

PREDICTED ROLE OF SECRETIN AND OXYTOCIN IN THE TREATMENT OF BEHAVIORAL AND DEVELOPMENTAL DISORDERS: IMPLICATIONS FOR AUTISM

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The long-term goal of our work is to create a novel treatment for autism and to explain its pathogenesis. Based on a theory that views emotions and emotional behavior as stemming from dysregulations of a unified brain/gut network, we propose a new paradigm for the treatment of mental illness. This chapter reviews evidence that two neuropeptides, secretin and oxytocin, are critical in the conditioning of infant adaptive behavioral patterns and that peptidergic mechanisms are abnormal in developmental disorders such as autism.

Our clinical observations in the treatment of autism justify our laboratory investigations into the role of peptides in the neurological manifestations of visceral diseases encompassing emotional/visceral brain regions abnormal in

autism. Importantly, our studies have thus far demonstrated that (1) visceral inflammation activates visceral/emotional brain regions in areas known to be abnormal in autism; (2) secretin, like oxytocin, activates many of the same visceral/emotional brain regions that are dysregulated in chronic cerebral and visceral disorders such as autism; (3) a structural basis for the mechanisms of action of secretin and oxytocin was clarified; (4) secretin as well as oxytocin is synthesized in the hypothalamus and may act on structures involved in the pathophysiology of autism; (5) secretin and oxytocin localize to perivascular and subependymal regions of the paraventricular hypothalamus, suggesting a chemosensory and secretory function.

We believe autism is the result of an adverse cascade of events that stems from one or more genetic/environmental insults. Over time, if uncompensated, the cascade leads to adverse conditioning of stress adaptation networks and results in various interrelated developmental psychological, neurological and immunological pathology, including autism.

Our laboratory is engaged in efforts to translate clinical experience in the treatment of autistic patients into bench findings. We believe that it is possible, regardless of etiology, to treat autism and related developmental disorders by intervening in stress response mechanisms with exogenous administration of peptide combinations.

I. Introduction

To date, there is no comprehensive treatment for the broad range of autistic symptomatology: seizures (Park, 2003); attentional/arousal dysregulation, attentional deficit hyperactive disorder (Booth *et al.*, 2003); obsessive-compulsive disorder (Hollander *et al.*, 2003); stereotypies (Militeri *et al.*, 2002); social isolation (Iqbal, 2002); attachment disorders (Kobayashi *et al.*, 2001; Tinbergen and Tinbergen, 1983); face recognition deficits (Ogai *et al.*, 2003; Schultz *et al.*, 2003); gaze aversions (Richer and Coss, 1976); gastrointestinal disorders (Gershon and D'Autreaux, 2003; Horvath and Perman, 2002; Horvath *et al.*, 1998; Torrente *et al.*, 2002); and altered heart rate variability (Corona *et al.*, 1998; Graveling and Brooke, 1978). Research in the field of autism and related disorders over the last twenty years has produced a large body of knowledge but has yet to produce any significant therapeutic outcomes. The search for even partially ameliorative interventions is a goal for all parents of autistic children.

Current pharmacologic treatments, such as anti-psychotics, mood stabilizers, antidepressants, anticonvulsants, and single peptides treat single symptoms, often with unacceptable side effects and/or limited therapeutic effects (Ansorge *et al.*, 2004; Coniglio *et al.*, 2001; Dunn-Geier *et al.*, 2000; Kern *et al.*, 2002; Lightdale

et al., 2001; Owley *et al.*, 2001; Posey and McDougle, 2000; Roberts *et al.*, 2001; Sandler, 1999). Psychotherapeutic measures have also been attempted with limited success (Diggle *et al.*, 2003; Langworthy-Lam *et al.*, 2002). Despite great efforts to understand the etiologies of autism and to devise treatments, autism and many severe behavioral disorders are still generally considered to be idiopathic and incurable.

The current paradigm for treating mental illness was greatly influenced by the work of Walter Cannon and Phillip Bard (Bard, 1928; Cannon, 1927). Their work set aside the visceral theory of emotions of William James and Carl Lange (James, 1884; Lange, 1885), who argued that emotional states of well- or ill-being are the result of visceral sensations (see Fig. 1A). Instead, Cannon and Bard argued that

