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EFFECT OF NEUROLOGICAL DISEASES ON HEART RHYTHM

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ABSTRACT. Neurological disorders including depression, anxiety, post-traumatic stress disorder (PTSD), schizophrenia, autism and epilepsy are associated with an increased incidence of cardiovascular disorders and susceptibility to heart failure. The underlying molecular mechanisms that link neurological disorders and adverse cardiac function are poorly understood. Further, a lack of progress is likely due to a paucity of studies that investigate the relationship between neurological disorders and cardiac electrical activity in health and disease. Therefore, there is an important need to understand the spatiotemporal behavior of neurocardiac mechanisms.

KEYWORDS: antipsychotic drugs; cardiovascular disease; ion channels; mental illness.

INTRODUCTION

Psychiatric disorders are widely prevalent globally, affecting about 25–30% of patients in Europe and the United States, with anxiety disorder and depression being the most common conditions (7% and 5% respectively). Cardiovascular disorders (CVDs) are the leading cause of death in the general population, but also among patients with neurological diseases, suggesting a link between these two populations.

In general, a complex set of behavioral and psychosocial aspects are mediators for increased CVD risk, including smoking, alcohol and substance abuse, poor diet and reduced physical activity that can lead to obesity, non-adherence to medications and sleep disorders, anger and hostility, social isolation and low socioeconomic status. These CVD risk factors are significantly present among subjects with mental illness, resulting in an additive effect over the disease-related biological risk factors that these patients have for CVD. Notably, drug therapies for the treatment of mental disorders predispose to a variety of physical illnesses (obesity, diabetes, thyroid disorders, gastrointestinal, respiratory and renal diseases, etc.), including CVD and arrhythmias. All-cause mortality in general, and cardiac mortality in particular, is higher in antipsychotic users compared to nonusers.

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Therefore, there is an urgent need for management strategies to reduce the CVD risk in this population group. A holistic understanding of the molecular mechanisms that underlie biological stressors is important in defining psychological and physical outcomes that determine vulnerability to disease conditions, and in particular CVD . This is also valid for CVD patients, in which psychological and psychiatric problems (such as depression and anxiety) that may arise following major cardiac events are often under-reported and undertreated. Therefore, a prompt identification and treatment of potential psychological conditions could help reduce the risk of further cardiac events and improve the outcome in cardiac patients.

In this review we discuss existing knowledge of the intimate and delicate interaction between neurological disorders and CVD, taking into consideration common and distinct pathological mechanisms. In particular, we discuss the potential involvement of pathological ion channel modulation in the etiology of neurological disorders with significant implications for CVD and ultimately arrhythmias. Our hope is that this review will be of great interest to a wide range of the scientific community and more specifically neurology and cardiology research investigators. In this context our goal is to further highlight unacknowledged common and unique molecular mechanisms of neurological channelopathies and cardiomyopathies that merits significant investigation.

A bidirectional relationship between mental illness and CVD is known to exist. Among mental illnesses, depression, post-traumatic stress disorder (PTSD), anxiety, schizophrenia and autism are the most commonly studied due to their crucial predisposition to adverse cardiac events. For example, depression is a mood disorder that varies from mild to major depressive symptoms and is characterized by sadness, pervasive low mood and loss of interest (anhedonia) lasting for 2 weeks or more. Depression and cardiovascular disorders are closely related. CVD can cause depressive symptoms, and the prevalence of depression in patients with CVD is 3 times higher than in the general population. Furthermore, depression has been reported to be an independent risk factor for cardiac events, increasing the incidence of CVD in previously healthy people.

Depression and anxiety are interlinked pathologies, but the associated mechanisms are unknown or poorly understood. Notably, patients with high levels of

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anxiety have an increased risk for sudden cardiac death (SCD). Indeed, hyperventilation, that may occur during an acute panic/anxiety attack, can induce coronary artery spasm, which in turn may eventually lead to myocardial ischemia and fatal ventricular arrhythmias.

Depressive and anxiety disorders have a high comorbidity and share symptoms with PTSD, a disease state defined by trauma and stressor-related diseases that may develop after a major traumatic event (including combat, sexual assault, etc.). Further, intrusive thoughts, negative cognitions and mood, avoidance and hyperarousal are associated with PTSD and this, in turn, leads to severe distress. For example, clinically relevant studies in the Veterans population have highlighted the association between PTSD and CVD, with PTSD patients having double the risk of developing adverse cardiac events. Moreover, experiencing a life-threating illness, including a major cardiac event, can elicit PTSD, and the persistence of PTSD symptoms can increase the likelihood of developing recurrent CVD.

Schizophrenia is another psychiatric disorder significantly associated with augmented risk for CVD. Schizophrenia is defined by the presence of two or more characteristic symptoms, including hallucinations, disorganized speech and delusions. Patients with schizophrenia are likely to have a 10 years lower life-expectancy compared to the general population, and this dramatic reduction is underscored by a high incidence of suicide and an elevated CVD risk.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by restricted interests, repetitive behaviors and difficulties in communication and social interaction. ASD is commonly comorbid with other psychiatric disorders (depression and anxiety), and also with epilepsy, suggesting the existence of shared biological mechanisms between these conditions. Congenital heart diseases (CHDs) such as atrial and ventricular septal defects have been associated with an increased risk of developing ASD and epilepsy. While the exact cause is unknown, studies have suggested that there could be common genetic links, environmental causes or it could be due to surgeries or other clinical outcomes due to CHD. For example, increased seizures for CHD patients, ingeneral and particularly after surgery, lead to deficits in neural development that might be due to cerebral hypoperfusion, and further reinforces an important physiological interplay between these disease pathologies. Furthermore, ASD patients are more likely to have hyperlipidemia, which is a known

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risk factor for diabetes, obesity and CVD. Others and we have demonstrated that pathological levels of the saturated free fatty acid, palmitic acid, led to adverse remodeling of major cardiac ion channels in distinct animal models. These findings suggest a higher likelihood of experiencing a fatal arrhythmia event and ultimately the transition to heart failure and sudden cardiac death in ASD patients with confounding hypercholesterolemia and/or hypertriglyceridemia. Future studies of the mechanisms of the neurological–cardiac axis that include patients with lipid metabolism disorders are likely to provide novel and additional insights that will improve knowledge of vulnerability of ASD patients to metabolic disorders and ultimately cardiac dysfunction.

