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Stress in schizophrenia: an integrative view

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Abstract

Stress and the development of a (schizophrenic) psychosis are inextricably related. The process by which stress actually affects psychosis is far less clear. The hypothalamic–pituitary–adrenal system, and in particular the release of corticosteroids, has been attributed an essential role. However, schizophrenia is a disorder in which many functions are distorted. Dysfunctions can be found in behavior, cognition, coping, physiology, pituitary–adrenal and immune functioning. In this short paper, these functions are discussed as to how they contribute to the way stress is appraised and processed. Schizophrenic patients are impaired in their biological response to stress by showing a blunted cortisol response to psychosocial stress. It is hypothesized that this reflects rather cognitive dysfunction, based on biological dysfunctions in those brain structures that are responsible for these processes, i.e. the prefrontal cortex and the limbic system. Considering the blunted cortisol response as a maladaptive stress response, its consequences are commented on with an emphasis on the immune system. Finally, the role of neuroleptics, and in particular the atypical ones, is discussed for their beneficial effect, beyond their fear-and anxiety-reducing properties, in restoring some of the cognitive dysfunctions schizophrenic patients display. By doing so, they may improve perception of the environment, enhance adjustment and thus a proper stress response. Integration of these processes in stress research described, may provide new vistas of the stress concept in schizophrenia.

Keywords: Schizophrenia; Stress; Cognition; Coping; Hypothalamic–pituitary–adrenal system; Immune system

"if stress is learning, learning is stress"
David de Wied, personal communication

"then this is what I learned from him, writing this paper"

1. Introduction

The involvement of stress in the development of psychiatric disorders, such as depression, post-traumatic stress disorder (PTSD) and schizophrenia, is generally accepted (Nemeroff, 1998; Heim et al., 2000; Walker and Difioro, 1997). However, the mechanism by which stress actually affects these disorders is far less clear. Moreover, the definition of stress that is being used in the literature is rather diverse and ranges from describing the stress stimulus, the feelings of discomfort that may arise from it or the behavioral, physiological, endocrine or immune responses that are elicited by it. Cannon (1929) was the first to introduce the terms "fight, fright or flight" and "homeostasis" to indicate that the stress response comprises a cascade of events, i.e. *activation* and *adaptation*. The adrenals were already attributed an essential role in this process for providing both the catecholamines to activate the organism to actively address the stressor and the corticosteroids to counteract the primary stress reactions and let the organism return to homeostasis (Cannon, 1929, 1935). Seley (1936) then described the *general adaptation syndrome* and extended the view on the role of the adrenal steroids, stating that the adaptive stress response was a nonspecific effect of any demand upon the body. Later, this concept was modified in the sense that he made clear that the type of stress imposed was able to determine the type of response that it would elicit (Seley, 1956). Until now, these concepts still hold in stress research, although a more dynamic approach to the term homeostasis, i.e. allostasis, has been proposed by McEwen (1998) to emphasize the

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plasticity of the endocrine adaptive system throughout life and its consequences for developing disease. However, in the recent literature, stress is predominantly described in terms of changes in hypothalamic–pituitary–adrenal function, whereas both the psychological aspects of stress processing and the involvement of the autonomic nervous system (ANS) are often neglected or studied separately. Therefore, the role of cortisol, as the sole stress hormone, may have been somewhat overestimated (for review, see Heim et al., 2000).

