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REVIEW **Open Access**

The angiotensin converting enzyme 2 (ACE2) system in the brain: possible involvement in Neuro-Covid

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Summary. The brain has its own intrinsic renin-angiotensin system (RAS) with all its components present in the central nervous system (CNS). Recent data demonstrate that also the main components of the angiotensin concerting enzyme 2 (ACE2) system (at least ACE2 itself, as well as the biologically active angiotensin (1-7) and its cognate receptor Mas) are expressed in the brain. Aside from these members, alamadine and MrgD are discussed as further members that have neuro-active roles in the CNS. Little is known about the possible functions of MrgD within the brain. Concerning angiotensin (1-7) acting through the Mas receptor, data were accumulating that this system is involved in numerous processes contributing to neuronal plasticity and even learning and memory. Malfunctions in the brain ACE2 system are associated with disturbances in neuronal plasticity. Since SARS-CoV-2 has a high affinity towards ACE2, Neuro-Covid may directly or indirectly depend on a disturbed balance in the ACE2 derived angiotensin system in the brain. Since the ACE2 system in the brain is far from being understood, a deeper understanding of e.g. the angiotensin (1-7) / Mas system is needed, especially with regard to the roles of angiotensin (1-7) in neuronal plasticity.

Key words: ACE2, Angiotensin (1-7), Distribution, Mas, MrgD, Neuronal plasticity

Introduction

The brain has its own intrinsic renin-angiotensin system (RAS) with all its components present in the central nervous system (CNS) (von Bohlen und Halbach and Albrecht 2006). In general, the different biological active forms of angiotensin are derived from the precursor protein angiotensinogen through several enzymatic pathways (see for details e.g. (von Bohlen und Halbach 2005; Wright and Harding 2013)): Angiotensin I (Ang I) is formed by the activity of renin, which acts upon the amino-terminal of angiotensinogen. Ang I serves as a substrate for angiotensin-converting enzyme (ACE) that hydrolyzes the carboxy-terminal to form the octapeptide angiotensin II (Ang II). Ang II can be converted to the heptapeptide angiotensin III (Ang III) by the glutamyl aminopeptidase A (AP-A). Furthermore, Ang III can be processed to angiotensin IV (Ang IV) by the aminopeptidase N (AP-N). In addition, it has been discovered that angiotensin II can be converted to angiotensin (1-7) (Ang(1-7)) by the activity of angiotensin converting enzyme 2 (ACE2). Aside from the fact that ACE2 is capable generating Ang(1-7), it is also true that ACE2 can convert angiotensin A (which is derived from Ang II) to alamandine (Fig. 1). Angiotensin A shares high similarities with Ang II, only differing in the N-terminal in which Asp1 is decarboxylated into Ala1 (Jankowski et al., 2007). Interestingly, Ang A can be directly generated from Ang II by the activity of MLDAD, the mononuclear leucocyte-derived aspartate decarboxylase (Hrenak et al., 2016). Alamandine [Ala1-Ang(1-7)] is a heptapeptide with amino acid sequence Ala-Arg-Val-Tyr-Ile-His-Pro, differing from Ang (1-7) only in the N-terminal alanine instead of aspartate residue (Hrenak et al., 2016). By using qRT-PCR the transcriptional profile of ACE2 has been mapped in different human tissues. ACE2 expression was not only found in renal or cardiovascular tissue, but also in tissue of the gastrointestinal tract and, among others, also in different brain tissues (Harmer et al., 2002).