Antipsychotic and antiepileptic medications have been reported to have a range of cardiac side-effects, including orthostatic hypotension, cardiomyopathy, QT prolongation and increased risk for SCD. Moreover, antidepressant drugs have been associated with adverse cardiac effects: the selective serotonin reuptake inhibitors (SSRIs) and particularly the tricyclic antidepressants are known to cause prolongation of the heart rate corrected QT interval (QT_c) on an ECG and predispose to ventricular arrhythmias. These cardiotoxic effects of psychiatric disorder therapeutics are of particular importance in patients with an underlying CVD.

Neurological conditions, including subarachnoid hemorrhage, can also be associated with cardiac dysfunction. In this context the Krzych lab demonstrated that the neurocardiogenic injury that follows a subarachnoid hemorrhage is characterized by ST-segment elevation and QT_c prolongation on the ECG, moderate elevation in Troponin C levels and myocardial necrosis. These clinical presentations are reminiscent of Takotsubo cardiomyopathy a cardiac condition that develops in response to severe psychological distress, or an intense emotional or stressful experience. A catecholamine-induced toxicity in cardiomyocytes has been identified as a common pathological mechanism between the two conditions, and further highlights a critical link and/or interplay between cellular functions of the brain and heart.

It is becoming increasingly clear that distinct biological, behavioral and psychosocial factors mediate the physiological link between mental illnesses and the increased risk of CVD. Therapeutic strategies are also known to increase the risk for CVD. In fact, antidepressants that target serotonin or norepinephrine reuptake, or antipsychotic drugs blocking dopamine receptors, are the most commonly used

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therapeutics in clinical interventions, and several of these drugs are known to be proarrhythmic, mainly due to their effect of cardiac hERG channels blockade.

Anti-inflammatory treatment strategies in neurological diseases have shown promising results mostly by limiting depressive symptoms. Therefore, a combination of therapeutics including those that target hyperinflammatory cellular signaling pathways, could help to improve outcomes in patients. Moreover, considering the elevated proinflammatory profile found in different psychiatric disorders and the proarrhythmic effect of specific cytokines, therapies that aim at lowering inflammation could both improve psychiatric symptoms and reduce the risk for CVD and arrhythmias.

The majority of studies on the association between arrhythmias and psychiatric disorders describe evidence for ventricular arrhythmias (LQT) but less is known for other forms of arrhythmias. Few trials have attempted to investigate the prevalence of atrial fibrillation in mental disorders, but found that panic disorder and likely anxiety, are associated with increased incidence of atrial fibrillation. Additional studies assessing the occurrence of other types of arrhythmias in psychiatric disorders could provide further insight into the pathological mechanisms of such diseases.

CONCLUSION

Further it is known that mental diseases are generally associated with behavioral and/or lifestyle changes including smoking, poor diet, reduced physical activity, alcohol and substance abuse and non-adherence to medications. Therefore, coupling therapeutics with clinical interventions that limit significant changes in individual or multiple combinations of life-style behaviors is likely to reduce the risk of developing cardiovascular diseases that predispose to heart failure.

Finally, the involvement of ion channels in the etiopathology of psychiatric disorders may support the evaluation of alternative targets for the development of pharmacological strategies. The evidence that subjects with a particular neuronal specific hERG isoform (KCNH2-3.1) associated with schizophrenia show a higher responsiveness to antipsychotic drugs and is a relevant example of ion channels as a therapeutic target. Therefore, a comprehensive investigation of the functional interplay between cardiac and neuronal ion channels in the pathogenesis of mental illness and CVD is likely to be rewarded by mechanism-based insights that will help to improve the clinical limitations of existing therapeutic and behavioral interventions in patients.

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Abbreviations

ANS	Autonomic Nervous System
ASD	Autism Spectrum Disorder
CHD	Congenital Heart Diseases
CVD	Cardiovascular Disorders
hERG	Human Ether-A-Go-Go-Related Gene
HPA axis	Hypothalamic–Pituitary–Adrenal Axis

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HRV	Heart Rate Variability
$I_{Ca,L}$	L-Type Calcium Current
IKr	Rapid Delayed Rectifier Potassium Current
Ito	Transient Outward Potassium Current
IL-6	Interleukin 6
IL-1β	Interleukin 1β
LQTS	Long QT Syndrome
PNS	Parasympathetic Nervous System
PTSD	Post-Traumatic Stress Disorder
QTc	Corrected QT interval
SCD	Sudden Cardiac Death
SNP	Single Nucleotide Polymorphisms
SNS	Sympathetic Nervous System
SQTS	Short QT Syndrome
SSRI	Selective Serotonin Reuptake Inhibitors
TNF-α	Tumor Necrosis Factor Alpha
TS	Timothy Syndrome