our own breed were used.

Groups of animals

A total of 24 experimental animals was divided into three groups of 8 animals. Intact animals formed control group CG. Animals with cytotoxic/intracellular brain edema induced by water intoxication were in the WI group. Animals with vasogenic/extracellular edema induced by osmotic BBB disruption formed group MA.

Water intoxication and BBB disruption

The method of cytotoxic/intracellular brain edema induction by water intoxication as well as the method of vasogenic/extracellular edema induction by 20% Mannitol application into internal carotid artery (ICA) was described in details in our previous papers (Kozler & Pokorny, 2003; Kozler *et al.* 2013; Kozler *et al.* 2018).

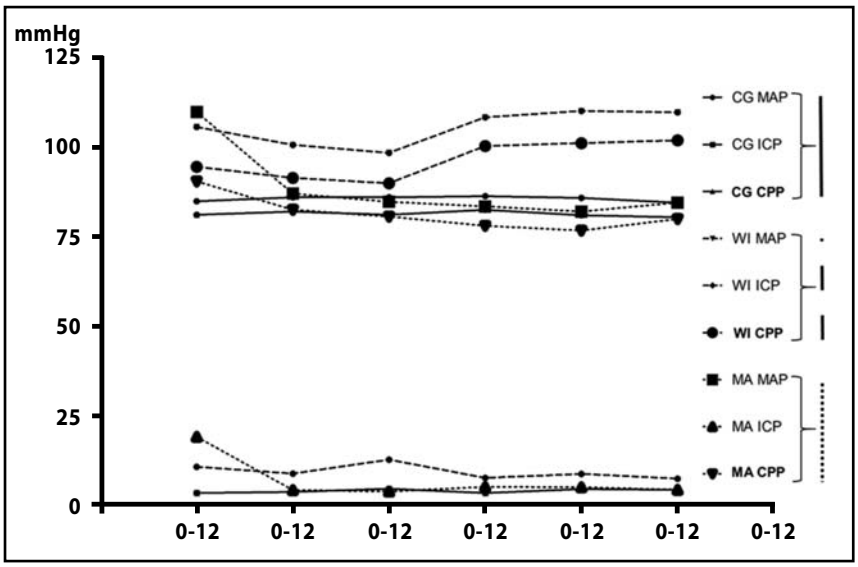

Fig. 1. Fluctuations of MAP, ICP and CCP values during 72 hours period.
Legend: CG MAP= mean arterial pressure in the control group; CG ICP= intracranial pressure in the control group; CG CPP= cerebral perfusion pressure in the control group. Fluctuations of pressures in CG animals are depicted by full lines. WI MAP= mean arterial pressure in the WI group; WI ICP= intracranial pressure in the WI group; WI CPP= cerebral perfusion pressure in the WI group. Fluctuations of pressures in WI animals are depicted by broken lines. MA MAP= mean arterial pressure in the MA group; MA ICP= intracranial pressure in the MA group; MA CPP= cerebral perfusion pressure in the MA group. Fluctuations of pressures in MA animals are depicted by dotted lines. Individual characters represent average values of pressures during consecutive 12 hour intervals

Pressure sensors implantation

The DSI™ telemetry system (Data Sciences International) was used to monitor ICP and MAP. Its implantable components were the transducer and two pressure sensors. The components were implanted in spontaneously breathing rats under inhalation anaesthesia by isoflurane (Florante®, AbbVie Ltd.).

The surgery necessary for the implantation of the intracranial sensor together with a pocket for transducer was prepared first. In the prone position, a midline skin incision was done over the frontal bone. Transducer was placed in a subcutaneous pocket formed on the back at the level of thoracic spine. The ICP pressure sensor was placed subdurally from the trephine located in the right frontal bone 2 mm in front of bregma; access to the intracranial space, adjustment of the sensor and its fixation are described elsewhere (Kozler *et al.* 2017). The wound was closed with a continuous suture. The animal was then turned to the supine position. By microsurgical approach the common carotid artery (CCA) was exposed on the right. From the arteriotomy a pressure sensor for MAP monitoring was introduced into the CCA lumen with the sensor tip directed at aortic arch in case of group WI. In group MA prior to the pressure sensor introduction, the 20% Mannitol was injected into internal carotid artery (ICA) (Kozler & Pokorny, 2003; Kozler *et al.* 2015). The wound was closed by continuous suture and inhalation anaesthesia was terminated. The rats were placed in a cage on a receiver that transmitted signals from the transducer to the PC hardware. The recorded and stored data were evaluated by software as the values of the pressure, and in the form of a pressure curve over the entire reference period, i.e. in 72 hours. Detailed information on pressure sensor design, transducer, transmission, registration and data analysis can be obtained at: www.datasci.com/solutions/neuroscience.