In general, when a stimulus is appraised as stressful by the individual, a process that is predominantly determined by the novelty and controllability of the stimulus itself (Huether, 1996), the ability to adequately cope with the stressor will determine, whether, and to what extent, a biological stress response will occur. An example of the stress response to a psychosocial stressor, i.e. a public speaking task, is given in Fig. 1. Coping is regarded as the psychological component in this process and comprises behavioral, cognitive and emotional responses in order to master a threatening situation and to reduce the impact of the stressor (Folkman and Lazarus, 1985). The higher brain areas that are involved in interpretation of the stressor and activation of the biological stress response are thought to be predominantly the prefrontal cortex and the limbic system, i.e. the amygdala–hippocampus complex. Through the prefrontal cortex, the limbic system is activated to arouse the stress-induced emotions of fear and anxiety. Probably the release of corticotropin releasing hormone (CRH) directs both the activation of the ANS as well as the hypothalamic–pituitary–adrenal axis (Huether, 1996). If a stress stimulus is not adequately responded to, for instance when the hypothalamic–pituitary–adrenal system is hyper- or hyporesponsive or not able to habituate, stress may enhance disease susceptibility (McEwen, 1998). This may be reflected in the hypercortisolemia that can be found in chronic depression or the hypocortisolemia that can be found in PTSD. In schizophrenia, such dysfunctions in the hypothalamic–pituitary–adrenal system are less obvious.

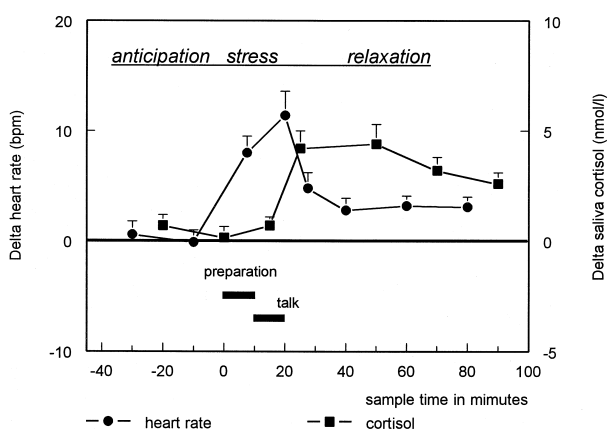

Fig. 1. The net effect of public speaking as psychosocial stress on heart rate and salivary cortisol secretion in healthy adult subjects (22♂/29♀). Delta values are calculated by subtracting control day values from test day values, expressed as mean ± SE.

Schizophrenia is a disorder in which many functions are distorted. Dysfunctions can be found in behavior, cognition, coping capability, physiology, hypothalamic–pituitary–adrenal and immune functioning. Typical antipsychotics, beyond their fear-and anxiety-reducing properties, restore most of the psychotic symptoms, such as delusions and hallucinations, but usually leave the negative symptoms, such as lack of drive or emotional withdrawal, unaffected (Wolkowitz end Pickar, 1991). The advantage of the atypical antipsychotics may be considered their beneficial effect just on these negative symptoms. Pharmacologically, the advantage of atypical antipsychotics has been ascribed to the fact that they not only interfere with dopamine, but have strong serotonin-blocking properties as well. With respect to stress, little attention has been given to the beneficial effect of antipsychotics on the different functional systems that contribute to the stress response. The present article, therefore, tries to highlight the various functional systems that underlie the mechanism of stress processing in schizophrenia and to discuss the beneficial effect of antipsychotic treatment upon them in order to obtain a more integrated view on stress and adaptation in schizophrenia.

2. Stress in schizophrenia

In schizophrenia, stress has been predominately described in terms of the impact of “life events” and expressed emotions (EE). In several studies, the impact of stressful “life-events” on psychotic decompensation and relapse frequency has been well established (Birley and Brown, 1970; Nuechterlein et al., 1994). Furthermore, the degree of EE within a family has been described to worsen or ameliorate decompensation in schizophrenic patients, respectively, once the disease has developed (Nuechterlein et al., 1992). Even more important may be the observation that in contrast to major life events, relative minor stresses, or the so-called “daily hassles”, seem to determine by large the subjectively experienced stress in schizophrenic patients, and, to some extent, the amount of positive symptoms that are expressed. These relative minor stresses may even be predictive of relapse susceptibility (Norman and Malla, 1994). The assumption that stress is involved in the actual onset of a schizophrenic illness is far less clear and usually only reported in a minority of patients (Gruen and Baron, 1984). Nevertheless, stress reduction through early intervention, social skill training and/or family education has been proven valuable in the management of psychosis (Falloon et al., 1985; Falloon, 1992; Liberman et al., 1986). This may hold even more so for the use of