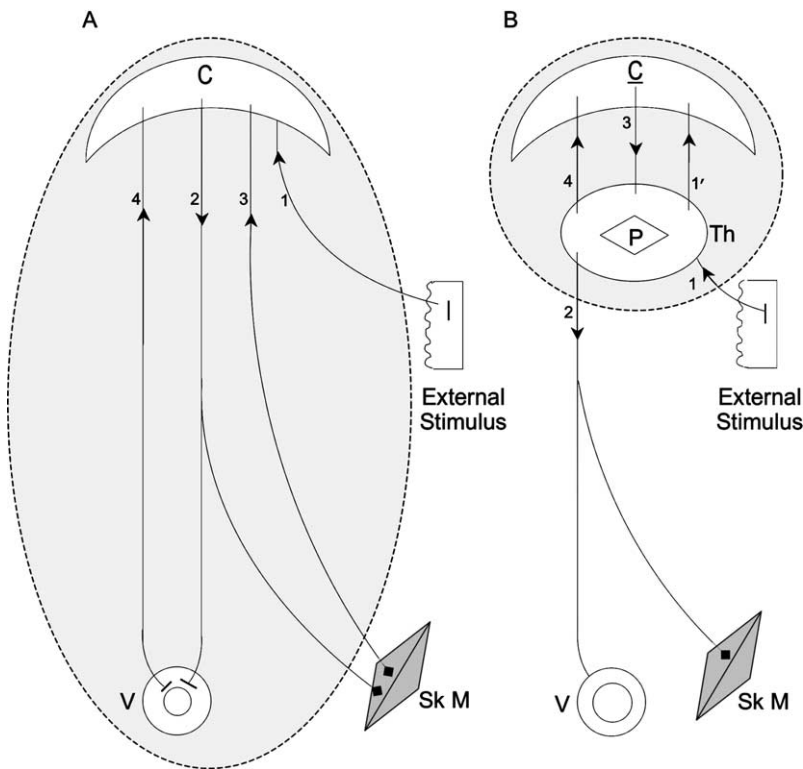


FIG. 1. Modified schematic of (A) James-Lange's visceral theory of emotion (1884–1885). (B) Cannon-Bard's revisionist thalamic theory of emotions (1927–1928) (Lissak and Molnar, 1975). According to James-Lange, emotions are the product of brain and gut, as indicated by bi-directional communication between viscera and brain and dotted line. Cannon-Bard believed emotions are generated entirely in the brain, as indicated by one-way communication from brain to viscera and dotted line. **C** = Cortex; **P** = Pattern Generator; **Sk M** = Skeletomuscle; **Th** = Thalamus; **V** = Viscera.

emotional reactions do not stem from the viscera but result rather from behavioral patterns generated by the thalamus/hypothalamus (Fig. 1B). However, there has since been a growing acceptance that the viscera play a role in the generation of emotions (Damasio, 1994; LeDoux, 1998). Nonetheless, the scientific and health care communities still assume to a very large extent that behavior originates in the brain and therefore, in order to affect behavior, one must intervene in the processes of the brain. This chapter will present findings that support a revised theory on the origin and nature of behavior, one that logically calls for a new paradigm in the treatment of developmental and behavioral disorders.

We will argue that rather than originating in the brain, developmental disorders arise from dysregulation of a unified brain/gut system and are the result of a cascade of interrelated psychological, neurological, and immunological reactions to unmodulated stress (see Fig. 2). Further, we will argue that it is possible to ameliorate developmental and behavioral disorders, regardless of etiology, by intervening in stress mechanisms with treatments that target both the brain and periphery simultaneously.

Clinical observations in the psychiatric practice of Welch form the framework for the concepts reviewed in this chapter (Tinbergen and Tinbergen, 1983; Welch, 1983, 1988; Welch and Chaput, 1988; Welch *et al.*, 2004c, 2006). Two seemingly disparate groups of patients, consisting of maternally deprived orphans and autistic children, were treated for two shared symptom complexes: behavioral symptoms such as lack of direct eye contact, indiscriminate approaches toward strangers, inability to respond to normal maternal nurturing, and odd or restricted food preferences, and gastrointestinal (GI) symptoms such as gut motility abnormalities, discomfort, and diarrhea. Welch developed an intervention that employs intense nurturing as a means of conditioning stress adaptation responses. The intervention led to concurrent amelioration of both behavioral and gut symptoms. In many cases following the intervention, direct eye contact between mother and child ensued, the child was able to benefit from normal nurturing, adverse behaviors were dramatically reduced, and GI symptoms abated. At the end of the intervention, mothers who had previously experienced childbirth often described feeling as though they had just given birth. These collective bedside observations led to a theory that the two groups share a common dysregulation of underlying stress mechanisms.