The procedure of pressure sensors implantation in group WI started immediately after completing water intoxication, in group MA the 20% Mannitol was injected into ICA during the procedure of pressure sensor implantation and the pressure monitoring started after.

RESULTS

Fluctuations of MAP, ICP and CCP values during 72 hours period (see Fig. 1) clearly show that CPP in all groups including WI and MA animals was constantly above the value of 70mmHg. CPP levels confirm constant cerebral blood flow (CBF) necessary for the normal brain function according the statement that for maintaining normal brain, pressure conditions should be ICP<20mmHg and CPP>70mmHg (Czonsyka & Miller, 2014; Kirkman & Smith, 2014).

The results showed differences between ICP values in CG, WI and MA groups (see Fig. 2). The highest

average value of ICP during 72 hours was documented in WI group, followed by average value in MA group. The average values of ICP in group WI and MA represent slightly elevated ICP while normal values should be below 5 mmHg. This is confirmed by the average value of ICP in CG group. The average value of ICP in group WI was significantly higher than the average value of ICP in group MA. This is clearly explained by fluctuations of ICP values depicted in Fig. 3.

The fluctuations of ICP values in control group were lower than 5 mmHg during the whole period of 72 hours (see Fig. 3). The values of ICP in WI group were elevated during the whole period of 72 hours with the peak elevation during 24-36 hours after the intervention. On the other hand, the values of ICP in MA group were elevated only in the first two periods with the maximum value at 0-12 hour interval while at the end of 12-24 hours interval the value fell to normal range and remained so till the end of monitoring period. This explains significantly higher average value of ICP during 72 hours in WI group in comparison with MA group. Fig. 3 clearly shows distinct pattern of ICP elevation in group WI from that in group MA.

DISCUSSION

Abnormal accumulation of body fluids brings about an increase of brain volume and ICP elevation because the brain is enclosed within the rigid skull. The increased brain volume can be observed prior to elevation of ICP (Michinaga & Koyama, 2015).

In case of vasogenic/extracellular brain edema the evidence brings the intracerebral occurrence of intravital dyes and the increase of brain water content after osmotic BBBd.

BBB permeability can be tested by different methods. The most widely used one in experimental models is that intravenously applied intravital dyes (tracers, markers) of molecular weight greater than 180 Da preclude passage across an intact barrier. In terms of molecular size, these markers represent a broad spectrum of dyes, in which Evans blue (EB, MW 961 Da) is one of the largest. In blood circulation, however, it becomes strongly, though reversibly, bound to the albumin fraction of proteins to give rise to a high-molecular complex (EBA 68 500 Da) (Broman, 1944; Kroll& Neuwelt, 1998; Lafuente *et al.* 1990; Pokorný *et al.* 2002; Wolman *et al.* 1981).

In our experimental model we proved the distribution of high-molecular EBA tracer injected into ICA after osmotic BBBd in extracellular brain compartment by way of fluorescence microscopy (Kozler & Pokorný, 2003) which means that owing to the distension of the tight junctions, BBB becomes permeable to high-molecular substances, which should be followed by water in the direction of osmotic gradient (Rapoport, 2000).

This method of osmotic BBBd has been used for long in humans where it allows high-molecular drugs to flow directly from the circulatory system into the brain and thus more effectively reach dispersed tumor cells. To prevent the development of brain edema a distinctive general anesthesia is used in human's protocol of BBBd (Kroll & Neuwelt, 1998; Martin et al, 2012).