antipsychotics and anxiolytics in the treatment of psychosis (Wolkowitz and Pickar, 1991). However, even when patients are adequately treated with antipsychotic medication and social support, they are only partially protected and still susceptible to stress (Barrelet et al., 1990). This suggests that schizophrenic patients may have an altered sensitivity to stress. This sensitivity to stress in schizophrenic patients has been conceptualized in the vulnerability-stress model with respect to etiology and pathogenesis of schizophrenia (Zubin and Spring, 1977; Walker and Difioro, 1997). In this model, schizophrenia is described as the result of a complex interaction between biological and psychosocial factors, the former being genetically determined, the latter being predominantly developed during life, which both contribute to the individual's vulnerability to develop a psychosis under stressful circumstances (Nuechterlein et al., 1994). Schizophrenic patients are hampered both in the effective use of coping strategies and in their cognitive performance. They also display abnormalities in ANS and hypothalamic–pituitary–adrenal function, particularly in their *response* to stress. It may therefore be concluded that patients with schizophrenia suffer from stress because they are maladapted to their environment, based on the aforementioned principles. Whether this is genetically determined or acquired during life or through disease remains difficult to discern. Support for at least some genetic involvement of maladaptation in schizophrenia may be derived from adoptive studies. Stress more easily triggers a psychosis in adoptees with a genetic load for schizophrenia as compared to those that have no such genetic background (Tienari, 1991). It has therefore been suggested that schizophrenic patients may already have a genetically altered sensitivity to their environment (Kendler and Eaves, 1986). From this point of view, it is necessary to get insight in, for instance, how the hypothalamic–pituitary–adrenal system develops during life and what factors determine how it is able to adapt to a constantly changing environment.

2.1. Coping

Coping is defined as the ability of an individual to use different coping strategies, i.e. behavioral, cognitive and emotional responses, in different stressful situations in order to be able to master this situation and reduce the impact of the stress that comes from it (Folkman and Lazarus, 1985). In order to cope successfully, one should rather be able to apply different strategies in various settings than rigidly apply the same strategies in different situations (Lester et al., 1994). In general, one can discriminate passive and active coping styles. Patients with schizophrenia tend to use passive and avoiding coping strategies in stressful situations. They seem less goal-directed. This may on one hand be helpful in avoiding stress in daily life, but may also be a limitation to their adaptive capabilities (Van den Bosch et al., 1992). Furthermore, this type of coping style has been described to be associated with poor cognitive functioning (Van den Bosch and Rombouts, 1997). Coping abilities seem best preserved in those patients who suffer the least from negative symptoms and have a high level of illness awareness (Middelboe and Mortensen, 1997). Although the trend in most studies is directed towards this kind of coping behavior in schizophrenic patients, the actual way coping is usually assessed differs in most. Many studies use their own coping questionnaire, which makes it difficult to make comparisons. Moreover, most studies only measure generalized coping behavior and hardly address coping in relation to an actual event. When exposed to the stress of a public speaking task, the preference for a passive coping style can be found in schizophrenic patients, which appeared to be negatively correlated to the magnitude of the cortisol response (Jansen et al., 2000a). This may be regarded as a first attempt to find biological correlates for coping behavior. Coping, however, is such a complex behavior that it will remain difficult to unravel its biological underpinnings.

