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LETTER TO THE EDITOR

Novel treatment targets for COVID-19: Contribution from molecular psychiatry

Dear editor,

The COVID-19 (SARS-coronavirus (CoV)-2) pandemic is keeping the world in suspense, also the world of psychiatry as documented in a rapidly increasing amount of manuscripts showing its detrimental influence on the medical care, clinical course and treatment of psychiatric patients as well as on the mental health of the general population around the world. Health care workers (HCW) and SARS-CoV-2 infected patients have been the most intensely studied special population groups so far. Population studies on the influence of the COVID-19 pandemic are currently much more frequent than clinical studies on this topic and revealed anxiety and depression to be the most prevalent pandemic-associated psychiatric symptoms in the general population. Their prevalences and intensities increased with increasing numbers and emotional proximity of close persons infected with SARS-CoV-2 as well as with the presence of chronic diseases (e.g. Mazza et al. 2020; Moghanibashi-Mansourieh 2020; Özdin and Bayrak 2020). Accordingly, a meta-analysis revealed that a considerable proportion of HCW experiences mood and sleep complaints due to the current pandemic (Pappa et al. 2020) while another very recently disclosed that the majority of SARS-CoV-2 infected patients will likely recover without developing mental illness. However, a significant proportion of SARS-CoV-2 patients develops delirium in the acute stage of infection (Rogers et al. 2020).

Besides the assumed direct impact of the SARS-CoV-2 virus on the metabolism of the central nervous system (CNS) (see below and Li et al. (2020)) and its influence on the choice and tolerance of psychopharmacotherapeutic drugs (Bilbul et al. 2020; Sisking et al. 2020), the COVID-19 pandemic can influence mental health also indirectly, particularly through lockdown consequences. The latter comprise social isolation, reduced availability of treatment facilities and the already evident economic recession as well as the fear of SARS-CoV-infection-induced health restrictions and death of oneself or of close persons. Thus, the COVID-19 pandemic is a global potent stressor and is therewith likely to trigger an excess of psychiatric cases after lockdown (e.g. Torjesen 2020). Stress is well-accepted to trigger the onset of mental diseases, particularly, but not exclusively, of MD, PTSD and anxiety disorders, in susceptible individuals. Related research gave rise to the gene X environment hypothesis of mental disorders (Papst and Binder 2020) of which many are associated with dysfunctions of the hypothalamus-pituitary-adrenal (HPA) axis (Zaba et al 2015; Rein et al. 2019), one of the two major stress hormone systems.

Intriguingly, a potential link between stress, MD and viral infection arose from molecular stress research in psychiatry. This link emerged, through a seemingly unlikely fortuity, from efforts directed at understanding the molecular mechanisms of action of the stress protein FK506 binding protein 51 (FKBP51) in psychiatry.

However, before continuing with FKBP51, we take a look at the neuroinvasive potential of SARS-CoV-2 which was reported to occur in several organs including the brain (Li, Long, et al. 2020; Li, Liu, et al. 2020; Hirsch et al. 2020; Baig et al. 2020) and has, interestingly, also been linked to acute COVID-19-associated respiratory failure (Li, Bai, et al. 2020). The neuroinvasive potential of SARS-CoV-2 is discussed based on the combined knowledge on SARS-CoV and SARS-CoV-2, given their high similarity (Baig et al. 2020; Li, Bai, et al. 2020) and on insight from animal models of SARS-CoV and Middle East respiratory syndrome (MERS)-CoV (Natoli et al. 2020). Both SARS-CoV and SARS-CoV-2 intrude cells mainly through binding of their spike proteins to angiotensin converting enzyme 2 (ACE2) anchored on cellular membranes (Song et al. 2018; Lan et al. 2020; Lu et al. 2020; Wan et al. 2020; Zhou et al. 2020). ACE2 is predominantly expressed in lung alveolar epithelial cells, but was also found in vascular-associated cells in several organs including the brain (Hamming et al. 2004; Qi et al. 2020). Spreading to the brain has been documented for SARS-CoV in a mouse model (Glass et al. 2004) and for transgenic mice expressing human ACE2 (Netland et al. 2008) as well as for other βCoVs in various model systems (Li, Bai, et al. 2020). Moreover, SARS-CoV viruses have been detected with several different analysis techniques in human *post mortem* brain, for instance in the pituitary, localised in neurons (Ding et al. 2004; Gu et al. 2005; Xu et al. 2005).

While direct molecular evidence for the occurrence of SARS-CoV-2 in the brain needs to accumulate and several potential routes are under consideration currently (see below), several clinical observations in patients with COVID-19 point to SARS-CoV-2-induced neurological symptoms. For example, hypogeusia and hyposmia were widely observed in SARS-CoV-2-infected patients; two independent clinical studies with large sample sizes reported that 85.6 and 70.2% suffered from olfactory and 88 and 54.2% from gustatory dysfunctions, respectively (Lechien et al. 2019, 2020). In accordance with these and

several other reports (for a recent review and meta-analysis see Tong et al. (2020)), and while the exact numbers and specificity are under debate (Passali and Bentivoglio 2020), it has been suggested that the symptoms of hypogeusia and hyposmia might be useful for initial diagnostic work-up in patients with suspected COVID-19 (Benezit et al. 2020).