Results of our experimental model showed that after the osmotic BBBd the water content significantly increased (Kozler *et al.* 2013). Not all authors studying the relationship between osmotic BBBd and rise of water content in the brain came to the same conclusion. Rapoport *et al.* (1980) described transient increase

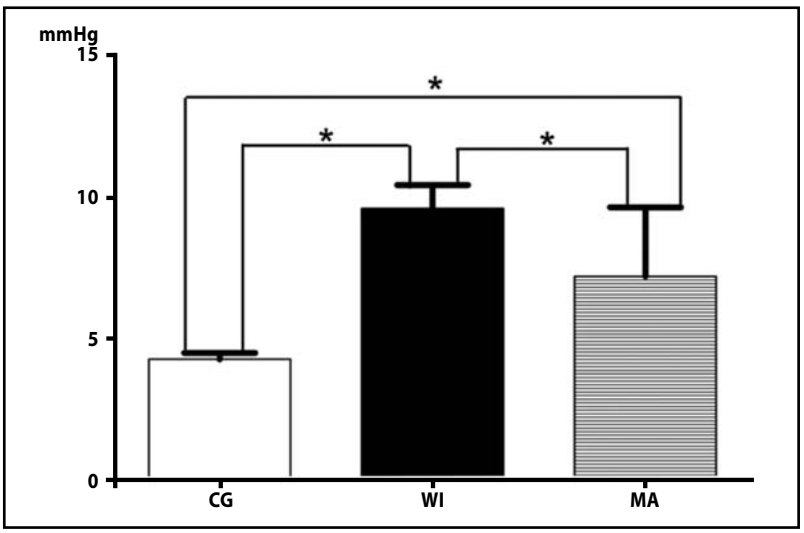

Fig. 2. Values of ICP during 72 hours period
Legend: CG = intracranial pressure in the control group; WI = intracranial pressure in the WI group; MA = intracranial pressure in the MA group. Columns represent average values of pressures from 8 animals in each group during 72 hours, mean ± SEM, significant differences are given, * $p < 0.5$.

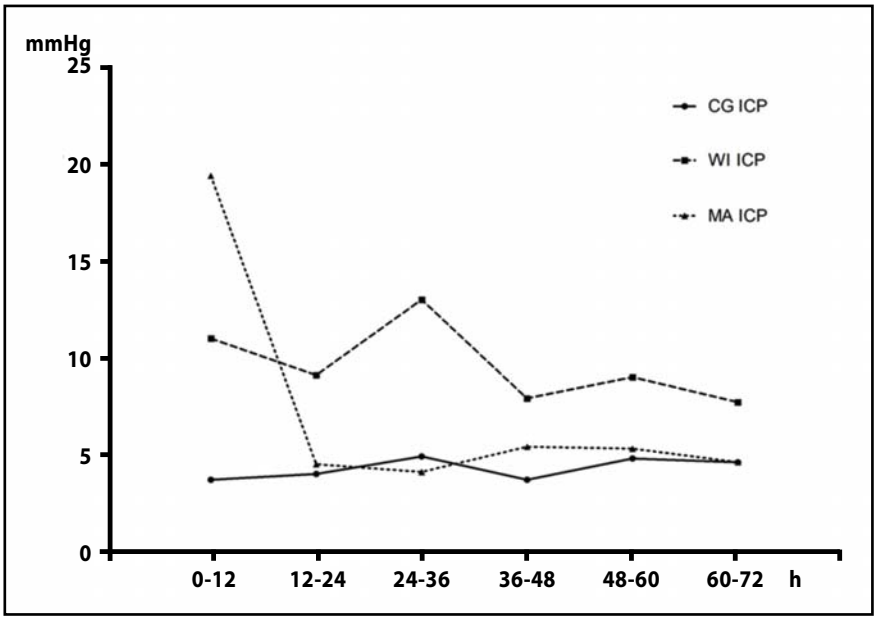

Fig. 3. Fluctuations of ICP values during 72 hours period
CG ICP= intracranial pressure in the control group (full line); WI ICP= intracranial pressure in the WI group (broken line); MA ICP= intracranial pressure in the MA group (dotted line). Individual characters represent average values of pressures during consecutive 12 hour intervals.

of water content (1.0-1.5 %) after the osmotic BBBd; Kaya *et al.* (2004) found significantly higher water content in rats with osmotically opened BBB. By contrast, Marchi *et al.* (2009) stressed that the osmotic BBBd was followed by protein extravasation and the total water content of the brain was not increased. However, they admitted, that as a result of the accumulation of osmotically active substances, including proteins, in the extracellular space some exchange of water between the cellular and extracellular compartment could develop. Similar findings published also Chi *et al.* (2000).

In case of cytotoxic/intracellular brain edema the evidence of its occurrence after WI brings increase of brain water content and decrease of CT density.