The ACE2 system in the brain

By using mass spectroscopy, ACE2 activity, e.g., has been found within the brainstem, pituitary, hypothalamus, hippocampus and cerebral cortex (Elased et al., 2008). In parallel, the distribution of ACE2 protein in the brain was analysed by using immunohistochemistry (Doobay et al., 2007). Based on immuno-

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fluorescence intensities, high ACE2 immuno-reactivities were seen e.g. in the cortex and caudate-putamen and moderate intensities were seen e.g. in different hypothalamic and thalamic nuclei, different raphé nuclei, as well as in the nucleus of the tractus solitarius, the motor root trigeminal nerve, and within the nucleus ambiguus. Furthermore, by using fluorescence-based double labelling, it could be shown that ACE2 was mainly expressed by neurons and not by glial cells within the adult mouse brain (Doobay et al., 2007). In addition, by using automated in-situ hybridizations, ACE2 mRNA has been found in the olfactory bulbs, and dentate gyrus of the hippocampus (Allen brain map: https://mouse.brain-map.org/gene/show/45849).

Based on the presence of the different biological active angiotensin derivates in the brain it is not surprisingly that the cognate receptors are also expressed in the brain. It is well established that Ang II acts through the specific angiotensin receptors type 1 (AT1) and type 2 (AT2) and that Ang IV mainly acts through the AT4 receptor. All these receptors are expressed in the brain and are involved in different specific functions (see for review e.g. (Wright and Harding 1995)). Aside from these classical routes of the RAS several alternative pathway, that contribute to the formation of different angiotensins and angiotensin fragments, have been described and, among others, even receptors for renin and pro-renin have been shown to exert biological activity (Nguyen 2010; Sihn et al., 2010) not only in the periphery, but also in the CNS (Schäfer et al., 2013; Bracke and von Bohlen und Halbach 2018). Thus, it is tempting to speculate that receptors for those angiotensins that are derived from ACE2 are also expressed in the brain. Indeed, specific receptors have been identified. In 2003, Ang(1-7) has been identified as an endogenous ligand for the G-protein coupled receptor Mas (Santos et al., 2003). Furthermore, it turned out that alamandine binds and activates a specific receptor, termed MrgD or MrgprD (Lautner et al., 2013). By automated in-situ hybridization, Mas mRNA has been detected especially in the hippocampal formation and in regions related to the olfactory system, whereas in other brain regions weaker in-situ signal have been detected (Allen brain atlas: https://mouse.brain-map.org/gene/show/16940).

Although being structurally homologous to Mas, several other receptors have been discovered, the so-called Mas-related G protein - coupled receptors (termed "Mrgprs" or "Mrgs"), which were initially recognized as a component of the RAS, but later most of their function turned out to be unrelated to the RAS (Bader et al., 2014). The exception might be represented by alamandine [Ala1-Ang(1-7)], which binds and activates MrgD (Lautner et al., 2013). Alamandine can be generated either from angiotensin A by ACE2 or by direct decarboxylation of Ang(1-7) (Lautner et al., 2013; Villela et al., 2014).

MrgD expression within the central nervous system is not investigated in detail yet. By automated in-situ hybridization, only very weak signals specific for MrgD mRNA have been detected in the mouse brain so far (Allen brain map: https://mouse.brain-map.org/gene/show/84319). Nevertheless, alamandine, through activating MrgD receptors, seem to influence neuronal activity. Thus, activation of the alamandine receptor MrgD contributes to enhanced neuronal excitability in

