Journal of Physiology - Paris xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Suicide attempts in children and adolescents: The place of clock genes and early rhythm dysfunction

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ARTICLE INFO

Article history:
Received 13 July 2017
Received in revised form 6 November 2017
Accepted 13 November 2017
Available online xxxx

Keywords:
Suicide
Suicidal behavior
Adolescence
Clock genes
Rhythms
Life events

ABSTRACT

Suicide remains one of the leading causes of death among young people, and suicidal ideation and behavior are relatively common in healthy and clinical populations. Suicide risk in childhood and adolescence is often approached from the perspective of nosographic categories to which predictive variables for suicidal acts are often linked. The cascading effects resulting from altered clock genes in a pediatric population could participate in biological rhythm abnormalities and the emergence of suicide attempts through impaired regulation of circadian rhythms and emotional states with neurodevelopmental effects. Also, early trauma and stressful life events can alter the expression of clock genes and contribute to the emergence of suicide attempts. Alteration of clock genes might lead to desynchronized and abnormal circadian rhythms impairing in turn the synchronization between external and internal rhythms and therefore the adaptation of the individual to his/her internal and external environment with the development of psychiatric disorders associated with increased risk for suicide attempts.

1. Introduction

Suicide attempts in children and adolescents remain a very important public health problem. Although people of all ages are at risk for suicide, it is more common among young people. Suicide was the second leading cause of death for 12–25 year olds and the third leading cause of death for 26–34 year olds (Centers for Disease Control and Prevention, 2017).

It is important to understand the determinants of suicide attempts, in order to prevent the first episodes, and the recidivism. Different generations of studies have focused first on the epidemiological data, on the social causes or social determinants associated with suicides, then on the links between clinical variables and suicide, neurobiological determinants, and more recently, genetic dimensions with a focus on models of early trauma and genetic vulnerability to stress. Those last epigenetic models did not imply early determinants of biological rhythms, like *clock genes*, which have been involved in psychiatric diseases.

This paper aims first to describe actual models of suicide risks in children and adolescents, and to propose that early rhythm dysfunctions linked with *clock genes* could be an interesting model that transcends nosographic approaches.

2. Socio-environmental determinants of suicide in children and adolescents

A distinction is typically made between proximal life events that would act as precipitating factors and distal ones that occur in childhood and predispose individuals to later suicide attempts in adolescence or young adulthood (Fergusson et al., 2000; Turecki et al., 2012).

The proximal factors would be recent life events, psychopathology, suicidal ideation and despair. These proximal risks would be modulated by age and socio-demographic factors, religion and spiritual beliefs, social support and social environment, and substance use (Turecki et al., 2012). They are involved in triggering the suicidal act. In accordance with the cumulative model of risk factors for suicide attempts, negative life events are likely to produce enhanced states of burdensomeness and decreased belong-

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https://doi.org/10.1016/j.jphysparis.2017.11.001
0928-4257/

ingness, thereby contributing to suicide attempts through an increased level of suicidal thoughts (Silverman et al., 2007).

Distal risks are more affected by developmental processes and include family history of suicide, early stress, personality traits, cognitive styles, chronic substance abuse and epigenetic factors. These distal risks may be modulated by gender, stressful life events, social support and the quality of the social environment.

Research has consistently shown that a history of attempted suicide (Borowsky et al., 2001; Fergusson et al., 2000; Lewinsohn et al., 1994; Wichstrøm, 2000) and depressive episodes (Apter and King, 2006; Giaconia et al., 2001) are the main predictors of successful suicides. Studies of risk factors for suicide include key mental disorders, particularly emotional disorders, substance abuse, and antisocial behavior (Beautrais et al., 1996).

Some life events could be identified as risk factors for attempted suicide. This is the case for suicide attempts by a friend (Borowsky et al., 2001; Larsson and Sund, 2008; Lewinsohn et al., 1994), alcohol poisoning (Borowsky et al., 2001; Wichstrøm, 2000), the use of toxic substances (Borowsky et al., 2001; Fergusson et al., 2005; Giaconia et al., 2001), or sexual abuse (Fergusson et al., 2005). At the family level, the death of a parent or the separation of parents are also risk factors (Agerbo et al., 2002; Beautrais, 2000; Beautrais et al., 1996; Brent et al., 1993; Fergusson et al., 2005; Gould et al., 1998; Johnson et al., 2002; Lewis et al., 1988; Tousignant et al., 1993; Wichstrøm, 2000). However, it is mainly the early events that could play a major role. The social environment of early childhood can induce stable changes that influence neurodevelopment and mental health. Research focused on early-life adversity revealed that early-life experiences have a persistent impact on gene expression and behavior through epigenetic mechanisms (Turecki and Meaney, 2016).

