Hypothesis

Breaching the Blood-Brain Barrier as a G
Psychiatric Disorder

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Abstract

The mechanisms underlying the development and progression of p
data suggest blood-brain barrier (BBB) breakdown and inflammat
put forward the "BBB hypothesis" and abnormal blood-brain com
dysfunction underlying disturbed cognition, mood, and behavior.
experiments, we propose that events within the "neurovascular
are associated with dysfunction of brain astrocytes, a local inflan
and increased network connectivity. Our hypothesis should be vali
BBB breakdown. Recently developed imaging approaches open
patients. We propose that molecular mechanisms controlling BBB
may become novel targets for the prevention and treatment of psy

1. Structure and Function of the Blood-Brain Barrie

More than a century ago, Ehrlich [1] demonstrated the lack of perr
dyes, which suggested the presence of a barrier to proteins in

suggested that the absence of central nervous system (CNS) pha
bile acids or ferrocyanide was due to the blood-brain barrier (BE
from brain.

Three barrier layers regulate molecular exchange at the interfaces
spaces: the BBB formed by the cerebrovascular endothelial cells be
plexus epithelium between blood and ventricular cerebrospinal fl
blood and subarachnoid CSF. Since individual neurons are extreme
greater than 20   m, of the various CNS barriers, the BBB
microenvironment of brain cells [3]. The BBB is present in the ca
6]). The components composing the BBB include endothelial cells
by tight junctions that are composed of specific proteins (e.g., cla
see [7]), pinocytic vesicles, and specific transport mechanisms. S
membrane, brain pericytes, and astroglial foot processes—creati
blood vessels from the brain tissue. All of these components enab
of most molecules into the brain, and that is actively involved in e
penetration. With the exception of very small lipophilic molecules
transport, and specific transporters exist for required nutrients suc

2. Blood-Brain Barrier Breakdown in Diseases

In numerous pathologies of the brain, and also in other vascular,
of the BBB is often compromised [3]. For example, the capillaries
of normal brain tissue, either as a result of a lack of inductive fact
such as vascular endothelial growth factor (VEGF). Moreover, the
some brain tumors [8]. In addition, evidence for the loss of agrin
adjacent to astrocytic endfeet [9] may contribute to BBB da
redistribution of astrocytic Aquaporin 4 (AQP4) in glioblastomas [1
) are often downregulated in BBB breakdown [12] and may
potassium molecules (described hereafter). Some neuropatholog
involve an early phase of BBB disturbance that precedes the disc
suggesting that vascular damage and increased BBB permeability
In epilepsy, the normal pattern of brain ATP-binding cassette (AE
upregulation of P-glycoprotein (Pgp) on astrocytes and the brain
antiepileptic drugs from the brain into the vascular compartmen
Kortekaas et al.[17] showed an elevated uptake of the Pgp s
tomography (PET) in the midbrain of patients with Parkinson's s
function in the BBB. In animal models of Alzheimer's disease,
close proximity to blood vessels, with toxicity on endothelium and
[18]. The ability of agents released during inflammation to incre
been described. Activation of endothelial bradykinin B2 rece
concentrations and tight junctions opening and may underlie E
coagulation occurs. In addition, bradykinin can activate NF-κB
interleukin-6 (IL-6), which can amplify the effect by acting back
(TNF) increases BBB permeability by direct action on the endothe
and IL-1   release from astrocytes [21]. During injury, several su
neurons, connective tissue, cells, and blood cells. Many of the
substance P, calcitonin gene-related peptide (CGRP), serotonin, hi
example, the release of IL-1   leads to a decreased concentration
occludin, and increases BBB permeability. TNF , histamine and in
cause changes in brain endothelial permeability [22]. Massive r
depolarization, may induce upregulation and release of metalopro

3. From BBB Breakdown to Psychopathology

We hypothesize that a primary vascular pathology, leading to BE
derived vascular components into the brain tissue and may caus
(extent, duration, and/or location), will result in disturbed thinkir
characterizing psychiatric patients. Here we will present clinical evi
hypothesize potential mechanisms linking altered vascular permea

3.1. Clinical Evidence

Clinical evidence for BBB breakdown in patients with psychopath
strongly suggest the existence of BBB pathology in a subset of
depression and schizophrenia. The main difficulties are, on the
reproducible comprehensive method for measuring BBB permeab
reliable and widely accepted animal models for human psychiatric i