2.2. Cognition

The cognitive deficits in schizophrenia have been extensively described over years and actually show that schizophrenic patients are recognized by having a general deficit that is already present early in the course of the disease process and remains relatively unaltered over time (Sharma and Mockler, 1998; Hoff et al., 1999; Purdon et al., 2000). Deficits have been described in many cognitive domains among which attention, executive functions, verbal and visual memory recall, working memory, visiospatial abilities and fine motor skills (Flor-Henry and Yeudall, 1979; Kolb and Whishaw, 1983; Palmer et al., 1997; Aleman et al., 1999). The main brain areas that are involved in these cognitive processes are the medio-temporal and prefrontal cortical regions, the motor cortex and the basal ganglia (Frith, 1995). They all contribute to the different cognitive dysfunctions described, indicating that cognitive impairment in schizophrenia reflects rather diffuse brain dysfunctioning, than a single structure defect (Saykin et al., 1994). Cognitive deficits haven been reported to be associated with poor social functioning (Brekke et al., 1997) and to be independent of psychotic symptoms (Laws and McKenna, 1997). The fact that cognitive impairments are a core feature of the schizophrenic syndrome and already present at an early stage may suggest that schizophrenic patients are, innate, less well adapted to their environment. In favor of this hypothesis is the notion that mild cognitive dysfunction in adolescents has been shown to be predictive of predisposition to schizophrenia in adulthood (Davidson et al., 1999). Moreover, cognitive impairments can already be found in first degree relatives

of schizophrenic patients (Sweeney and Haas, 1992; Staal et al., 2000). From this perspective, cognitive impairment in schizophrenic patients is less supportive for the development of adequate coping and thus stress management. Antipsychotics, particularly at an early stage, are able to improve cognitive performance in schizophrenic patients and may even protect against deterioration of the disease process (Gold et al., 1999). Atypical antipsychotics, seem preferential in this respect, since they lack the inhibiting effect of typical neuroleptics on motor behavior, and seem able to improve attention, and more specific working memory processes (Sharma and Mockler, 1998; Purdon et al., 2000). Thus, neuroleptics enhance cognitive functioning and may therefore be also beneficial for the adjustment to the environment besides their antipsychotic effect.

Already at the pre-attentive level of the attention process, schizophrenic patients show impairments. Schizophrenic patients seem less able to detect and process novel stimuli (Baribeau-Braun et al., 1983). They are also less able to focus their attention to one source of incoming information when several sources are offered (McGhie and Chapman, 1961). Thus, schizophrenic patients display a loss of the selective function of attention. Furthermore, schizophrenic patients have difficulty in filtering incoming stimuli. This process of "sensory gating" prevents the normal functioning brain from a sensory overload by filtering out irrelevant stimuli. Quantification of the sensory gating process can be assessed by suppression of the "P50" potential and the prepulse inhibition (PPI) of the startle reflex. The P50 is a cortical evoked potential wave, appearing in the electroencephalographic spectrum about 50 ms after the administration of an auditory stimulus. When a conditioning stimulus is presented before the testing stimulus, the P50 potential to the testing stimulus will be diminished. The PPI of the startle reflex measures the eye blink reflex with electromyography in response to a rather loud auditory stimulus. When preceded by a weak pre-pulse stimulus, the actual startle reflex is reduced. Both P50 suppression and PPI appear to be correlated at an early stage in healthy individuals (Oranje et al., 1999). In schizophrenia, defects in both P50 and PPI have been reported. Schizophrenic patients show less reduction of the P50 potential in response to a stimulus, both in medicated and unmedicated condition (Freedman et al., 1983). They display less reduction of the startle reflex in response to the pre-pulse stimulus (Braff and Geyer, 1990) and have a deficit in the habituation of the startle reflex (Geyer and Braff, 1987). A loss of sensory gating can also be found in first degree relatives of patients with schizophrenia (Siegel et al., 1984) and in subjects at high risk for developing schizophrenia (Dawson et al., 1995). Together with the notion that the loss of sensory gating seems independent of psychotic state, it may be suggested that it reflects rather a trait than a state phenomenon (Baker et al., 1987). Thus, in schizophrenia, a loss of sensory gating may result in an overflow of the brain of irrelevant stimuli and may therefore alter perception of the environment. This may have repercussions for the way a stress stimulus is interpreted. Another consequence is the lack of habituation to repetitive stimuli that they display. By not being able to habituate, which is generally considered the simplest form of learning, schizophrenic patients may have difficulty in learning from their encounters. Typical neuroleptics do not seem to have much effect on PPI dysfunction (Braff et al., 1999). Atypical neuroleptics, however, seem to be able to restore the PPI to some extent and are preferential in this respect over typical neuroleptics (Kumari et al., 1999; Oranje et al., work to date). By doing so, they may improve interaction with the environment and, through this, may add to their protective effect against stress.

