

Health Research Unit (UIS)
School Of Health Sciences (ESSLei)
Polytechnic Institute of Leiria
Morro do Lena – Alto do Vieiro
2411-901 Leiria, Portugal

INVITED RESEARCH ARTICLE

Psychostimulants and brain edema

Ricardo Alexandre Leitão^{1,2}; Ana Paula Silva^{1,2}

¹ Laboratory of Pharmacology and Experimental Therapeutics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

² Institute for Biomedical Imaging and Life Sciences (IBILI), Faculty of Medicine, University of Coimbra, Coimbra, Portugal

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Corresponding Author:
Ana Paula Martins
apmartins@fmed.uc.pt

Abstract

Psychostimulants consumption is a serious social and health problem worldwide. The increase in drug abuse has a huge socio-economic impact in society, and more precisely carries great costs in health treatments. In fact, it is well known that cocaine, 3,4-methylenedioxymethamphetamine (MDMA), amphetamine (AMPH) and methamphetamine (METH) have several neurotoxic effects, such as neurodegeneration, neuroinflammation and blood-brain barrier (BBB) disruption. Additionally, the increase of brain water content, a pathological condition also known as brain edema, has been associated with drugs use. Disturbances in the well-regulated water homeostasis may occur under several pathological conditions leading to severe alterations in brain function. Although several studies demonstrated a link between the abuse of psychostimulants and brain edema, very little is known about the underlying mechanisms that explain such brain alterations.

The water transport across cell membrane is regulated by bi-directional water channels called aquaporins (AQPs). Noteworthy, the AQP4 channel has an important role in water transport across BBB, being one of the most important at the Central Nervous System (CNS). In fact, alterations in AQP4 can originate cerebral edema due to abnormal increase in water content and consequent brain swelling. Furthermore, inflammatory mediators also seem to have a role in brain edema formation since the modulation of their action has a beneficial impact in brain edema outcome.

With the present review, we aim to summarize relevant information regarding the impact of psychostimulants on brain edema. Nevertheless, it is also evident that many questions remain unanswered. Thus, in order to improve the clinical outcome of human abusers, it is of crucial importance to understand what the role of AQP4 is.

Keywords: Brain edema, cocaine, methamphetamine, water imbalance, 3,4-methylenedioxymethamphetamine

Introduction

The consumption of psychostimulants has been increased over the last years. In accordance with the last report from United Nations Office on Drugs and Crime (UNODC, 2014), cocaine is the second most abused drug, followed by amphetamines.

It is well described the deleterious brain effects of the abovementioned drugs, including neurodegeneration, neuroinflammation, oxidative stress, and BBB dysfunction (Silva et al., 2010; Gonçalves et al., 2014). However, the impact of these drugs in brain water homeostasis remains to be fully clarified.

Brain edema

Brain edema formation in several brain pathologies, including drug addiction, is well documented. However, the cellular and molecular pathways responsible for this phenomenon remain unclear, which highlight the importance of unraveling such mechanisms in order to identify new approaches to tightly control brain water homeostasis. The increase in brain water content can occur in either extracellular or intracellular space, and this water imbalance is usually accompanied by an increase in intracranial pressure, which is a serious medical condition. Since the skull has very little space to expand, the brain swelling can lead to a squeezing of brain microvasculature and consequently to a drastic decrease in oxygen and nutrients supply followed by brain cell death (Adeva et al., 2012; Papadopoulos and Verkman, 2013).

