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Altered circadian patterns of salivary cortisol in individuals with schizophrenia: A critical literature review

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ABSTRACT

This article focuses on stress vulnerability in schizophrenia through an integrated clinical and biological approach. The objective of this article is to better understand the relationships between vulnerability, stress and schizophrenia. First, the concept of vulnerability is defined and several models of vulnerability in schizophrenia are reviewed. Second, a section is developed on the biology of stress, and more specifically on the stress responses of the hypothalamo-pituitary adrenal (HPA) axis. Then, studies of cortisol circadian rhythms are summarized, suggesting hyper-reactivity of the HPA axis in patients with schizophrenia and high risk individuals for schizophrenia. The results support the models of stress vulnerability in schizophrenia and the hypothesis of high cortisol levels as an endophenotype in this disorder. In conclusion, this article highlights the interest of studying the cortisol circadian rhythms in schizophrenia and opens the perspective to identify high risk individuals for schizophrenia by measuring circadian patterns of salivary cortisol.

1. Introduction

Schizophrenia is a frequent mental disorder occurring with a prevalence of 1%, defined by positive symptoms (such as hallucinations and delusion), negative symptoms (such as avolition and reduced emotion expression), ambivalence and desorganization during at least a one month-period. Several models of stress vulnerability have been proposed for schizophrenia. The objective of this article is to better understand the relationships between vulnerability, stress and schizophrenia. First, it is necessary to define the concepts of vulnerability and stress, and the current available biological methods to measure stress responses, such as cortisol measures.

2. Vulnerability

2.1. Definition of vulnerability

Vulnerability is a current concept, in both somatic medicine and psychopathology. Latin etymology "*vulnus*, *vulneris*" which means "*injury*" clarifies the meaning. Vulnerability is then the quality of what or who is vulnerable, or what or who may be injured, exposed to a physical or moral wound.

Although vulnerability to schizophrenia has been first discussed in the era of Bleuler, the concept of vulnerability has been updated mainly by Zubin and collaborators (Zubin and Spring, 1977; Scotto and Bougerol, 1997). According to Zubin and Spring (1977), vulnerability is not specific to schizophrenia and can be applied to other mental disorders. Vulnerability is present in all individuals on a continuum from normal (low/absent vulnerability) to pathological (high vulnerability). Consequently, children highly vulnerable to schizophrenia might develop psychotic symptoms of schizophrenia in response to minor events. Inversely, children with low vulnerability to schizophrenia might develop symptoms of schizophrenia only in exceptional circumstances, such as major stressful life events. These stressful events may occur at different periods of life, including during the prenatal period. Prenatal stressful life events possibly related to the development of schizophrenia are described in the next section. Finally, the originality of Zubin and Spring was to consider vulnerability as a permanent and chronic risk for schizophrenia. Then, it would be more appropriate to speak about chronic vulnerability to schizophrenia rather than chronic schizophrenia.

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2.2. Prenatal stress and schizophrenia

Several authors have associated prenatal stress, especially during the third trimester of pregnancy (between the 25th and 28th week of pregnancy), with developmental disorders, such as schizophrenia and autism (Beversdorf et al., 2005; Previc, 2007). One study advanced that schizophrenia onset is associated with exposure of the pregnant mother to the loss of her husband in the second or third trimester of pregnancy (Huttunen and Niskanen, 1978). However, another study suggested that severe stress provoked by the death of a relative occurring during the first trimester of pregnancy, may increase the risk of schizophrenia in offspring (adjusted relative risk, 1.67) (Khashan et al., 2008). This study did not find a relationship between schizophrenia and death of a relative occurring during the two other trimesters of pregnancy or during a period of six months before pregnancy. Other authors have associated schizophrenia and unwanted pregnancy (Myhrman et al., 1996). Van Os and Selten (1998) examined the effect of prenatal exposure to the May 1940 invasion of The Netherlands on later incidence of schizophrenia. They showed that the cumulative incidence of schizophrenia was higher in the exposed cohort, especially in those exposed in the first trimester of pregnancy. They suggest that prenatal stress during pregnancy contributes to vulnerability for schizophrenia. According to Shalev and Weiner (2001), prenatal stress could be considered as a neurodevelopmental factor involved in the physiopathology of schizophrenia, especially in males. Similarly, Khashan et al. (2011) reported male vulnerability to prenatal stress given that they found an association between prenatal exposure to severe life events and risk of male offspring affective disorders (10–30 years of age), whereas this association was not observed in female offspring. This male vulnerability to prenatal stress, taken together with genetic abnormalities found on the sex chromosomes in individuals with schizophrenia, might be of interest given the male prevalence of schizophrenia (hospital-based studies suggest a higher rate of schizophrenia in males, American Psychiatric Association, 2000). Indeed, cytogenetic deletions on the short arm of the X-chromosome encompassing the steroid sulfatase (STS) gene have been observed in schizophrenia (Milunski et al., 1999) and STS is also mapped on the pairing region of the Y-chromosome (Le Roy et al., 1999). Markham and Koenig (2011) and Weinberger (1995) suggested that prenatal stress could lead to brain dysfunction which might contribute to the pathogenesis of neuropsychiatric illness such as schizophrenia and depression, in particular at puberty when pubertal changes occur. However, there are some discrepancies with regard to results on sex-specific effects of prenatal stress exposure. Thus, maternal anxiety (12–22 week of pregnancy) was associated in male and female adolescents with a high, flattened cortisol day-time profile, which in turn was associated with depressive symptoms in female adolescents only at 14–15 years (Van den Bergh et al., 2008a, 2008b). Similarly, Torche and Kleinhaus (2012) found female vulnerability to prenatal stress exposure but at an earlier period of life: earthquake exposure in early pregnancy resulted in a significant decline in gestational age and an increase in preterm delivery, especially in females compared to males. It could be stated that the sex-specific effects of prenatal exposure might be different according to offspring age (i.e., female vulnerability to impaired gestational age and male vulnerability to psychopathology occurring later), but some studies (Gérardin et al., 2011) reported a male vulnerability to prenatal stress and prenatal depression even at birth (e.g., lower scores of motor skills and regulation of states).