Welch attributed the striking changes observed between mother and child in the therapy to the simultaneous release of natural endogenous peptides, especially the bonding peptide oxytocin (Uvnas-Moberg 1989; Welch *et al.*, 2004c, 2005, 2006). A serendipitous discovery involving secretin (Horvath *et al.*, 1998) provided an additional candidate for the hypothesized peptidergic mechanism, as well as further support for a brain/gut theory of developmental disorders. Secretin, given as a single dose probe of abnormal GI function in three autistic boys, resulted in improved eye contact and verbal communication. Welch reasoned that treatment with continuous exogenous combined secretin/oxytocin peptides

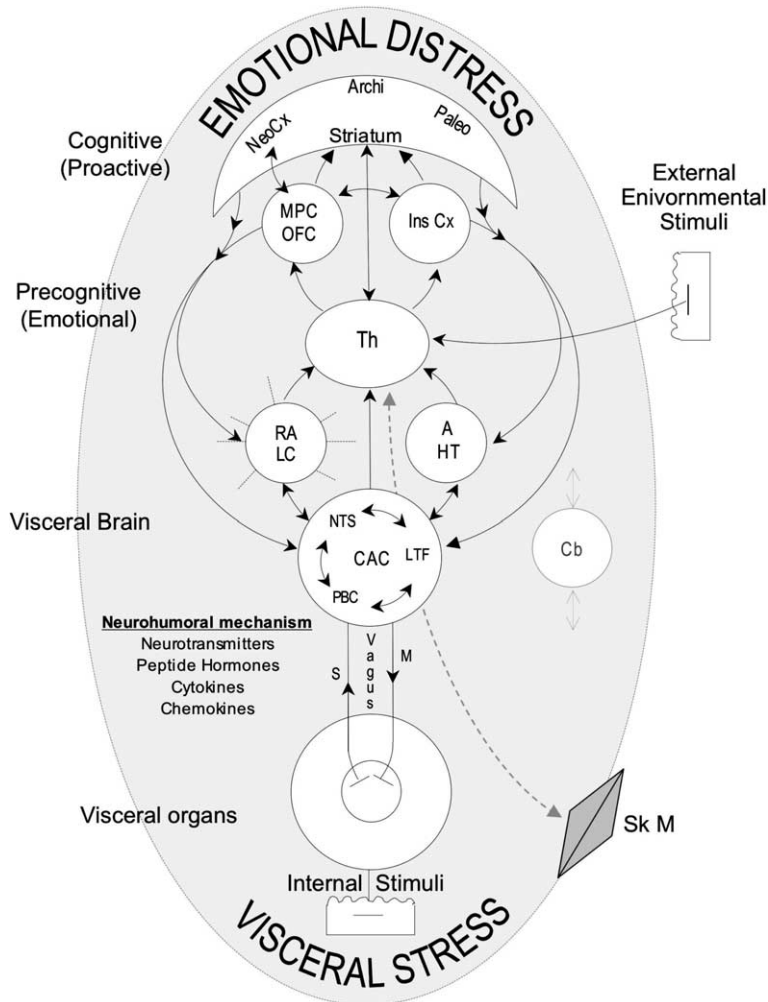


FIG. 2. Abbreviated schematic of the Welch-Ruggiero unified brain/gut theory of emotions. The simplified figure illustrates the fundamental circuits linking the viscera and emotional brain. The structures shown are sites of action of transmitters and peptides in mediating neurohumoral mechanisms sustaining adaptive behaviors accompanying arousal. Shaded area indicates viscera and brain are one system with bi-directional communication between the two, a theory that is in line with James-Lange (Fig. 1A). Most behavioral and pharmacologic therapies continue to target the brain and cognitive processes, assuming as did Cannon-Bard that emotions arise in the brain as a system separate from the viscera (Fig. 1B). **A** = Amygdala; **C** = Cortex; **CAC** = Central Autonomic Core; **Cb** = Cerebellum; **HP** = Hypothalamus; **Ins Cx** = Insular Cortex; **LTF** = Lateral Tegmental Field; **LC** = Locus Coeruleus; **M** = Motor; **MPC** = Medial Prefrontal Cortex; **NTS** = Nucleus of Solitary Tract; **OFC** = Orbital Frontal Cortex; **PBC** = Parabrachial Complex; **RA** = Raphe; **S** = Sensory; **Sk M** = Skeletal Muscle; **Th** = Thalamus; **V** = Viscera.

might replicate the physiological conditions that are elicited in normal reciprocal mother-infant interactions and ameliorate behavioral and GI symptoms in autism (Welch 1983, 1998, 2003b, 2005).