2.3. The autonomic nervous system

Fear and anxiety as well as arousal are often described in terms of increased activity of the autonomic nervous system. Both heart rate, blood pressure and skin conductance activity may be used as read-out parameters. The former two reflect both sympathic and parasympathic activity, whereas the latter reflects only sympathic activity. An increased heart rate in schizophrenia is a consistent finding in literature, although most studies are concerned with response activity to stimuli, rather than with measurements under basal condition. Although this would suggest that schizophrenic patients are in a constant state of increased arousal, or highly vigilant, the use of medication, particularly those with anticholinergic activity, has been suggested to be, at least in part, due to this phenomenon (Tarrier et al., 1979; White et al., 1987; Jansen et al., 2000a). The same may hold for skin conductance measurements, although here, two different mechanisms appear to be involved. One may discriminate *tonic skin conductance level* (SCL) and the *nonspecific skin conductance responses* (NS-SCR), both reflecting arousal and activation, and the stimulus specific *phasic* or *skin conductance orienting response* (SC-OR), rather reflecting attention and information processing (Dawson et al., 1994). There are two major findings in schizophrenia. There is a group of patients that displays high tonic SCL and a high frequency of NS-SCR (White et al., 1987; Kim et al., 1993; Dawson et al., 1994). These patients also display high systolic blood pressure and heart rate levels (Gruzelier and Venables, 1975). This highly state of arousal is thought to be related to psychotic episodes, and to be predominantly caused by environmental stress (Dawson et al., 1994). Second, there is an increased rate of nonrespondance with respect to the SC-OR, as compared to the nonrespondance rate in the normal population (Gruzelier and Venables, 1972; Bernstein et al., 1982; Bernstein and Riedel, 1987; Dawson and Nuechterlein, 1984; Ohman, 1981). This nonrespondance in schizophrenic patients is not based on a physical dysfunction, since they may respond, provided the

intensity of the stimulus is increased. This suggests that nonrespondance reflects either a heightened threshold for SC-OR, or a state of under-arousal in these patients that may also be considered attentional dysfunction. In this respect, nonrespondance at SCL may resemble nonrespondance at the cortical potential level, both reflecting attentional deficits. Although both tonic SCL, nonspecific response rate and the SC-OR are sensitive to the anticholinergic activity of psychotropic medication, the effects of medication on the SC-ORs is less marked. Nonrespondance with respect to SC-OR is found in medicated and unmedicated patients (Straube, 1979; Nuechterlein and Dawson, 1984; Zahn et al., 1991), suggesting that it is not merely a side effect of a peripheral cholinergic deficit caused by medication. Nonrespondance seems not only related to negative symptoms, but more to severity of symptoms of the whole schizophrenic syndrome. There is an association with poor cognitive functioning, but not always with poor social adjustment (Ohman et al., 1989; Ohman and Ohlund, 1989; Wieselgren et al., 1994; Brekke et al., 1997). It has been postulated that an increased tonic SCL may be a state-sensitive episode indicator, whereas phasic electrodermal hyporesponsiveness may be regarded as a mediating vulnerability factor (Dawson et al., 1994) also present in subjects at high risk for schizophrenia (Dawson and Nuechterlein, 1984). However, increased SCL and hyperresponsiveness have also been found in subjects at high risk for schizophrenia (Dawson and Nuechterlein, 1984; Hollister et al., 1994), indicating that probably both an increased state of arousal and attentional deficits, as reflection of nonresponsivity may be trait characteristics. If this would be the case, both phenomena may alter perception of the environment in their way at different stages in a psychotic process.

