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Cortisol responsivity in chronic schizophrenia: The effects of treatment environment

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CORTISOL RESPONSIVITY IN CHRONIC SCHIZOPHRENIA: THE EFFECTS OF TREATMENT ENVIRONMENT

by

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Cortisol Responsivity in Chronic Schizophrenia:

The Effects of Treatment.

BY

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CORTISOL RESPONSIVITY IN CHRONIC SCHIZOPHRENIA: THE EFFECTS OF TREATMENT ENVIRONMENT

Sonia Anne Partridge, Ph.D.

University of Nebraska, 1994

Advisor: Will Spaulding

Cortisol secretion has predictable features including a stable diurnal rhythm with additional secretory activity occurring to challenging, stressful or novel events followed by rapid habituation with subsequent exposure to the same stimuli. The present study examined cortisol functioning in long-term hospitalized chronic schizophrenic individuals under two conditions: the everyday ambient environment of a hospital ward and during exposure to a novel, challenging situation. A subsequent retest four months later examined whether habituation had occurred following reexposure to the challenge task. Subjects were drawn from two treatment environments that differed in level of active treatment programming. One was an intensive, Biopsychosocial Rehabilitation Program that provided an all waking hours active treatment program aimed at building functional skills. The second was a custodial ward where the primary focus of treatment was psychotropic medications in the context of custodial care. The findings indicated that treatment environment was related to cortisol responsivity.

Subjects from the active treatment program showed an expected increase in cortisol while completing a challenging, novel task at time-one and no increase in cortisol at time-two, suggesting habituation to the task. They also showed stability in cortisol taken under ambient ward environment conditions. Subjects from a custodial ward had lower levels of cortisol overall and did not show an expected increase in cortisol during challenge and showed instability in cortisol taken during ambient environment. Previous research finds a pattern of cortisol dysregulation in schizophrenia characterized by tendencies towards hyporesponsivity and hyperresponsivity. The current research suggests that active treatment programming that provides opportunities for daily challenge may lead to a normalizing of cortisol response in chronic schizophrenic individuals. HPAC dysfunction in chronic schizophrenic populations and the implications for treatment programming is discussed.

Dedicated to

my Grandmother

Priscilla Partridge

and Friends

Paul and Brad

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Given that even moderate changes in everyday stress can exacerbate symptomatology of schizophrenia (Liberman et al, 1986), understanding this process may improve treatments for normalizing stress-vulnerability in this population. At one level, physiological and endocrinological mechanisms mediate this process. One endocrinological indicator of stress arousal is circulating levels of cortisol, a hormone produced by the adrenal glands.

The present study extends understanding of cortisol secretion in normal individuals to a schizophrenic population. As will be reviewed in detail below, normal cortisol response has some predictable characteristics with two prominent features being a diurnal rhythm within a normal blood level range (Mason, 1968). Outside of this normal rhythm, additional secretory bursts occur in response to broad range of novel, stressful or challenging stimuli with rapid adaption following further exposure to the same stimuli (Mason, 1968). The present study examines cortisol functioning in schizophrenic individuals under two conditions: the everyday ambient environment of a hospital ward and during exposure to a novel, challenging situation. A subsequent re-test examined whether adaption occurred following re-exposure. Subjects were drawn from three treatment environments differing in intensity of active treatment to investigate whether long-term exposure to

particular treatment environments impacts patterns of cortisol responsivity.

The review of the literature begins with a description of the endocrinology of cortisol as it applies to the physiology of the stress response. This is followed by a review of the literature on cortisol in normal populations and schizophrenic populations.

Psychophysiological Bases of Stress

A broad range of neural, endocrine, immune, behavioral and psychological systems are involved in the stress response. While humans are continuously exposed to an array of internal and external events, the experience of "stress" depends on the interaction of individual biological and psychological sensitivities with the occurrence of specific events (Folkman, Schaefer, & Lazarus, 1979). Furthermore, time and experience are important mediating factors in the stress-response. Exposure to stressful events may lead to a variety of deleterious consequences (Newberry, Joikens-Madden & Gestenberger, 1991). For example, continual exposure to moderate stressors can result in somatic complaints (such as gastrointestinal problems) as shown by research on the impact of persistent negative stress on physical health (Everly, 1989.) Severe, uncontrollable stress may result in "physiological exhaustion" as shown in animal research with severe stressors (Selye, 1946).

While "stress" is typically viewed as a bad, some

researchers argue that certain "stress" has negligible long-term impact and is a growth-promoting and positive aspect of life. Dienstbier (1989) argues that challenge experiences can have positive long-term consequences by providing learning and mastery opportunities thereby building "physiological toughness" which strengthens the individual to face future challenges. In support of this view, research finds that individuals high on personality characteristics such as internal locus of control, personal efficacy and willingness to seek out challenge are less susceptible to the deleterious effects of stress, possibly due to having learned successful coping strategies through experience (Kobasa, 1979).

In summary, a thorough analysis of stress responsivity requires consideration of "stress profiles", where outcomes for specific individuals depends on the confluence of psychological, physiological, environmental factors in the context of prior experience.