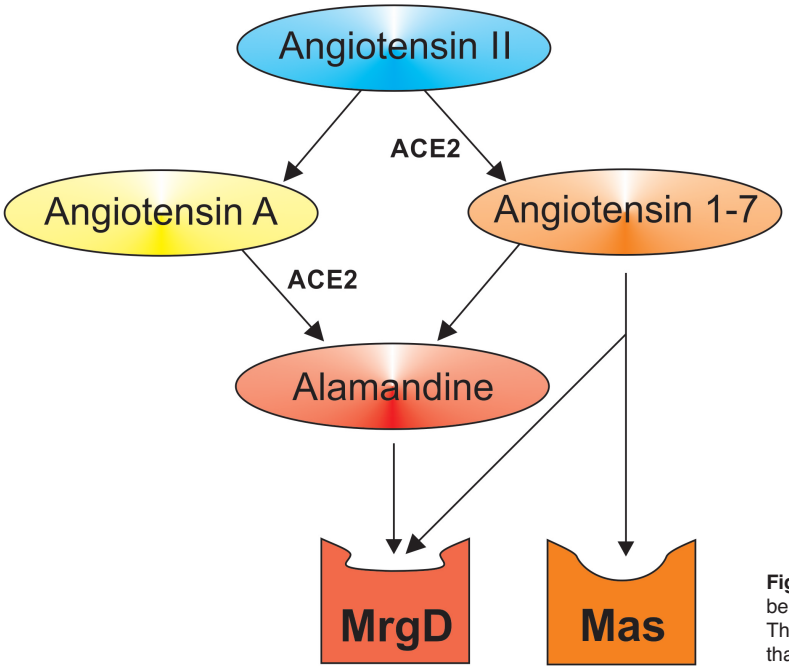

Fig. 1. Schematic overview on the angiotensin derivates that can be formed either directly of indirectly from the activity of ACE2. These angiotensin derivates can act through specific receptors that are expressed in the nervous system.

dorsal root ganglia (Crozier et al., 2007). Moreover, alamandine, through MrgD receptor, seems to be capable of inducing antidepressant-like effect in transgenic rats with low brain angiotensinogen (Almeida-Santos et al., 2021) and alamandine, injected into the paraventricular nucleus, has been shown to increase blood pressure and sympathetic activation in spontaneously hypertensive rats (Shen et al., 2018). In addition, MrgD has been shown to represent a receptor for Ang(1-7) (Tetzner et al., 2016).

Taken together, ACE2, Ang(1-7) and alamandine as well as the receptors Mas and MrgD are expressed in the adult brain. However, the expression of MrgD seems to be low, whereas the Mas receptor seems to be widely expressed. This hints for a major role of the angiotensin (1-7) / Mas system (as compared to alamandine / Mrgd) in the brain. The enzymes necessary for the formation of Ang(1-7) are also expressed in different areas within the adult brain. Based on the neuronal effects induced by Ang(1-7) via the Mas receptor, disturbances in the ACE2 system might have consequences for neuronal excitability and neuronal (network) functions.

Roles of the ACE2 system in the brain

The ACE2 system in the nervous system, via action of MrgD receptors, is involved in pain sensation. ACE2 mRNA and protein are expressed by dorsal root ganglion (DRG) neurons and ACE2 mRNA is also expressed by a subset of nociceptors that express MrgD mRNA (Shiers et al., 2020). MrgD has been found to be specifically expressed in circuits involved in nociception (Zylka et al., 2005) and seems also to play a crucial role in neuropathic pain (Wang et al., 2019). Thus, it can be speculated that disturbances in the ACE2-MrgD-axis might be involved in headache. In general, the brain RAS is altered in migraine. For example, patients with migraine had altered Ang II and Ang(1-7) serum levels indicating at least a participation of RAS in migraine pathophysiology (Bhering Martins et al., 2020).

