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Hypothesis

Possible Role of Platelet GluR1 Receptor Comorbid Depression and Cardiovascula

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Abstract

The exact nature of the comorbidity between cardiovascular disea poorly understood. The proposed mechanisms include various bio behaviors such as physical inactivity. One possible link between M viscosity. Recently, it was discovered that platelets express functi isoxazolepropionic acid (AMPA) receptors, for example, glutamate of AMPA receptor could play a role in comorbid MDD and CVD activation via direct or indirect effects on platelet GluR1 phosph novel view on the pathobiological mechanisms of comorbid MDD role of AMPA receptors in regulating platelet activation and thro putative effects of psychoactive AMPA-modifying drugs on platelet putative effects of such drugs on CVD.

1. Introduction

Epidemiological studies have identified a high incidence of como major depressive disorder (MDD). These studies note that patien [1]. Further, they prompted the American Heart Association to

patients with coronary heart disease, a recommendation that still r
of the MDD-CVD association is poorly understood. The proposed
that is, biochemical and molecular pathways as well as the hy
symptoms and cardiovascular events could be driven by health beh

One prominently hypothesized link between MDD and CVD includ
these patients [4–7]. It has been suggested that serotonin and i
with MDD in a way that leads to increased platelet activation an
shown that this abnormal activation of platelets can be attenuatec
serotonin reuptake inhibitors (SSRIs) [8–10].

Recently, it was discovered that platelets express the alpha-an
(AMPA) receptors for the excitatory neurotransmitter glutamate
AMPA receptor subtype, glutamate receptor 1 (GluR1), mediates
activation, and they suggested that the GluR1 receptor is a novel a
of glutamate receptor could play a role in comorbid MDD and CVD.

2. Presentation of the Hypothesis

Ionotropic glutamate receptors are ligand-gated ion channels tha
methyl-d-aspartate), kainate, and AMPA receptors. GluR1, one of
plasticity at excitatory synapses in a manner which is positively
protein kinase A (PKA) site, and at Ser831-GluR1, a calcium/ca
kinase C (PKC) site [12, 13].

Recent work by Morrell et al. [11] demonstrated that activated pl
subunits; glutamate increases agonist-induced platelet activatio
receptors depolarized platelets (an important step in platelet a
antagonist or platelets derived from GluR1 knockout mice were
lacking GluR1 have a prolonged time to thrombosis in vivo [11]. T
thrombus formation and may contribute to development of CVD.

It has been noted that plasma concentrations of glutamate are alt
with the severity of depression [14], and antidepressant therapy
other hand, measurements of the platelet response to glutama
supersensitive in MDD [16].

Considering the crucial role of increased GluR1 phosphorylation
subunits and in the consequent increased activity of these AM
alterations of protein kinase systems (including PKA) in mood diso
phosphorylation in MDD may contribute to comorbid MDD and CVD

3. Antidepressants and GluR1 Phosphorylation

The trafficking of the GluR1 from intracellular pools to cell mer
receptor phosphorylation. It has been suggested that phosphor
actions [19]. However, the data on medication-induced alteratio
increase and a decrease of GluR1 phosphorylation were observ
various antidepressants influence the phosphorylation of different
[20] reported that treatment with fluoxetine increases phosphor
addition, another antidepressant, tianeptine, which enhances th
increased Ser831 phosphorylation in the frontal cortex and CA3

phosphorylation only in the CA3 region. Behavioral analyses sh
Ser831 and Ser845 when treated with saline exhibit increased imı
like behavior) compared to their wild-type counterparts. Chronic t
type mice but not in phosphomutant GluR1 mice [21]. Recent fi
minocycline has antidepressant-like neuroprotective effects, and i
rat model of depression [22]. In vitro and in vivo studies showed
both Ser845 and Ser831, and it increases the surface content of
ketamine, which causes acute and sustained antidepressant-l
phosphorylated GluR1 at Ser845 [24].

4. Platelet Activation and Antidepressants

Antidepressants, particularly SSRIs, have been associated with ab
serotonin reuptake inhibition, for example, fluoxetine, paroxetine,
abnormal bleeding and modifications of hemostasis markers [25]
bestow protection from myocardial infarction, even compared to
demonstrated in some clinical studies [26]. More recent studies
effects relevant to platelet activation and that, in some instances
known antidepressants, in addition to their main effects (e.g., s
molecular pathways (e.g., GluR1 signaling and phosphorylation),
platelet activation via direct or indirect effects on platelet GluR1 ph

5. Testing the Hypothesis

The hypothesis that altered platelet GluR1 phosphorylation in MDD
be best tested in a clinical setting. Since several studies have alre
receptor activation in MDD patients versus controls, this approac
platelet GluR1. Moreover, future clinical studies could focus on pa
vitro studies with human platelets are warranted to verify whether
induced by kinase inhibitors and activators) influence the extent
whether they influence platelet activation.

The hypothesis that drugs used for treatment of MDD may interfe
animal models and in a clinical setting. It would be useful to comp
developed specifically to target AMPA receptors. These studies wo
mechanisms of action of these drugs on GluR1 receptors could sigr
and in blood cells such as platelets.

With respect to the recently discovered role of AMPA receptors in
significant role in thrombosis, it appears that the information abou
platelet AMPA receptors would be critical in evaluating the putati
testing the here-proposed hypothesis could provide a novel view o
and CVD.

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