Water intoxication reduces the amount of solutes in the extracellular compartment due to their marked dilution and causes hypoosmolality, with plasma hyponatremia being its constant factor. This creates an osmotic gradient that activates water movement from the extracellular space into the cells. Accumulation of water in cells triggers a cascade of events that leads to the failure of cellular metabolism and to the development of cytotoxic edema (Go, 1997; Kimlberg, 1995; Klatzo, 1967).

Results of our experimental model of cytotoxic/intracellular edema induced by water intoxication proved that the water content significantly increased (Kozler *et al.* 2013; Kozler *et al.* 2018). On top of that we used three different volumes of distilled water applied, corresponded to 20%, 30% or 40% of animal´s body weight, and we found that the larger was the volume of distilled water the higher water content in the brain was achieved. Water intoxication model is used as a standard experimental model of cellular brain edema which should be confirmed by hyponatremia (Michinaga & Koyama, 2015). In our experimental model, WI resulted in plasma levels of sodium lower than in healthy rats (by 20 mmol/l) (Kozler & Pokorný, 2003). It is therefore possible to conclude that WI brings about higher water content in the brain with the real increase in brain volume due to cytotoxic/intracellular edema.

In our experimental model (Kozler & Pokorný, 2014; Kozler *et al.* 2018) we studied the CT density in group of intact rats and in the group of rats after WI. Scans with a pixel size 0.125 mm were done in regions of interest (ROI) corresponding to the area of coronary sections in three different positions, with bregma being the reference mark (bregma +2.43 mm, bregma –2.92 mm and bregma –12.73 mm) in both groups of animals. The CT density of the brain tissue in each scan was stated as mean values of Hounsfield Units (MV HU). Under physiological conditions the CT density of the human brain is in the range of 29-38 HU (Kucinski *et al.* 2002; Mangel *et al.* 2002). If, under pathological conditions, the density decreases at least by 12 HU, the radiological criterion for the presence of brain edema is fulfilled (Clasen *et al.* 1981; Torack, 1982). The overall average density decrease in the group after WI, was 32.48 MV HU, high enough to conclude that rats after WI had brain edema which according to its way of origin should be of cytotoxic/intracellular type.

We can conclude that the above described findings document the occurrence of brain edema in experimental model of osmotic BBBd as well as in experimental water intoxication model.

The results of this study clearly showed (see Fig. 1) persisting cerebral blood flow (CBF), necessary for the normal brain function during the period of 72 hours. Constant CBF is maintained by homeostatic process known as cerebral autoregulation. The optimal CBF is supported either by vasoconstriction of small brain arteries when MAP or CPP increases and by vasodilation in case MAP or CPP decline (Armstead, 2016; Lassen, 1959; Smith, 2015). Besides this, normal brain function depends on another homeostatic process known as intracranial volume homeostasis (Kellie, 1824; Monro, 1783) which prevents the detrimental increase of ICP in case of brain volume enlargement.

Both of the above mentioned homeostatic processes were working properly during the period of 72 hours in this study in view of the fact that ICP level was never above 20mmHg and CPP level was never below 70 mmHg (Czonsyka & Miller, 2014; Kirkman & Smith, 2014). From this evidence we learned of the fact that neither osmotic BBBd model nor water intoxication model is potent enough to threaten constant cerebral blood flow.

We found substantive differences in the levels and fluctuations of ICP in this study. Slightly elevated values of ICP were present at the group of osmotic BBBd model (MA group) as well as at the water intoxication model (WI group). The difference between the average values of ICP during 72 hours in these groups and the average value of ICP during 72 hours in the control group was statistically significant (see Fig. 2). As the occurrence of brain edema after osmotic BBBd and after WI was clearly proved these findings match up to the statement that the increase in brain volume is observed prior to elevation of ICP (Michinaga & Koyama, 2015). Besides this, the results of this study showed a statistically significant difference of the average values of ICP during 72 hours between the MA group and the WI group when the average values of ICP were higher in WI group.

This result is affirmed by the fluctuations of ICP values (see Fig. 3). The fluctuations of ICP values in the WI group were slightly elevated during the whole period of 72 hours with the peak elevation at 24–36 hours interval. On the other hand the fluctuations of ICP values in MA group were elevated only in the first two periods with the maximum value at 0–12 hours interval while at the end of 12–24 hours interval the value has fallen to normal range and remained so till the end of the monitoring period. This phenomenon is intimately interconnected with the resolution of edema.