Concerning the brain ACE2 system, the major effects in the brain might be attributed to the Ang(1-7)/Mas system. It is likely that most of the Ang(1-7) mediated effects in the brain are based on the activation of Mas receptors, since, based on our current knowledge, Mas, in contrast to MrgD, is highly expressed in the CNS in distinct areas within the adult brain (Freund et al., 2012). These brain areas including areas involved in olfaction or areas related to the limbic system as e.g. the hippocampal formation or the amygdala. Within the brain, Mas has been shown to affect neuronal excitability (von Bohlen und Halbach et al., 2000) and deletion of Mas has an impact on behaviour (Walther et al., 2000). In 2005, it has been shown that Ang(1-7) enhances hippocampal long-term potentiation (LTP) through the Mas receptor (Hellner et al., 2005), indicating that Ang(1-7) / Mas signalling has an impact on neuronal plasticity. Moreover, lack of the Mas receptor affects adult neurogenesis within the hippocampus, a morphological correlate of processes attributed to hippocampal neuronal plasticity associated with learning and memory (Freund et al., 2014). Indeed, it has been shown that Ang(1-7) / Mas dependent changes in neuronal plasticity can translate into altered behaviour. Among others, it has been shown that the Ang(1-7) / Mas axis integrity is required for the expression of object recognition memory (Lazaroni et al., 2012), since ablation of Mas or blockade of Mas in the CA1 area of the hippocampus, impairs this type of memory in mice (Lazaroni et al., 2012). Ang(1-7) seems also to influence anxiety-related behaviour. In one study it has been described that central administration of Ang(1-7) induces anxiolytic-like effects in the elevated plus maze (Bild and Ciobica 2013). In another study, reduced anxiety-like behaviour has been observed in transgenic rats with chronically overproduction of Ang(1-7) (Kangussu et al., 2017). At least in the limbic system, the ACE2 system plays a specific role in neuronal excitability and neuronal plasticity that even contributes to altered mechanisms contributing to learning, memory and behaviour.

Neuronal hyper-excitability is a mechanism underlying epilepsy (Di Bonaventura et al., 2017) and based on the finding mentioned above, it is tempting to speculate that the ACE2 system, comparable to the brain RAS (Pereira et al., 2010), might have an impact on neuronal hyper-excitability and therefore in epilepsy. As already mentioned, Mas mRNA is highly expressed in hippocampal neurons. It has been shown that brief seizure episodes lead to a significant and transient increase in Mas mRNA in the hippocampus 2 - 6 h following seizure (Martin and Hockfield, 1993). Interestingly, long-term intracerebroventricular infusion of Ang(1-7) in an animal model of temporal lobe epilepsy has been shown to induce antiepileptic effects (Gomes et al., 2020). These results indicate that Ang(1-7) plays an important role in the suppression of epilepsy via fast changes in the Ang(1-7) / Mas axis.

Possible involvement of the brain ACE2 system in Neuro-Covid

SARS-CoV-2 (Severe Acute Respiratory Syndrome (SARS) - Corona virus 2), first reported in the end of the year 2019 in China, is causative for the COVID-19 (coronavirus disease 2019) pandemic that has infected more than 100 million people and caused the death of more than 2 million people worldwide in the beginning of 2021. The spectrum of clinical manifestations observed during COVID-19 infection varies from rather asymptomatic to critical life-threatening clinical conditions and evidence are accumulating that COVID-19 not only affects the respiratory system, heart, liver, or kidney, but also the central and peripheral nervous system (Tancheva et al., 2020). Headache, dizziness, taste and smell dysfunctions, and impaired consciousness were the most frequently described neurological symptoms, the latter more often among

patients with a severe or critical disease course (Chen et al., 2021). It is also becoming clear that the neurological and psychological disturbances that occur during the acute phase of the infection may persist well beyond the recovery.

SARS-CoV-2 exhibits neurotropism through its affinity for ACE2 (Yan et al., 2020). The neurotropism of COVID-19 accords with the wide spectrum of neurological, psychiatric and psychological symptoms and syndromes affecting the entire nervous system in the time course of infection (Tancheva et al., 2020; Tremblay et al., 2020; Chen et al., 2021). Since ACE2 is expressed in the brain (Xia and Lazartigues 2008), it can be speculated that SARS-CoV-2 might bind to ACE2 expressing cells in the brain. Along this line, a study in 2008 hinted that the SARS-CoV enters the brain primarily via the olfactory bulb, and infection results in rapid, transneuronal spread to connected brain areas (Netland et al., 2008). Likewise, ACE2 has been shown to act as cellular receptor on the cell membrane that allows the transmission of SARS-CoV2 (Yan et al., 2020). Currently it is not fully understood, how SARS-CoV2 can enter cells, but binding of the viral spike protein (S protein) to ACE2 seems to be one of the elementary processes (Hoffmann et al., 2020). For a direct interaction of the virus with cells located in the brain, ACE2 expressing cells should exist. Moreover, given there is a role for neuroactive peptides, generated by the activity of ACE2, disturbances in neuronal functions can be expected. This disturbances may translate into altered behaviour or in specific symptoms of a disease.