Brain edema can be divided in four categories: vasogenic, cytotoxic, osmotic and hydrostatic edema. The difference between all categories is the pathological condition that triggers the water accumulation. Interestingly, in some conditions like infarct, two types of brain edema may co-exist being the cytotoxic edema the first to appear followed by the vasogenic edema, which can be present during several days (Hackett, 1999). The vasogenic edema begins with the disruption of the brain microvasculature that will allow the accumulation of water in the extracellular space. In this type of brain edema the white matter seems to be the first and the major area affected, and can be caused by different conditions such as brain trauma, tumors, focal inflammation, ischemia and hypertensive encephalopathy (Adeva et al., 2012). On the other hand, in the cytotoxic edema the brain microvasculature stays intact and the accumulation of water occurs in the intracellular space. Therefore, the water imbalance can be due to a malfunction of sodium and potassium pumps and/or water channels (Harring et al., 2014; Khanna et al., 2014). This type of edema is present in several intoxications, including with dinitrophenol, isoniazid or hexachlorophene, and also in Reye's syndrome, hypothermia, ischemia, stroke or hypoxia. Additionally, the osmotic edema is more common in conditions of hyponatremia and hemodialysis (Adeva et al., 2012), and is caused by an alteration of osmolality between cerebral-spinal fluid and plasma, where the osmolality in the brain is higher than in the plasma. This condition creates a pressure gradient that will lead to an increase in water flow into the brain. Finally, the hydrostatic edema is observed in hypertension, and is characterized by a water flow into the brain parenchyma due to an increase in cerebral capillary pressure (Adeva et al., 2012).

Some causes of brain edema

Since there are several types of brain edema it is also expected different etiologies. As previously mentioned, vasogenic edema involves disruption of BBB. Thus, one of the first causes leading to this type of brain edema can be a disorganization and/or down regulation of intercellular junction proteins. In fact, it was already demonstrated that in a mouse model of acute liver failure, the BBB disruption is related with brain edema (Chen et al., 2009). Interestingly, the same work showed that matrix metalloproteinase 9 (MMP-9) is involved in such effects, since its inhibition prevented the BBB disruption and the consequent brain edema (Chen et al., 2009).

In the cytotoxic edema, the disruption of the BBB is not observed, and can be caused by an ionic or water imbalance, that forces water accumulation in brain parenchyma, or by the dysfunction of a system that somehow regulates the brain water homeostasis.

Noteworthy, some molecules that have been implicated in brain edema are reactive oxygen species (ROS), vascular endothelial growth factor, and pro-inflammatory cytokines (Walcott et al., 2012). Nevertheless, some of these factors can also be involved in vasogenic edema, such ROS that have been pointed as key players in BBB dysfunction (Abdul-Muneer et al., 2014; Panahpour et al., 2014). The increase of ROS can be found in conditions like hypoxia, diabetic ketoacidosis and acute liver failure, in which brain edema is one of the clinical manifestations (Fraser et al., 2011).

Another target that plays a crucial role in the formation of brain edema is the water channel AQP4. This protein is formed by four monomers with six transmembrane domains each, with both terminals (carboxyl and amino) in the intracellular space and its own functional channel (Nag et al., 2009). AQP4 is one of the most expressed aquaporins in the brain tissue, along with type 1 and 9, and can be found in astrocytes endfeet that surround the brain microvessels (Tait et al., 2008). This water channel has two main isoforms originated by alternative splice, known as M1 and M23, that are able to form orthogonal arrays of particles forming supramolecular structures (Zelenina, 2010). Interestingly, AQP4 can have a role in both formation and resolution of cerebral edema, and also in K⁺ clearance during neuronal activity (Zelenina, 2010). In fact, in several neuropathologies, such as trauma, ischemia, tumors of astrocytic origin, epilepsy and neuromyelitis optica, it was demonstrated that the expression of AQP4 is altered (Papadopoulos and Verkman, 2013). Nevertheless, many questions remain unanswered particularly related with the molecular mechanisms that regulate AQP4 function and its possible involvement on BBB dysfunction.