2.4. The hypothalamic–pituitary–adrenal axis and stress responsivity

Unlike in depression and PTSD, where hypercortisolemia and hypocortisolemia respectively have been well established, in schizophrenia disruptions of basal hypothalamic–pituitary–adrenal rhythmicity or cortisol concentrations are less obvious. Hypercortisolemia has been described in schizophrenic patients (Gil-Ad et al., 1986; Whalley et al., 1989; Breier and Buchanan, 1992), as well as impairments on the dexamethasone suppression test (for overview, see Tandon et al., 1991), and the combined CRH/dexamethasone test (Lammers et al., 1995). Although they are less pronounced as compared to findings in depression, it has been suggested that increased cortisol levels in schizophrenia reflect the depressive symptoms in this disorder or the negative symptom complex that is often intermingled with depressive symptoms. If this would be the case, one could argue whether one should interpret hypercortisolemia as related to “mood” or “stress”. However, many studies have shown basal cortisol concentrations in schizophrenic patients not to be different from those of controls (Kemali et al., 1985; Roy et al., 1986; Van Cauter et al., 1991; Risch et al., 1992; Rao et al., 1995; Jansen et al., 2000a). Here, the use of neuroleptics should be considered in interpreting the findings. Acute administration of neuroleptics decreases plasma levels of cortisol due to their anticholinergic activity (Meltzer, 1989; Wik, 1995). This may hold even more so for the use of atypical neuroleptics for their strong serotonin blocking properties (Kahn et al., 1994; Scheepers et al., submitted). However, chronic use of neuroleptics appears to restore this initial decrease, since under these circumstances usually unaltered cortisol levels are found (Meador-Woodruff and Greden, 1988). Moreover, normal cortisol concentrations can be found in both medicated and unmedicated patients (Rao et al., 1995).

Relatively little research has been performed on the biological aspects of stress and adaptation in schizophrenia (see Table 1). Few studies report a blunted cortisol response in schizophrenic patients in anticipation of a stressful event such as lumbar puncture (Breier et al., 1988), a surgical procedure (Kudoh et al., 1997, 1999) or a set of psychological and physical stresses such as cold pressor, mental arrhythmic and noise (Albus et al., 1982). We reported a blunted cortisol response with intact autonomic function during a public speaking task (Jansen et al., 1998). In a second study, this blunted cortisol response appeared to be selective for the psychosocial stress, since it was not found when physical exercise was used as stressor (Jansen et al., 2000a). A normal cortisol response has also been reported when metabolic stress was induced upon schizophrenic patients (Kathol et al., 1992; Breier and Buchanan, 1992; Elman et al., 1998). Since direct pharmacological stimulation of the hypothalamic–pituitary–adrenal axis by serotonin agonists such as *m*-chlorophenylpiperazine induce a normal increase of pituitary–adrenal hormones in schizophrenic patients (Kahn et al., 1994; Scheepers et al., 2000 submitted), one may assume that the axis itself is intact. Thus, it may be, that stress *processing* in schizophrenic patients is normal to some extent and is only partially impaired in relation to more psychological/psychosocial events.

2.5. The immune system and stress responsivity

More recently, the immune system, besides the endocrine system, is subject of investigation in psychiatric disorders as a second system strongly responding to stress. Even more than with the endocrine system, findings are often contradictory, not only for the large amount of immune parameters that can be measured, but also for the susceptibility of this system for a variety of confounding factors (Haack et al., 1999). In schizophrenia, but also in depression, changes in the levels of various cytokines have