Many COVID-19 patients suffered from olfactory dysfunctions, but also symptoms such as headache, ataxia and epileptic seizures have been reported and even a prevalence for depression and anxiety has been found (Leonardi et al., 2020; Soltani et al., 2021). These symptoms might directly or indirectly be related to disturbances in the brain ACE2 system. MrgD has been shown to be involved in pain sensation (see above) and might contribute to headache. Concerning the occurrence of epileptic seizures, direct and indirect effects of a disturbed brain ACE2-system might be possible. A direct effect might be caused by the Covid-19 cytokine storm induced in the CNS, followed by mitochondrial dysfunctions (Nikbakht et al., 2020). Moreover, disturbances in the Ang(1-7) / Mas system can lead to hyperexcitability, which might be reflected in Neuro-Covid by the occurrence of seizures in some cases. Given the importance of the Ang(1-7) / Mas system in neuronal plasticity, disturbances in the ACE2 system may be causative for specific neurological or pathophysiological conditions. Unfortunately, the ACE2 system in the brain is far from being understood and therefore it can only be speculated what Neuro-Covid is or what it is not. More studies are required to get a deeper insight in the ACE2 system in the brain and especially in the neurobiological activities of the angiotensin derivates that were generated by the activity of ACE2.

Possible ways of SARS-CoV-2 entering the brain via the ACE2 system

Given that SARS-CoV-2 interacts with the brain ACE2 system and that disturbances in the brain ACE2 system contribute to Neuro-Covid, there must be a possibility for SARS-CoV-2 to interact with ACE2 expressing cells in the brain. In general, the transport of substances into the brain is significantly hindered by the blood-brain barrier (BBB). A number of factors, like molecular weight or lipophilic character, play significant roles in allowing or limiting the movement of substances through the BBB (Kumar et al., 2020). This is not only true for biological active substances or pathogens, but also for drugs. Thus, this is a major problem for e.g. the application of drugs into the brain in the treatment of e.g. neurodegenerative diseases such as Morbus Alzheimer or Morbus Parkinson. Since the BBB protects the brain from pathogens, but despite that barrier, some pathogens can enter the brain, there might be some alternative routes for entering the CNS. Indeed, potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain have been described.

For a hematogenous invasion, the virus may infect endothelial cells of the BBB or the blood cerebrospinal fluid barrier and then spread toward the CNS. The virus might bind to cells in the periphery, causing endothelial damage and entering the blood circulation. Alternatively, the virus might infect circulating immune cells and thus may also use the lymphatic pathway via lymph nodes and after invation of the peripheral lymphoid tissue, the virus eventually enters blood circulation via the flow of the lymph fluid (Li et al., 2020). Moreover, the brain has its own lymphatic drainage system, the so-called "glymphatic system" (Jessen et al., 2015), which is involved in the clearance of the brain tissue from debris. A functional glympathic system is thought to play a protective role in Morbus Alzheimer. The glymphatic system is thought to represent a cerebrospinal fluid-mediated clearance pathway for the removal of potentially harmful molecules, such as amyloid beta, from the brain (Harrison et al., 2018). However, this lymphatic drainage pathway in the brain can be disturbed under pathological conditions (Cheng and Haorah 2019). It might be possible that under pathological conditions, the virus can enter the glymphatic system and thereafter enter into the CNS.

Based on histological analysis, focussing on the expression of ACE2 in different tissues, there is evidence to suggest that the enteric nervous system and the chorid plexus (arguing for route via the cerebrospinal fluid) may serve as alternative routes for a neuro-invasion by SARS-CoV2 (Briguglio et al., 2020; Deffner et al., 2020).