The temporal variations of suicide have been studied. A seasonal peak of suicide in the spring and early summer has been reported in many studies from different countries (Christodoulou et al., 2012). Circadian variations exist in suicide, depending on age with an evening peak for youth, whereas a morning peak is found for older adults. There is a peak for completed suicide in the early morning, whereas a peak in suicide attempts occurs rather in later afternoon (Benard et al., 2015). This could reflect the involvement of biological rhythms in the occurrence of suicide in children and adolescents.

3. Neurocognitive hypotheses in children and adolescent suicide: Brain dysfunctions?

With advances in molecular biology, genetics, functional imagery, and research in psychopathology, new perspectives have been added. It should be noted, however, that the neurobiology of suicide has long been associated with that of mood disorders (Ernst et al., 2009).

During typicall development, risk-taking and the search for novelty are marked in adolescence and are associated with well-known mechanisms of cerebral maturation. Structural neuroimaging studies have revealed that the decrease in the proportion of gray matter with age reflects the reduction in the number of synapses and the complexification of the axonal branches (Dayan et al., 2010). The neural circuitry undergoes a major reorganization in adolescence, particularly in those regions of the brain involved in executive functions, the self and social cognition. Functional neuroimaging has shown that these regions play also a key role in the regulation of behavior and emotion, and in the perception and evaluation of risk and reward. Accordingly, "impulsivity, risk-taking behavior, and novelty-seeking may provide a mechanism to expand the range of possibilities that will then provide the appropriate feedback for optimal sculpting of the brain" (Luna et al., 2001). In cognitive psychology, risk-taking has been associated with an increased tendency towards sensation-seeking and immediate reward-seeking, and a lack of inhibition (Tamm et al., 2002). Some authors, focusing on cognitive abilities, have suggested that adolescents are less liable to consider the negative repercussions of rewarded behavior in hypothetical scenari (Reppucci, 1999).

In young adults, alterations in the decision-making process, attention-focused problem solving, or verbal fluency are reported (Jollant et al., 2011). Such anomalies increase the risk of these individuals exposing themselves to accidents or adverse life events. Recent data suggest that exposures to trauma have a cumulative effect on physical health in Western populations (Sledjeski et al., 2008). It is now known that cognitive impairment is associated with a history of attempted suicide, independently of depressive comorbidity (Antypa et al., 2010; Jollant et al., 2011).

4. Early trauma and stress: Epigenetic models

The stress experienced at a young age, in a period of life characterized by high neuronal plasticity, can predispose adolescents to psychological disorders. Although biological mechanisms have been studied extensively, the consequences on cerebral functional organization have been less investigated. Alterations of white matter were observed in maltreated adolescents during their childhood, and these disturbances were associated with increased psychopathological vulnerability (Huang et al., 2012).

Following stress exposure, the hypothalamus produces corticotrophin –releasing a hormone (CRH), which stimulates the anterior pituitary to release simultaneously adrenocorticotropic hormone (ACTH) and Beta-Endorphin. Then ACTH stimulates the adrenal cortex to produce glucocorticoids such as cortisol. This cortisol participates in adaptive stress responses. When the system is mature, cortisol has a feedback effect on all the stages used previously to limit their secretion and cortisol levels return quickly to normal levels. However, when the system is not yet mature, the receptors of each of the affected effectors undergo desensitization. The secretion of cortisol is diminished but above all the immature feedback results in a cortisolemia that remains elevated much longer. Over time, this excess of repeated cortisol, at each stress, is deleterious to certain areas of the brain with glucocorticoid receptors, such as the hippocampus, amygdala and frontal cortex. The consequence on cerebral development is important (Jackowski et al., 2011) and early life events can have long-term consequences for human health (Barker, 2007).

Repeated exposure to stress during childhood, such as maltreatment, leads to a desensitization of hippocampal glucocorticoid receptors, a demodulation of CRF neurons, a reduction of hypothalamic CRF receptors, and an increase in the number of CRF extra hypothalamic receptors. These abnormalities can lead to increased anxiety and depressive vulnerability, vulnerability to addictions and eating disorders, psychotraumatic disorders, and a greater risk of suicide (Teicher et al., 2003, 2006).

Studies carried out in animals have examined the bases underlying different manifestations. The separation of rhesus monkeys from their mothers at birth has consequences on the regulation of emotions and on cortisol levels (Barrett et al., 2009). Experiments in rats on maternal behavior show that their impact on the corticotropic axis (Liu et al., 1997) and on the subsequent behavior of rats in relation to stress involve a change at the DNA level (Weaver et al., 2004, 2006). The consequences can be long-lasting; in rats it has been shown that early and long separations can lead to disorganization of the CRF system in adulthood (Ladd et al., 1996).

Please cite this article in press as: Olliac, B., et al. Suicide attempts in children and adolescents: The place of clock genes and early rhythm dysfunction. J. Physiol. (2017), https://doi.org/10.1016/j.jphysparis.2017.11.001