Table 1
Stress tests used in schizophrenic patients

References	Subjects	Methods	Results
Albus et al. (1982)	12 schizophrenic patients, 63 healthy controls	Autonomous and cortisol response to psychological stress (cold pressor, noise, mental arithmics and active relaxation)	Blunted cortisol responses in schizophrenic patients
Breier et al. (1988)	10 drug-free schizophrenic patients, 12 drug-free depressed patients, eight healthy controls	Plasma ACTH, cortisol and growth hormone response to lumbar pucture stress	Blunted ACTH, cortisol and growth hormone response to stress in schizophrenic patients, but not in depressed patients, nor the healthy controls
Kathol et al. (1992)	five schizophrenic patients, seven depressed patients, 13 healthy controls	Plasma ACTH and cortisol response to 2-deoxyglucose induced hypoglycemia	Normal ACTH and cortisol responses in schizophrenic patients, but blunted responses in depressed patients
Breier and Buchanan (1992)	nine schizophrenic patients, seven healthy controls	Plasma progesterone and cortisol response to 2-deoxyglucose induced hypoglycemia	Increased progesterone response to stress in schizophrenic patients, but normal cortisol responses to stress
Kudoh et al. (1997)	22 schizophrenic patients, 20 matched controls	Plasma ACTH and cortisol response to a routine surgical procedure	Blunted ACTH and cortisol response in patients
Jansen et al. (1998)	10 schizophrenic patients, 10 matched controls	Heart rate and salivary cortisol response to public speaking stress	Normal heart rate response, but blunted cortisol response in patients
Elman et al. (1998)	13 schizophrenic patients, 11 healthy controls	Plasma ACTH and cortisol response to 2-deoxyglucose induced hypoglycemia	Increased ACTH response in patients, but normal cortisol response
Kudoh et al. (1999)	25 schizophrenic patients, 25 normal patient controls in need of abdominal surgery	Plasma norepinephrine, ACTH and cortisol in response to surgical stress	Decreased norepinephrine, ACTH and cortisol responses to surgical stress
Jansen et al. (2000a)	18 schizophrenic patients, 18 matched healthy controls	Heart rate and salivary cortisol response to (1) public speaking stress and (2) physical exercise stress	Normal heart rate response to both (1) the public speaking stress and (2) exercise. Blunted cortisol response to (1) the public speaking stress, but normal cortisol response to (2) exercise

been reported (Maes et al., 1995; Naudin et al., 1996, 1997; Wilke et al., 1996; Frommberger et al., 1997), both in medicated and unmedicated patients (Bessler et al., 1995). However, negative findings have also been reported (Rapaport et al., 1997). Different cytokines are produced from two types of T-helper cells: Th1 and Th2 cells. Th1 cells produce the *pro-inflammatory cytokines* (gamma-interferon, interleukin-1, interleukin-2, interleukin-6 and tumor necrosis factor-alpha and -beta (TNF-α and TNF-β)), which promote delayed-type cell-mediated immunity (Salgame et al., 1991) and are thought to facilitate the development and exacerbation of autoimmune diseases. Th2 cells produce *anti-inflammatory* cytokines (interleukin-4, interleukin-5, and interleukin-10, which provide help for B cell differentiation and humoral responses (Yssel et al., 1992), involved in allergic reactions or parasitic infections. During acute stress, there is an activation of the immune system, reflected by an increase in the number of circulating B cells, T cells and natural killer (NK) cells and a decreased production of macrophage- and lymphocyte derived cytokines. (Herbert and Cohen, 1993). This decreased number of lymphocytes probably reflects a change in lymphocyte distribution by which lymphocytes are present in the right compartments and at the right time to enhance immune vigilance for potential immune challenge (Dhabhar et al., 1995). This means that the decreased number of immune effector cells points to enhancement of immune preparedness. On the other hand, a decreased production of certain cytokines and a decreased proliferative response of lymphocytes to mitogens in vitro point to immunosuppressive effects in order to prevent unrestrained amplification of immune processes. Although it has been suggested that certain cytokines, such as interleukin-6 and interleukin-2, are particularly related to either depression or schizophrenia, it has also been suggested that changes in immune parameters reflect a rather nonspecific stress response in patients in general (Frommberger et al., 1997). However, most studies are concerned with single measurements and only at basal condition, making it far premature to draw conclusions with regard to involvement of specific cytokines in psychiatric disorders. To the contrary, direct administration of different cytokines, such as gamma-interferon and interleukin-2, are able to induce either depressive (Meyers, 1999) or psychotic symptoms (Denicoff et al., 1987). These phenomena emphasize the possibility that indeed immune mediated effects of stress may have repercussions for their effect upon the brain. Where typical neuroleptics do not seem to interfere with immune parameters (Pollmächer et al., 1997), the atypical neuroleptic clozapine appears to affect several immune factors sub-

stantially (Maes et al., 1997; Monteleone et al., 1997). Whether these effects are merely pharmacological or have any functional relevance remains to be investigated.