In order to answer to this crucial question, several studies were performed to unravel the role of AQP4 in different types of brain edema. In fact, Manley and collaborators (2000) demonstrated that survival of AQP4 knockout (KO) mice was increased after water intoxication, compared to wild-type animals. Additionally, the neurological outcome in KO animals was better than in the wild-type animals. Moreover, the authors concluded that water accumulation occurred inside the cells, more precisely inside the astrocytic endfeet that surround the brain vessels (Manley et al., 2000). On the other hand, Papadopoulos and collaborators (2004) showed that, when compared to wild type mice, AQP4 KO animals subject to an experimental model of vasogenic brain edema, by freeze-injury, have a larger water accumulation, a bigger elevation of intracranial pressure, and accelerated neurological deterioration. Thus, in this particular case of brain edema the authors concluded that the AQP4 is necessary to the resolution of vasogenic edema (Papadopoulos et al., 2004). Nevertheless, more recently it was demonstrated that the inhibition of AQP4 with a novel specific inhibitor, TGN-020, has a protective effect regarding the increase of brain water content after an injection of water in a volume equal to 20% of body weight and vasopressin, a protocol that causes brain edema without BBB disruption, thereby mimicking a cytotoxic edema (Igarashi et al., 2011).

Another player that seems to be involved in brain edema formation is the vascular endothelial growth factor (VEGF) (Bailey et al., 2009). This is a molecule able to stimulate angiogenesis, inducing new blood vessels formation during development and after injury. Noteworthy, brain tumors are able to produce and release VEGF in order to increase blood and nutrients supply needed for grow and metastization (Trevisan et al., 2014). Low oxygen supply will produce hypoxia-inducible factor leading to an upregulation of VEGF. Thereby, a hypoxia condition will increase the levels of VEGF that, in turn, will increase the BBB permeability and to brain edema formation (Adeva et al., 2012).

Besides the above mentioned factors, pro-inflammatory molecules, like tumor necrosis factor alpha (TNF- α), are able to induce BBB disruption (Candelario-Jalil et al., 2007) and brain edema (Kim et al., 2013). In fact, it was already demonstrated that both IL-1 β and TNF- α lead to an upregulation of AQP4 in cultured astrocytes (Asai et al., 2013). Moreover, a very recent work by Liu and collaborators (2014a) showed that knockdown of interleukin 1 beta (IL-1 β) diminished astrocyte swelling, a marker of cytotoxic edema, in an animal model of hypoxia-ischemia. Also, a mixed solution of IL-1 β , TNF- α and interferon gamma cause an upregulation of AQP4 in cultured astrocytes (Asai et al., 2013).

Therapeutic approaches

The current treatments available for brain edema consist mainly in osmotherapy, control of arterial blood pressure, and surgical decompression as the last effort to relieve the increase in intracranial pressure. In the osmotherapy the most used drug is mannitol, which is a powerful drug that forces fluid to go from brain parenchyma into vascular space. However, mannitol can also lead to a general hypotension and acute renal failure. Other agent that can be used in osmotherapy is a hypertonic saline, which shows the same effectiveness as mannitol in reducing the brain water content but without the diuretic effect of mannitol. However, it can cause an imbalance in blood serum sodium levels (Walcott et al., 2012). Additionally, barbiturates, like pentobarbital, are used mainly when osmotherapy fails. The barbiturates act by reducing both intracranial blood volume and the metabolic demand within brain parenchyma (Walcott et al., 2012). Other approach to treat brain edema related with brain tumors is the administration of corticosteroids. However, they show no therapeutic benefit in edema formation due to ischemia or intracerebral hemorrhage (Heiss et al., 1996).

Beside the positive results of the abovementioned treatments under several conditions, they act via a nonspecific or indirect manner. Thus, it is very important to better understand the underlying mechanisms of brain edema in order to identify a more effective approach. Several transporters and receptors have been raised as important mediators in the treatment of brain edema. One of those transporters is the Na-K-Cl cotransporter, which is responsible for the active transport of sodium, potassium and chloride in and out of the cells. In fact, after 3,4-Methylenedioxymethamphetamine (MDMA) use it was observed an alteration in sodium homeostasis, causing a decrease in sodium blood levels, hyponatremia (Ghatol and Kazory, 2012), whereas methamphetamine (METH) consumption increased sodium levels (hypernatremia) (Sharma and Kiyatkin, 2009). Regarding the receptors that seem to be involved in brain edema, the vasopressin receptor is one of the most promising therapeutic target. Conivaptan, an antagonist of vasopressin receptor, has been used in the treatment of brain edema due to its inhibitory effect in the development of hyponatremia, which is associated with the formation of brain edema (Walcott et al., 2012).