Qualitative evaluation of BBB disruption in patients is most fre
modalities, such as magnetic resonance imaging (MRI), computer
CT (SPECT), following the peripheral administration of nonp
accumulation of the contrast agent indicates BBB breakdown. Altho
studying anatomical brain lesions and are most often used as diagr
psychiatric patients, the currently used imaging protocols are re
contrast agent accumulation (e.g., as compared with SPECT [25]).
temporal lobes in the region of the amygdala and hippocampus ha
progressive insomnia, short-term memory loss, depression, a
syndrome [26]. In order to increase method sensitivity and allow
has recently been developed using dynamic contrast enhanced in
Zaharchuk [29]). These methods have not yet become available
studies relate a relatively small number of patients with brain tumo
no published studies in psychiatric patients.

Quantitative evaluation of BBB functioning in the clinical setti
cerebrospinal fluid (CSF) for serum proteins (e.g., albumin) or p
[30]). However, neither of these measures is routinely assessed
clinical studies are available. BBB dysfunction has been indica
measuring increased albumin and IgG CSF levels [31, 32]. Muller
between CSF-serum albumin ratio and the patients' negative sym
be higher in elderly depressed women [33] and in patients suf
controls [34]. Interestingly, nondemented women who develope
initial higher CSF-serum albumin ratio compared to those wh
dysfunction may precede the clinical symptoms and be related
studies are supported by morphological studies demonstrating a
functions. These include degeneration and focal necrotic changes
alterations accompanied by accumulation of collagen fibrils, decr
pinocytotic vesicles and loss of tight junctions [35, 36].

S100B is primarily a brain-specific, astrocytic calcium binding pr
Information about the functional implication of S100B secretion
suggests it exerts trophic or toxic effects depending on its concent
convincingly demonstrate increased S100B levels in the seru
schizophrenia as well as depression [38, 39]. The observed increa
BBB permeability [30]. However, increased plasma levels of S100

active secretion from glia cells, or to their destruction [40, 41].

3.2. BBB-Induces Astrocytic Transformation and Dysfunction

Astrocytic end-feet surrounding capillaries in the central nervou
expression [42], and are considered an integral part of the BBB.
hours) transformation of the normally occurring "resting astrocyt
mechanisms underlying astrocytic transformation in the injured b
indicates that extravasation of the most abundant serum protein
factor for astrocytic transformation via the transforming growth f
astrocytes are observed in ischemic, inflammatory, and traumatic
change observed in the epileptic brain. Transformed astrocytes
expression that includes the upregulation of GFAP and S100B
glutamine synthase, as well as the inward rectifying potassium cr
(see [43] and unpublished data). These robust changes in gene e
the extracellular environment, specifically increased concentrations
with neuronal activity and strongly affect their excitability [12, 43
transformed astrocytes upregulate the expression of cytokines and
(described hereafter).

Is there evidence for the transformation of astrocytes in the brair
involve BBB breakdown and astrocytic response increase the risk
personality changes, depression, anxiety, dementia, and perhap
adrenal (HPA) axis is activated by stress, and its activity is seen u
mental and physiological distress. Stress activates the HPA ax
hormone (CRH), leading to secretion of catecholamines and glucoc
mediated through mast cells, which regulate BBB permeability.
breakdown [46, 47], which can be blocked by pretreatment wi
Interestingly, antalarmin has been also shown to block stress-indu

Recently, direct evidence support the presence of an astrocytic r
with no obvious preceding injury. Most studies based the "astrocy
increased serum or CSF levels of the astrocytic S100B protein. In
consistently show increased S100B levels in patients suffering f
psychotic stages of disease. Furthermore, this increase remains ir
relevant negative symptoms, whereas S100B normalizes in recov
cannot be regarded as a confounding factor, as these findings ha
(for review, see [41]). While these studies did not differentiate b
BBB permeability for S100B (when measured in serum), in a recer
cell-density of S100B-immunopositive glia in different brain regi
prefrontal (DLPF), orbitofrontal, superior temporal cortex, and hi
matched controls). They reported that cortical brain regions conta
in the schizophrenia group compared to controls. This effect was p
and particularly in the DLPF brain area. Glial pathology has also re
combined clinical study and a meta-analysis of published studie
mood disorders and 132 healthy controls [39], the authors conc
elevated during acute major depressive or manic episodes. Ad
decreases reliably during antidepressive treatment together with cl

3.3. BBB Breakdown, Astrocytic Transformation, and Brain I

There is strong clinical evidence in subgroups of patients with de
disease are associated with elevated plasma levels of pro-inflamma

C-reactive protein (for review, see [50]). Multiple studies have sho
with antidepressant treatment, indicating that one potential me
decreased inflammation. In a rare prospective study [51], an ir
levels of C-reactive protein and increased capacity of leukocytes t
in elderly individuals without a prior history of depression, sugges
It is not as yet entirely clear how inflammatory cytokines affect mo

Another clue for immune-to-brain communication associated with
chronic neuropathic pain. Activation of phagocytic immune cells
peripheral nerve leads to the release of proinflammatory cyt
proinflammatory substances [52]. The inflammatory response m
among these patients.