Physiology of the Stress Response

Seyle's (1946, 1979) "General Adaption Syndrome" model was one of the first to describe the role of physiology in the stress process. First, an "Alarm" stage involves sympathetic nervous system arousal and neuroendocrine action; adrenal medullary stimulation; and the release of ACTH, cortisol, growth hormone, prolactin, thyroid, gonadotropin and a perception of anxiety. Second, a

"resistance" stage occurs where the body attempts a return to homeostasis through built in physiological feedback mechanisms. At this stage, if adaption occurs, "immunity" to further reaction may be achieved. If homeostatic processes are unsuccessful and the stressor is persistent overtime, an "exhaustion" stage is possible with related enlargements in lymphatic structures, organ dysfunction, poorer resistance to disease, and psychological disturbance such as depression. Much of Selye's research was done with animal models using severe physical stressors.

The physiological stress response stimulates three broad biological systems: the neural axes, the neuroendocrine axes, and the endocrine axes (Everly, 1989). A number of endocrine systems are implicated in response to stress. Four endocrine systems have been implicated in response to stress: the hypothalamic-pituitary-adrenal-cortical axis; the somatotropic axis; the thyroid axis; and the posterior pituitary axis (Everly, 1989; McCubbin, Kaufman, & Nemeroff, 1991). The action of the Hypothalamic-Pituitary-Adrenal-Cortical (HPAC) axis, which produces cortisol, is discussed in detail below.

Hypothalamic-Pituitary-Adrenal-Cortical Axis

The hypothalamic-pituitary-adrenal cortical axis, HPAC, (also called the adrenal cortical axis) is the endocrine system that produces cortisol (Kaplan, 1988). The HPAC axis involves activation of the septal-hippocampal complex which

send impulses to the paraventricular nucleus of the hypothalamus, where corticotropin releasing factor (CRF) secretory neurons are located (Newberry et al, 1991). CRF is released into the hypothalamic-hypophyseal portal system and descends the infundibular stalk to the anterior pituitary. The pituitary responds by releasing adrenocorticotropic hormone (ACTH) into circulation. ACTH targets the adrenal cortex on the superior poles of the kidneys. ACTH here stimulates the release of glucocorticoids and corticosterone into systemic circulation. Circulating glucocorticoids regulate rate of secretion through a negative feedback relationship by acting on the hypothalamus to suppress CRF output which limits pituitary ACTH output.

Biosynthesis of Cortisol. Cortisol is produced by the adrenal glands, located on the temporal lobes of the kidneys. The kidneys are highly vasculated, thereby facilitating rapid disbursement of products into the blood stream and throughout the body (Kaplan, 1988). The adrenal glands consist of three functional zones; the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. The zones differ in terms of biosynthetic properties and secretions thus produced.

Cortisol is produced by various biochemical actions on cholesterol (Kaplan, 1988). Cholesterol is taken from the blood by plasma membrane receptors that bind low density

lipoproteins that contain cholesterol. The LDL-Cholesterol is taken into the cells and the cholesterol is esterified and stored in cytoplasmic vacuoles. It remains stored until ACTH stimulates the cholesterol esterase to release cholesterol, thereby providing the base for steroid synthesis. Steroids are produced as needed as little is stored in a ready state for use. The three classes of hormones produced are the glucocorticoids (cortisol and corticosterone), mineralocorticoids (aldersterone and deoxycorticosterone) and androgens (DHEA, DHEA-5, androstenedione).

Cortisol is produced in the middle zona fasciculata of the adrenal gland. The biosynthesis of cortisol is thought to occur as follows. The HPAC releases circulating ACTH which binds to the adrenal plasma membrane receptor on the kidneys. ACTH activates adenylate cyclase which results in increasing cyclic AMP leading to cholesterol release. ACTH stimulation concurrently results in the rate-limiting 20,22-desmolase reaction which leads to the conversion of cholesterol to /\ 5- pregnenolone, the first step in cortisol bio-synthesis. Cortisol is produced through various enzymatic reactions, "/\ 5-pregnenolone is converted to 17 alpha- Hydroxypregnenolone -> 17 alpha-hydroxyprogesterone -> to 11- Deoxycortisol -> to cortisol" (Kaplan, 1988, based on schematic figure, pp 249.)

Temporal Variation in Cortisol: A salient feature of

cortisol is temporal variation in release and circulating levels (Kaplan, 1988). Cortisol is secreted in a circadian pattern with episodic bursts of release. Cortisol production follows release of ACTH by 15-30 minutes and has a half-life of about 70-90 minutes. The highest levels of cortisol occur during the early morning before wakening and absolute levels decrease throughout the day. Based on sample sizes of over 600 normal adults Kirschbaum & Hellhammer (1989) provide the following estimates of normal salivary cortisol concentrations at various times throughout the day: 7-9 a.m., 14.32 +/- 9.1 nmol/l; at 3-5 p.m., 4.50 +/- 3.5 nmol/l; and at 8-10 p.m., 1.96 +/- 1.7 nmol/l. There are between 7-15 releases of ACTH and cortisol throughout the day. The rise and fall of ACTH and cortisol form into a mutual regulatory pattern such that a normal set-point or range of each is achieved under normal circumstances. Under normal stress conditions, cortisol is secreted at the rate of 8-25 mg per day.

The glucocorticoids are essential for life as they are involved in metabolic and catabolic processes as well as the regulation of important body functions under conditions of stress and inflammation with a principle outcome being mobilization of energy reserves (Kaplan, 1988). Cortisol is involved in gluconeogenesis, the conversion of protein in muscles into glucose and glycogen. Normal circulatory processes and renal function requires cortisol. Cortisol