Furthermore, the potential routes of SARS-CoV-2 to the brain are also largely discussed (Yashavantha Rao and Jayabaskaran 2020), whereby it is not possible to discuss all interesting facets here (Saavedra 2020). It is generally assumed that neurotropic coronaviruses enter the CNS via olfactory neurons, and subsequently spread to other sites within the brain (Barnett et al. 1993) or that they enter the brain from the bloodstream (Ng Kee Kwong et al. 2020). Evidence has been provided for spreading of coronaviruses through transsynaptic communication (Matsuda et al. 2004; Dube et al. 2018; Li et al. 2012, 2013) which likely involves processes of endo- and exocytosis (Li et al. 2013). Another, repeatedly discussed, scenario is that the massive inflammatory response induced by viral infection causes damage of the blood-brain barrier (BBB), thereby facilitating viral entry into the brain (McCray et al. 2007). In the context of psychiatric diseases, compelling evidence has been provided from animal experiments that BBB integrity is compromised by chronic stress exposure possibly entailing the development of stress-related mental diseases such as MD (Menard et al. 2017; Dudek et al. 2020). Whether or not this renders patients suffering from MD more vulnerable to coronavirus infection remains speculative as of now.

As reviewed elsewhere (Fries et al. 2015, 2017; Rein 2016), the stress protein FKBP51 originally was introduced to the field of biological psychiatry because of its impact on the glucocorticoid receptor, and therefore on the neuroendocrine settings of the HPA axis (Wochnik et al. 2005; Touma et al. 2011; Rein 2016; Fries et al. 2017). In turn, several studies revealed genetic associations of its gene *FKBP5* with stress-related diseases, in particular MD and PTSD (Zannas and Binder 2014; Baker et al. 2018; Criado-Marrero et al. 2018). This amplified the interest in understanding the molecular actions of FKBP51 and the resulting increased efforts revealed several of its molecular interactions and functions (Rein 2016, Hähle et al. 2019). These include, but are not limited to, epigenetic effects through regulation of protein phosphorylation and activity of DNA methyltransferase I (Gassen, Fries et al. 2015) that impact on the signalling pathway of glucose and serum regulated kinase 3β (Gassen et al. 2016) and the regulation of autophagy (Gassen et al. 2014; Gassen, Hartmann, et al. 2015).

Regulation of autophagy by FKBP51 is linked to stabilisation of the key autophagy regulator Beclin1 (Gassen et al. 2014, 2015). The mechanism could be deciphered very recently: FKBP51 calibrates the activity of the ubiquitin E3 ligase S-phase associated kinase protein (SKP) 2 by orchestrating protein interactions with kinases and phosphatases. This affects ubiquitination and thus stability of Beclin 1 (Gassen et al. 2019). Thanks to decades of research in the field of autophagy, a link between autophagy and coronavirus replication appeared highly likely (Levine et al. 2015; Abdoli et al. 2018). This could be confirmed for the MERS-CoV virus (Gassen et al. 2019). Furthermore, it could be shown that through inhibiting SKP2 autophagy is stimulated and MERS-CoV replication inhibited (Gassen et al. 2019). In this line, targeting autophagy and endocytosis might be a novel therapeutic strategy in SARS-CoV-2 treatment, as suggested also by other authors (Carmona-Gutierrez et al. 2020; Yang and Shen 2020).

This unexpected mechanistic link may be intertwined with molecular processes relevant for molecular psychiatry in multiple ways. Given the increasingly recognised importance of autophagy for neuronal function (Lieberman and Sulzer 2020), effects of autophagy modulating viruses on brain function appear possible. In addition, autophagy modulating compounds may not only affect replication of coronaviruses, but also neuronal function more directly. Of note, several antidepressants are known to modulate autophagy (Rein 2019). Whether or not they are suitable for treatment of coronavirus infection remains to be elucidated. Excitingly, a French research team has reported a lower incidence of symptomatic COVID-19 among psychiatric patients than among staff and thus currently plans to assess the anti-SARS-CoV-2-potential of another psychotropic drug with known antiviral potential, i.e. the antipsychotic chlorpromazine, in a randomised single blind controlled phase III trial (Plaze et al. 2020). Of note, chlorpromazine is an autophagy modulator (Li et al. 2019). Without rushing to conclusions, and given the complex relationship between autophagy and coronaviruses (Abdoli et al. 2018), further investigating autophagy-inducing compounds for their effect on both neuronal function and viral replication is warranted. In any case, the unexpected contribution from molecular psychiatry to potential viral treatment regimes not only is a showcase for the success of translational research in its broadest meaning, but also pleads for expanding the support for this type of research strategy.

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Disclosure statement

None to declare.

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