Psychostimulants and brain edema

Cocaine and brain edema

To our knowledge, Barroso-Moguel and collaborators (1997) published the first study showing that cocaine [30 mg/kg/day intraperitoneal (i.p.)] can induce brain edema. Such effect was observed in both male and female rats in several brain regions such as occipital, parietal and frontal cortex, cerebellum, hippocampus, and substantia nigra, with

the first sign of cerebral edema appearing after 7 days and still present after 90 days post-cocaine administration (Barroso-Moguel et al., 1997; Barroso-Moguel et al., 2002). Furthermore, a case report published by Gyori and Lew (2007) described that an African-American male that consumed cocaine and alcohol, showed an increase in brain water content, observed by computed axial tomography (CT) scan. In association with brain edema, this patient also suffered a middle cerebral artery infarct, which is already proved to be associated with brain edema (Ratilal et al., 2014).

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and brain edema

The first data was published in 1996 reporting the case of two female teenagers showing a mild to moderate brain edema analyzed by CT due to MDMA and alcohol consumption (Matthai et al., 1996). Moreover, the edema observed was associated with hyponatremia, situation characterized by low levels of sodium in the blood flow. The electrolyte imbalance were controlled, and returned to basal levels within 24h, using a medical protocol that consists in severe fluid restriction (Matthai et al., 1996). Nevertheless, one patient recovered without neurological sequelae, but the other teenager was diagnosed with anterograde and retrograde memory loss (Matthai et al., 1996). Moreover, Kramer and collaborators (2003) reported a case of a male admitted to the emergency hospital department after the consumption of heroin, cocaine and MDMA, which also showed cerebral edema. In this case, the recovery only occurred after 4 days of hospitalization (Kramer et al., 2003). Other case report demonstrated a severe case of brain edema and hyponatremia after MDMA abuse by a 26-years-old woman (Claffey, 2011). More recently, it was published that a 20-years-old woman showed a severe parenchymal edema together with a suppression of basal cisterns and acute severe hyponatremia (Ghatol and Kazory, 2012). In order to control the ionic imbalance observed in the hospitalized woman, physicians administered a 20% solution of mannitol, and in the following hours the serum sodium levels returned to normal values, and an improvement in mental status of the patient was observed (Ghatol and Kazory, 2012).

Unfortunately, not always is possible to successfully treat these patients, and fatal cases of MDMA intoxication have also been reported. An Asian-American woman that showed brain edema (Kalantar-Zadeh et al., 2006) associated with hyponatremia died 12h after the hospitalization, despite the attempts to control the ionic and water homeostasis. Other fatal case of MDMA intoxication was described in a 13-years-old girl, who was declared dead 30h after MDMA use, with a massive brain edema (Sauvageau, 2008). In this particular case the clinicians concluded that the cause of death was an anaphylactic reaction to MDMA (Sauvageau, 2008).

Notwithstanding the very well documented association of MDMA abuse and brain edema, not much is known regarding the underlying mechanism that explain such phenomenon. Thus, in attempt to unravel the cellular basis of these effects, some animal studies have been performed. Sharma and Ali (2008) demonstrated for the first time that MDMA administration (40 mg/kg, i.p) to both Wistar rats and C57 Balb mice caused both brain edema and BBB disruption in the cerebral cortex, hippocampus and cerebellum (Sharma and Ali, 2008).