Xu *et al.* (2010) assert in their paper on traumatic brain edema that in all brain edema types, excess fluid leaves the brain parenchyma along three different routes: across the blood-brain barrier into the bloodstream, across the ependyma into the ventricles, and across the glia limiting membrane into CSF in the subarachnoid space. Vasogenic edema is generally believed to be cleared primarily by bulk flow of fluid through the extracellular space and glia limitans into the ventricles and subarachnoid space. This way of vasogenic/extracellular edema resolution is generally accepted (Bloch *et al.* 2007; Reullen, 2010; Stummer, 2007; Xu *et al.* 2010). On the other hand the way of cytotoxic/intracellular edema resolution is not so clear. Nevertheless there exists the conception dealing with the cell death in case of cytotoxic edema. Broadly speaking it is possible that in cytotoxic edema, the excess water initially resides in the intracellular compartment but ultimately moves to the extracellular space due to cell death and regulatory volume decrease. Therefore, excess water elimination routes in cytotoxic edema may be the same as those in vasogenic edema (Barros *et al.* 2002; Liang *et al.* 2007; Xu *et al.* 2010).

It should be stressed that in this study we used purely experimental models of brain edema (WI, BBBd) without any parallel pathological process, unlike the cited papers where various types and degrees of tissue damage were always present (cold injury, ischaemic or traumatic brain injury, and brain tumor).

We applied in this study a novel method that provides the chance of long-term telemetric monitoring of the MAP and ICP for the determination of current CPP in freely moving rats (Guild *et al.* 2015; Hiploylee & Colbourne, 2014) under physiological conditions and with increased ICP due to the induced cerebral edema. This method also offers the pattern of ICP elevation during the period of monitoring.

Results of this study documented two basic pathophysiological phenomena related to the way of experimental brain edema induction.

The first one was already mentioned above and signifies that neither osmotic BBBd model nor water intoxication model is potent enough to threaten constant cerebral blood flow.

In the experimental model of osmotic BBBd the elevation of ICP corresponding to volume enlargement started very early but was of a short duration. This finding matches up to the generally accepted way of vasogenic/extracellular edema resolution (Bloch *et al.* 2007; Reullen, 2010; Stummer, 2007; Xu *et al.* 2010). In our purely experimental settings, without any pathological condition, the bulk flow of fluid through the extracellular space and glia limitans into the ventricles and subarachnoid space is very fast. Furthermore this phenomenon fulfils the requirement of outwitting the blood-brain barrier for therapeutic purposes when the osmotic BBBd must be rapid, short-term and fully reversible (Kroll & Neuwelt, 1998; Martin *et al.* 2012; Rapoport, 2000).

In water intoxication model a slight elevation of ICP was present during the whole period of monitoring (72 hours/3 days) which excludes the cell death as a cause of water movement from intracellular to extracellular space, so the resolution of cytotoxic edema did not arise.

(Barros *et al.* 2002; Liang *et al.* 2007; Xu *et al.* 2010). This finding matches up to the studies by Barzó *et al.*

(1997) on time course of edema types after experimental diffuse brain injury when cytotoxic/intracellular type persists up to 14 days after injury.

CONCLUSION

A novel method for long-term telemetric monitoring of MAP and ICP to determine current CPP and for the monitoring the time course of ICP in freely moving rats under physiological conditions and with increased intracranial pressure due to the induced cerebral edema was used in this study. Vasogenic/extracellular edema was induced by osmotic BBBd while cytotoxic/intracellular edema was induced by the water intoxication model.

This study documented two basic pathophysiological phenomena related to the way of experimental brain edema induction. The first one signifies that neither osmotic BBBd model nor water intoxication model is potent enough to threaten constant cerebral blood flow.

In the experimental model of vasogenic/extracellular edema the elevation of ICP started very early but was of short duration whereas in the experimental model of cytotoxic/intracellular edema slight elevation of ICP was present during the whole period of monitoring.

It could be stated that purely experimental models of brain edema (WI, BBBd) without any parallel pathological process are capable to disclose basic pathophysiological phenomena.

CONFLICT OF INTEREST

There is no conflict of interest.