3. Concluding remarks

Considering all functional systems described, it can be learned that in schizophrenia, dysfunction of these systems may all contribute to the way stress is processed in schizophrenic patients. When regarding the type of stress response to psychosocial stress, at the level of the hypothalamic–pituitary–adrenal axis, blunting of the cortisol response could be interpreted as reflecting rather cognitive dysfunction, i.e. misinterpretation of the situation or the stress stimulus, based on biological dysfunction in those brain structures that are responsible for these processes. For instance, to be able to perform in a public speaking task, it is necessary to generate some goal-directed behavior and to interpret the context of a social situation. Both the prefrontal cortex and the limbic system (i.e. the amygdala–hippocampus complex) are involved in these processes. These regions have been widely described in schizophrenia to be dysfunctional and this has been a/o attributed to dysfunction of the mesolimbic, mesocortical dopamine tracts here. Schizophrenic patients are therefore probably not able to respond properly to a certain stimulus (Weinberger, 1987). In favor of this hypothesis is the observation in healthy subjects that the administration of a low dose dopamine is able to facilitate the cortisol response to a cognitive performance, that in itself, in a control condition, is not challenging enough to elicit such a cortisol release (Oranje, work to date). If the above-described indeed reflects some of the biological underpinnings of stress responsiveness and thus vulnerability, this should be investigated in first degree relatives of schizophrenic patients and in subjects at high risk, not only for the overlap in cognitive dysfunction that these subjects already display. In childhood-onset schizophrenia, a similar pattern of cortical pathology can be found as in adult-onset schizophrenia (Bertolino et al., 1998) and we reported a similar disturbance in psychosocial stress response in children at high risk for developing schizophrenia (Jansen et al., 2000b), but not in autistic children (Jansen, work to date). Furthermore, Alzheimer patients, sharing similar cognitive dysfunction with schizophrenic patients, also show a blunting of their cortisol response to lumbar puncture stress (Petrie et al., 1999). However, the stress response as reflected by the release of cortisol, is only the final step in a cascade of preceding events and is meant to adapt the organism to the environment. If the psychosocial stress response such as described in schizophrenia may then be regarded as maladaptation, it may be suggested that malfunction of the hypothalamic–pituitary–adrenal system, as mediator of the stress response, has repercussions for the effect of stress upon psychosis. This could be explained by the fact that the hypothalamic–pituitary–adrenal system, by not releasing cortisol, is not able to properly restore the effects that have been set in motion by the stressor, i.e. catecholamine release, activation of the immune system or other factors that are still unknown. The impact of these factors, for which the cytokines with their psychomimetic properties seem the most promising, may provide some further insight in the mechanism underlying stress sensitivity in schizophrenia. Both the hypothalamic–pituitary–adrenal and immune system have reciprocal effects upon each other and the central nervous system. It is suggested, at least in animals, that the hypothalamic–pituitary–adrenal system directs the Th1/Th2 balance for the preference that corticosteroids display for Th2 cells (Daynes and Araneo, 1989). If this would indeed be the case, failure to produce adequate amounts of cortisol may influence the Th1/Th2 balance in favor of the Th1 cells and the corresponding cytokines. Regarding this, the Th1-related IL2 is of interest, since this cytokine is thought to be mainly involved in schizophrenia, is thought to be particularly related to cognitive impairment (Müller and Ackenheil, 1998), and is known to be able to elicit psychotic symptoms (Denicoff et al., 1987).

Finally, neuroleptic treatment is not only effective in the reduction of stress by reducing fear and anxiety and psychotic symptoms. Neuroleptics, with a preference for the atypical ones, appear effective in restoring some of the cognitive dysfunctions that schizophrenic patients display as well. By doing so, they may enhance perception of the environment, improve adjustment and a proper stress response. The integration of all these processes in stress research may provide new vistas of the stress concept in schizophrenia, and improve stress management in the future.

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