Thus, we hypothesize that primary BBB breakdown will enhance b
) In the event of a peripheral inflammatory response, BBB br
cytokines into the brain, thus inducing the activation of astrocyte
Prolonged and pronounced BBB breakdown will directly induce a lo
(as explained above) that will secrete cytokines locally.

Increased cytokine levels may also be involved in depression
Inflammatory mediators may also alter network properties and ne
affecting synaptic plasticity: inflammatory mediators can, throug
kynurenic acid—an NMDA receptor antagonist, and quinolinic acid
cells in the central nervous system that express the complete
quinolinic acid [54]. Therefore, inflammatory mediators acting on
kynurenic acid, leading to increased activation of NMDA recepto
glutamate levels may also activate astrocytes and microglia leadir
vicious cycle.
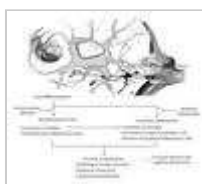
3.4. From BBB Breakdown via Astrocytic Transformation and

Our hypothesis directly links BBB breakdown, the consequent tra
resultant local inflammation to network dysfunction, which may u
the dysfunction of astrocytes and the inflammatory response are
extracellular potassium and glutamate. Together with increased
depolarize neuronal membranes, thus further allowing the activatio
in extreme cases the excess of NMDA receptors activation may le
that neurotoxicity in psychiatric disorders has not been unequivo
conditions, enhancing NMDA receptors activation results in abno
synaptic strength and (or) loss of pathway specificity. Such reduc
of larger neuronal networks in response to stimuli, Manifested a
related behavioral responses, depending on the involved network.
network will be larger, leading to epileptic activity [13] and delaye

Interestingly, a recent study demonstrated that in the KA rat
homosynaptic long-term plasticity with disturbed heterosynaptic c
connectivity between neighboring neurons has been also found in
authors suggested that this local hyperconnectivity may render c
once activated, make them more autonomous, isolated, and more

4. Summary and Future Perspectives

Figure 1 summarizes the sequence of events occurring within th
proposed hypothesis leads to network hyperconnectivity and psy
injury to the BBB, due to vascular or brain pathology, will dist
sequence of events that will finally result in abnormal pla
hyperconnectivity. Our hypothesis put together findings obser
pathophysiological picture. These findings include, for example, inc
for BBB breakdown, increased brain astroglial markers within the l
markers—the result or cause of astroglial activation, and changes
some cases, neurons loss. The hypothesis further explains the hig
acute stress reactions, and vascular pathologies (e.g., systemic
associated with BBB breakdown. It may also explain the relation
process in some psychiatric patients as well as the freque
hyperexcitable and hypersynchronized network.

Figure 1: *The BBB Hypothesis of Psychiatric*
unit in the presence of abnormal blood-brain
diffusion of serum proteins (e.g., albumin, s
pathways, and inducing the transformation
associated with impaired extracellular home
potassium and glutamate) and a local inflan
activation of microglia) and is enhanced in th
Together, neuronal network dysfunction develc

Our hypothesis raises many questions regarding the location (whe
BBB damage sufficient to induce the described disease process. W
and human patients and raise the importance of time line, long-ter
challenge the proposed hypothesis. A better understanding of BI
signaling molecules is essential for the identification of new thera
recently developed approaches for measuring BBB breakdown in
(or during the early phases of the disease). The use of novel mole
in the future, facilitate better understanding of their role in differei
disease. Future studies are also needed to uncover the interacti
specific transmitter systems which have been reported to play a rc
that our hypothesis—if found valid—will offer previously unfores
psychiatric diseases. It may also explain and encourage the use
some early stages of the disease [7 - 9]. Astrocytic dysfunction n
during the development of the disease.

In summary, the "BBB hypothesis" for impaired neuronal r
interactions between components at the "neurovascular unit" a
blood-brain communication as a potentially important cause an
disorders.

Acknowledgments

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