ACKNOWLEDGMENTS

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REFERENCES

1 Armstead WM (2016). Cerebral Blood Flow Autoregulation and Dysautoregulation. Anesthesiol Clin **34**: 465–477.
2 Barros LF, Castro J, Bittner CX (2002). Ion movements in cell death: from protection to execution. Biol Res. **35**: 209–214.
3 Barzó P, Marmarou A, Fatouros P, Hayasaki K, Corwin F (1997). Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging. J Neurosurg **87**: 900–907.
4 Bloch O, Manley GT (2007). The role of aquaporin-4 in cerebral water transport and edema.
5 Broman T (1944). Supravital analysis of disorders in the cerebral vascular permeability in man. Acta Med Scand. **118**: 79–83.
6 Chi OZ, Lee DI, Liu X, Weiss HR (2000). The effects of morphine on blood-brain barrier disruption caused by intracarotid injection of hyperosmolar mannitol in rats. Anesth Analg **90**: 603–608.
7 Clasen RA, Huckman MS, Von Roenn KA, Pandolfi S, Laing I, Lobick JJ (1981). A correlative study of computed tomography and histology in human and experimental vasogenic cerebral edema. J Comput Assist Tomogr. **5**: 313–327
8 Czonsyka M, Miller C (2014). Monitoring of cerebral autoregulation. Neurocrit Care **21**: S95–S102
9 Go KG (1997). The normal and pathological physiology of brain water. Adv Tech Stand Neurosurg. **23**: 47–142.
10 Guild SJ, McBryde FD, Malpas SC (2015). Recording of intracranial pressure in conscious rats via telemetry. J Appl Physiol **119**: 576–581.
11 Hiploylee C, Colbourne F (2014). Intracranial pressure measured in freely moving rats for days after intracerebral hemorrhage. Exp Neurol **255**: 49–55.
12 Kaya M, Gulturk S, Elmas I, Kalayci R, Arican N, Kocyildiz ZC, Kucuk M, Yorulmaz H, Sivas A (2004). The effects of magnesium sulfate on blood-brain barrier disruption caused by intracarotid injection of hyperosmolar mannitol in rats. Life Sci. **26**: 201–212.
13 Kellie G (1824). "Appearances observed in the dissection of two individuals; death from cold and congestion of the brain". Trans Med Chir Sci Edinb **1**: 84–169.
14 Kimelberg HK (1995). Current concepts of brain edema. Review of laboratory investigations. J Neurosurg. **83**: 1051–1059.
15 Kirkman MA, Smith M (2014). Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/CPP-guided therapy: a standard of care or optional extra after brain injury? Br J Anaesth. **112**: 35–46.
16 Klatzo I (1967). Presidential Address. Neuropathological aspects of brain edema. J Neuropathol Exp Physiol. **26**: 1–14.
17 Kozler P, Marešová D, Pokorný J (2017): Methylprednisolene modulates intracranial pressure in the brain cellular edema induced by water intoxication. Physiol Res. **66 Suppl. 4**: S511–S516.
18 Kozler P, Maresova D, Pokorny J (2018). Cellular brain edema induced by water intoxication in rat experimental model. Neuro Endocrinol Lett. **39**: 209–218.
19 Kozler P, Pokorný J (2003). Altered blood-brain barrier permeability and its effect on the distribution of Evans blue and sodium fluorescein in the rat brain applied by intracarotid injection. Physiol Res. **52**: 607–614.
20 Kozler P, Pokorny J (2014). CT density decrease in water intoxication rat model of brain oedema. Neuro Endocrinol Lett. **35**: 608–612.
21 Kozler P, Riljak V, Pokorný J (2013). Both water intoxication and osmotic BBB disruption increase brain water content in rats. Physiol. Res. **62**: S75–S80.
22 Kozler P, Sobek O, Pokorný J (2015). Signs of myelin impairment in cerebrospinal fluid after osmotic opening of the blood-brain barrier in rats. Physiol Res. **64 Suppl. 5**: S603–608.
23 Kroll RA, Neuwelt EA (1998). Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. Neurosurgery **42**: 1083–1100.
24 Kucinski T, Väterlein O, Glauche V, Fiehler J, Klotz E, Eckert B, Koch C, Röther J, Zeumer H (2002). Correlation of apparent diffusion coefficient and computed tomography density in acute ischemic stroke. Stroke. **33**: 1786–1791.
25 Lafuente JV, Pouschman E, Cervós-Navarro J, Sharma HS, Schreiner C, Korves M (1990). Dynamics of tracer distribution in radiation induced brain oedema in rats. Acta Neurochir. **51** Suppl: 375–377.
26 Lassen NA (1959). Cerebral blood flow and oxygen consumption in man. Physiol Rev **39**: 183–238.
27 Liang D, Bhatta S, Gerzanich V, Simard JM (2007). Cytotoxic edema: mechanisms of pathological cell swelling. Neurosurg Focus. **22**: E2
28 Mangel L, Vönöczky K, Hanzély Z, Kiss T, Agoston P, Somogyi A, Németh G (2002). CT densitometry of the brain: a novel method for early detection and assessment of irradiation induced brain edema. Neoplasma. **49**: 237–242.
29 Manley GT, Fujimura M, Ma T, Noshita N, Filiz F, Bollen AW, Chan P, Verkman AS (2000). Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. Nat. Med. **6**: 159–163.
30 Marchi N, Betto G, Fazio V, Fan Q, Ghosh C, Machado A, Janigro D (2009). Blood-brain barrier damage and brain penetration of antiepileptic drugs: role of serum proteins and brain edema. Epilepsia **50**: 664–677.