The virus may also take a direct neural pathway, whereby the virus enters nerve terminals and replicates

and, thereafter, the virus might be transported retrogradely to the soma and invade the CNS (Li et al., 2020).

In addition, it is thought that the olfactory bulb may serve as the entry site for prion-like propagation in neurodegenerative diseases (Rey et al., 2018) that may be causative for the olfactory deficits that occur in numerous neurodegenerative disorders and are accompanied by pathological changes in related brain regions (Rey et al., 2018). Furthermore, airborne infectious, allergic and pollution agents are among the most common inflammatory factors which may affect brain function via a nose-to-brain interface (Tonelli and Postolache 2010). The nasal route has also been reported for successful administration of drugs in the treatment of Morbus Alzheimer (Kamei 2017; Agrawal et al., 2018). Likewise this route has been used for drugs coupled to nanoparticles for successful application in an animal model of Parkinson's disease (Arisoy et al., 2020). Several studies have shown that intranasal administration resulted in similar or even in a greater delivery of the drugs to the olfactory lobes and the brain as compared to intravenous delivery (Charlton et al., 2008; Kamei 2017; Agrawal et al., 2018). Concerning the brain RAS, it has been shown that AT2 receptor agonists have neuroprotective effects in ischemic stroke. However, systemic administration of the AT2 agonist is not suitable for translation into humans, since AT2 receptor agonists are BBB-impermeable (Bennion et al., 2018). Therefore, the nose-to-brain route of AT2 receptor agonist administration was tested with promising results (Bennion et al., 2018).

SARS-CoV2 might be capable of binding to structures that define the nose-to-brain route, since the ability of SARS-CoV to cause neuronal death in mice by invading the brain via the nose close to the olfactory epithelium, has already been shown (Netland et al., 2008). ACE2 expressing cells and neurons might be vulnerable for an infection and, recently, further evidence support the view of a nose-to-brain route, since ACE2 has been detected in the olfactory epithelium and respiratory epithelium of the nasal septum, the nasal conchae, and the paranasal sinuses (Klingenstein et al., 2020).

Summary and outlook

The brain has its own intrinsic ACE2-system with all its components present in the CNS. Ang(1-7) and alamandine are both biologically active and they mediate their actions through the receptors Mas and MrgD. Since MrgD, in contrast to the Mas receptor, seems to be expressed only in low levels in certain brain areas, the major effects of the ACE2-system in the brain might be attributed to the Ang(1-7) / Mas system. The Ang(1-7) / Mas system affects neuronal excitability and neuronal plasticity and therefore, the Ang(1-7) / Mas system is thought to play a role learning and memory as well as in certain forms of behavior. This indicates that disturbances in the ACE2 system may be causative for specific neurological or pathophysiological conditions. Since SARS-CoV-2 has a high affinity towards ACE2, it is feasible to speculate that the virus might interfere with the brain ACE2 system. Indeed, different possible ways that allow the virus to enter the CNS have been described. Thus, Neuro-Covid may directly or indirectly depend on a disturbed balance in the ACE2 derived angiotensin system in the brain. However, our knowledge concerning this topic is mainly hampered by the fact that the ACE2 system in the brain is far from being understood. Therefore, a deeper understanding of the Ang(1-7) / Mas system is needed, especially with regard to the roles of Ang(1-7) in neuronal plasticity. The understanding of the roles of that system in neuronal plasticity will allow to get insight in pathophysiological mechanisms that are due changes in the brain ACE2 system. This may provide important basis for a better understanding of the symptoms of Neuro-Covid. In addition, focussing on the brain ACE2 system may help getting insight in pathophysiological processes that are related to altered neuronal plasticity as well as in processes that are associated with neurodegenerative diseases as e.g. Morbus Parkinson or Morbus Alzheimer.

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