Methamphetamine and brain edema

Regarding this drug of abuse, the first report was published by Berankova and collaborators (2005), where the authors documented a case of a 31-year-old male that

after an intravenous dose of METH fell into coma, followed by unsuccessful medical rescue of the patient. The autopsy revealed that brain edema was the cause of the death (Berankova et al., 2005). Another case was published by Ago and collaborators (2006) reporting a clinical case of a man that showed a severe brain edema with an intense hyperthermia that reached 42°C, who was declared dead after 9 days of the hospitalization.

Besides clinical studies, there are several data proving not only the association of brain edema with METH administration, but also the association of increased water content with BBB disruption. The first study demonstrated that METH (9 mg/kg, subcutaneous) administered to adult male Long Evans rats caused hyperthermia in the nucleus accumbens and led to BBB disruption with a significant brain edema (Kiyatkin et al., 2007). Moreover, authors showed that animals presented astrogliosis (astrocyte activation), which is a marker of neuroinflammation represented by upregulation of glial fibrillary acidic protein (GFAP) (Kiyatkin et al., 2007). Additionally, brain edema was also observed in the cortex, hippocampus, thalamus and hypothalamus (Sharma and Kiyatkin, 2009). Afterwards, the same group demonstrated that increased expression of heat-shock protein (HSP) 72 was correlated with brain edema (Kiyatkin and Sharma, 2011). HSP72 belongs to the chaperon protein family HSP70, and it has already been described an upregulation of HSP72 in heat stress (Horowitz and Robinson, 2007), and in METH abusers (Kitamura, 2009). These results are in accordance with a previous work showing that hyperthermic brain injury leads to HSP 72 upregulation and brain edema (Westman et al., 2000). More recently, Northrop and Yamamoto (2012) used an acute METH administration protocol that consist of 4 doses of 7.5 mg/kg (i.p.) with 2h between each injection, which is known as a binge protocol and more similar to human abuse (Krasnova and Cadet, 2009). In this study METH caused a pronounced hyperthermia, but brain edema was only observed in animals subject to unpredictable stress in conjugation with METH administration (Northrop and Yamamoto, 2012). Thus, at least in this particular case, METH by itself was not able to cause brain edema. In summary, METH can lead to brain edema with BBB disruption (Kiyatkin et al., 2007; Sharma and Kiyatkin, 2009; Kiyatkin and Sharma, 2011), but the available literature do not elucidate about the type of brain edema that was observed, as well as the underlying mechanisms that explain such brain edema.

General conclusion

Brain edema is an extremely deleterious condition and common to different brain pathologies. The increase in water content can cause an increase in brain volume, which in turn will increase intracranial pressure. Moreover, this water imbalance can lead to an abrupt decrease in oxygen and nutrients supply and an extravasation of blood serum proteins into the brain parenchyma. Additionally, neurobehavioral alterations can be observed under such pathological conditions. In fact very recently, it was demonstrated that in major depressive disorder in humans (Rajkowska et al., 2013), and in animal models of depressive-like behavior (Liu et al., 2012) the protein levels of AQP4 were lower than in non-depressed controls. Furthermore, in models known to induced BBB disruption, such as transient middle cerebral artery occlusion (Liu et al., 2014b) and experimental stroke model by caudate nucleus hemoglobin injection (Ding et al., 2014), the animals showed a worse neurological outcome, measured by neurological severity scores and rotarod tests, when compared to control animals (Ding et al., 2014; Liu et al., 2014b). In these studies the BBB disruption prevention could also prevented brain edema

and also the neurological deficits observed in experimental animal models (Ding et al., 2014; Liu et al., 2014b). Therefore, it is crucial to better understand the causes and consequences of brain edemas. In fact, the lack of knowledge about the molecular mechanisms that trigger brain edema limit the identification of more specific targets for the successful treatment of such brain condition. Noteworthy, AQP4 seems to be an important player in brain edema since this channel is the most expressed water channel in the brain. Nevertheless, very little is known about the effect of psychostimulants in the expression and function of AQP4. Thus, despite the well described effect of drugs of abuse in brain water content, the underlying mechanisms that explain brain edema remain to be fully clarified.

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