It is noteworthy that the role of prenatal stress or anxiety in psychiatric disorders, such as schizophrenia but also autism or depression, cannot be reduced to cause-and-effect relationships given the interactions between genetic factors and environmental factors including several psychosocial factors (Previc, 2007).

2.3. The model of Zubin and Spring: at the crossroad of stress and vulnerability

Zubin and Spring (1977) have developed a model on the relationship between stress and vulnerability (Fig. 1), including a threshold to detect the pathology. Stress can be defined as all biological and psychological disturbances caused by any aggression on an organism and generating biological or psychological responses in this individual. In this context, the "*stressors*", i.e. the agents which produce stress, can be endogenous (genetic, neurophysiological, biochemical, etc.) or exogenous (in reference to the external environment).

Norman and Malla (1993) have reported a relationship between "*stressors*" and worsening of symptoms in patients with schizophrenia. However, according to these authors, patients with schizophrenia would not be more exposed to "stressors" than the general population, but they would be more vulnerable and reactive to stress. In order to evaluate the role of stress and "stressors" in patients with schizophrenic, it is therefore necessary to measure indirectly vulnerability and stress reactivity in these patients.

Thus, the Zubin and Spring's model is not a simple model of vulnerability, but a stress-vulnerability model. In addition, Zubin and Spring (1977) laid the foundations of a threshold-dependent model for vulnerability to schizophrenia, also extended to other mental disorders. They have finally introduced the concept of "*vulnerability markers*" and certainly did not expect such important consequences in terms of very wide use of this concept following its first description. Other models of stress-vulnerability for schizophrenia have been described and are discussed in the next section.

2.4. Other models of stress-vulnerability

2.4.1. Model of Nuechterlein and Dawson

The model of Nuechterlein and Dawson (Nuechterlein and Dawson, 1984; Scotto and Bougerol, 1997; Christau, 2003), developed as early as 1984, improved regularly, is essentially based on

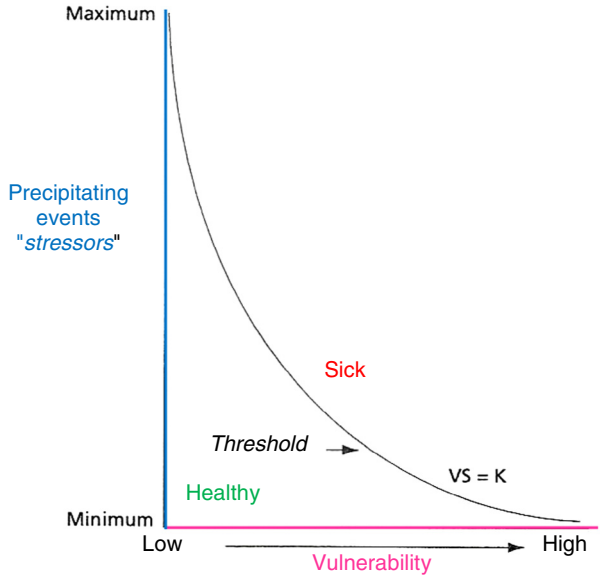

Fig. 1. Stress-vulnerability model of Zubin and Spring (adapted from Zubin and Spring, 1977) The equation of the curve is VS = K; V: degree of vulnerability; S: stress induced by the triggering event, the "stressor"; K: constant.