31 Martin JA, Maris AS, Ehtesham M, Singer RJ (2012). Rat model of blood-brain barrier disruption to allow targeted neurovascular therapeutics. J Vis Exp. **30**: e50019.
32 Michinaga S, Koyama Y (2015). Pathogenesis of brain edema and investigation into anti-edema drugs. Int J Mol Sci. **16**: 9949–9975.
33 Monro A (1783). Observations on the structure and function of the nervous system. Edinburgh: Creech & Johnson.
34 Murakami K, Kondo T, Yang G, Chen SF, Morita-Fujimura Y, Chan PH (1999). Cold injury in mice: A model to study mechanisms of brain edema and neuronal apoptosis. Prog. Neurobiol. **57**: 289–299.
35 Nag S. Cold-injury of the cerebral cortex: Immunolocalization of cellular proteins and blood-brain barrier permeability studies (1996). J. Neuropathol. Exp. Neurol. **55**: 880–888. Neurosurg Focus. **22**: E3
36 Oury TD, Piantadosi CA, Crapo JD (1993). Cold-induced brain edema in mice. Involvement of extracellular superoxide dismutase and nitric oxide. J. Biol. Chem. **268**: 15394–15398.
37 Pokorný J, Hrachovina V, Langmeier M, Trojan S (2002). Long-term changes of the blood brain barrier permeability from the view of reparation plasticity. Physiol Res. **51**: 35P
38 Rapoport SI (1970). Effect of concentrated solutions on blood-brain barrier. Am J Physiol. **219**: 270–274.
39 Rapoport SI (2000). Osmotic opening of the blood-brain barrier: principles, mechanism, and therapeutic applications. Cell Moll Neurobiol. **20**: 217–230.
40 Rapoport SI, Fredericks WR, Ohno K, Pettigrew KD (1980). Quantitative aspects of reversible osmotic disruption of the blood-brain barrier. Am J Physiol. **238**: 421–431.
41 Reulen HJ (2010). Bulk flow and diffusion revisited, and clinical applications. Acta Neurochir Suppl. **106**: 3–13.
42 Smith M (2015). Cerebral perfusion pressure. Br J Anaesth **115**: 488–490.
43 Stummer W (2007). Mechanisms of tumor-related brain edema. Neurosurg Focus. **22**: E8
44 Torack RM (1982). Computed tomography and stroke edema: case report with an analysis of water in acute infarction. Comput Radiol. **6**: 35–41.
45 Wolman M, Klatzo I, Chui E, Wilmes F, Nishimoto K, Fujiwara K, Spatz M (1981). Evaluation of the dyeprotein tracers in pathophysiology of the blood-brain barrier. Acta Neuropathol. **54**: 55–61.
46 Xu M, Su W, Xu QP (2010). Aquaporin-4 and traumatic brain edema. Chin J Traumatol. **13**: 103–110.
47 Yamaguchi M, Wu S, Ehara K, Nagashima T, Tamaki N (1994). Cerebral blood flow of rats with water-intoxicated brain edema. Acta Neurochir. Suppl. (Wien) **60**: 190–192.
48 Yang B, Zador Z, Verkman AS (2008). Glial cell aquaporin-4 overexpression in transgenic mice accelerates cytotoxic brain swelling. J. Biol. Chem. **22**: 15280–15286.
49 Yeung PK, Lo AC, Leung JW, Chung SS, Chung SK (2009). Targeted overexpression of endothelin-1 in astrocytes leads to more severe cytotoxic brain edema and higher mortality. J. Cereb. Blood Flow Metab. **12**: 1891–1902.