The relationship between brain/gut stress and developmental disorders such as autism is the framework for our scientific investigations. Prefrontal perceptual encoding mechanisms that regulate HPA stress axis and autonomic output to the viscera and immune system are impaired by gestational stress (Berger *et al.*, 2002). It is well established that early environmental stressors can permanently alter perceptual, emotional, intellectual, and social development; in autistic children, all of these are impaired. (Dawson *et al.*, 1998a,b). Autism is associated with high rates of visceral and immune disorders (Gupta *et al.*, 1998, 2000; White *et al.*, 2003) and familial autoimmunity is a risk factor (Szatmari, 1999).

We hypothesize that autism and associated disorders are the result of an adverse cascade of psychoneuroimmunological events that derive from one or more gene/environmental insults or unmitigated stressors. We also hypothesize that early intervention can interrupt the adverse cascade of events, thereby compensating for such insults and averting the further on-going sequelae that lead to severe chronic developmental disorders. Environmental insults can occur in utero or postnatally. Without intervention, the infant's stress profile will result in a failure to activate specific developmental programs, such as glucocorticoid and GABA receptor compositions. The cascade leads to a disruption in the stress-regulatory system of the developing infant, impairing ability to benefit from the caregiver's nurturing or stress-modulation. This disruption results in an interruption of key genetic developmental programs that are normally activated by peptidergic mechanisms. In the face of genetic/environmental stressors, the excess demands on the infant's stress-regulatory mechanisms make peptide modulation critical.

The failure we further hypothesize, persists until the peptide balance is restored. The earlier the silenced or arrested gene programs are activated by successful intervention, the less stress-induced damage will occur. Conversely, the longer the infant is unable to receive stress modulation, the more the infant's adaptation to environmental and emotional challenges is adversely conditioned. In such cases, in the face of unremitting environmental and emotional challenge, the infant adopts various maladaptive defense strategies that result in regressive adverse behaviors and a range of pathology. In the case of autistic children adverse behaviors include stereotypical movements, approach/avoidance behaviors, obsessiveness, compulsiveness, and tantrums.

We will report findings from our laboratory and we will review findings on transmitters and peptides that have been found to be dysregulated in developmental disorders, including peptidergic mechanisms that reset biological systems perturbed pre- and/or postnatally by unmodulated stress. We will examine the role that hypothalamic/gut peptides play in the modulation of these systems, especially as occurs naturally in the process of maternal nurturing. Finally, we will discuss the hypothesis that peptidergic mechanisms may lead to new clinical and

pharmacologic therapies, and chart a future course for research and treatment of autism and related disorders.

II. Background

A. GABA, GENES, ENVIRONMENT, AND PEPTIDES

The fact that GABA inhibitory transmitter systems are genetically altered in autism (Lamb *et al.*, 2002; Ma *et al.*, 2005) is complicated by the fact that GABA receptor genes could also be activated or silenced environmentally (Caldji *et al.*, 2003, 2004). These findings may corroborate our clinical observations. Welch observed that autistic infants who were unable to engage in reciprocal bonding behaviors in response to maternal cues showed dramatic physiological change following successful treatment with intense maternal/infant nurturing (Tinbergen and Tinbergen, 1983; Welch, 1983, 1988; Welch and Chaput, 1988; Welch *et al.*, 2004c, 2006). Hofer may have identified the same phenomenon when he referred to “hidden regulators” of the mother/infant interaction (Hofer, 1994). Recent genetic research using animal models may offer a more compelling explanation of the phenomenon in terms of powerful cellular mechanisms underlying maternal/infant interactions.

Environmental effects can determine the activation status of a gene. It is common to think of gene effects as fixed. In fact, genes are activated or silenced continuously. Therefore, when environmental events silence or fail to activate a gene program, the outcome can be as deleterious as a genetic defect or abnormality, such as the GABA_A receptor gene abnormality on Chromosome 15q11 associated with autism (Menold *et al.*, 2001).

GABA gene/environment interactions found in low-nurture rearing environments may be pertinent to children who do not or cannot benefit from normal maternal nurturing, such as in orphans and autistic children with abnormal face recognition and sensory processing. In animals, the level of maternal nurture that the offspring receives determines which gene programs for GABA receptor subunits are activated. The level of maternal care can permanently alter subunit composition of the GABA_A receptor complex in brain regions that regulate responses to stress, including the amygdala. However, cross-fostering animal offspring of low-nurture mothers to high-nurture mothers reverses the subunit composition by selectively producing specific GABA receptor subunits (Caldji *et al.*, 2003). This finding may explain Welch’s clinical observations that intense components of maternal nurture can ameliorate behavioral symptoms of low-nurture orphans.

In another experiment, cross-fostering of low-nurture animals to high-nurture mothers raised the numbers of glucocorticoid receptors in areas of hippocampus that determine stress reactivity (Meaney, 2004; Meaney and Szyf, 2005; Weaver