ABSTRACT

There is a need for a new pathophysiological model explaining and linking the role of non-genetic factors believed to contribute to origins of many chronic physical diseases. This article presents a theoretical model for explaining the confusing and often contradictory findings regarding the role of environmental influences in chronic illness. A case study of type 1 diabetes is presented to illustrate the applicability of this model. Type 1 diabetes is a disease that has been widely studied, for which clear diagnostic criteria exist, and for which development of effective prevention strategies represents significant challenges.

The model is formulated from the large database of research on our increasing understanding of the interaction between environmental factors, physiology, and autonomic regulatory function. The model integrates data from research in the fields of the experience-dependent maturation of the nervous system and the neurophysiology of traumatic stress. This article describes how disruptions in early bonding and attachment, including adverse events such as traumatic stress, are capable of causing 1) long-term imbalances in autonomic regulatory function and 2) relative dominance of sympathetic or parasympathetic activity.

The proposed model of autonomic dysfunction suggests that ongoing mechanisms promoting high glucose in the context of decreasing insulin production in type 1 diabetes represents a state of relative sympathetic dominance. It is further proposed that this state is influenced by environmental factors, which affect autonomic, immune and endocrine systems during critical period programming. The model also identifies a link between the many seemingly unrelated non-genetic risk factors, and appears capable of explaining contradictions and enigmas in epidemiological and clinical studies regarding non-genetic origins of type 1 diabetes, including the role of stress, variation in age of onset, and duration of the preclinical phase. The case study and model are also helpful for understanding similar environmental contributions to origins of other chronic illnesses, such as multiple sclerosis, rheumatoid arthritis and Parkinson’s disease.
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INTRODUCTION

One of the unexplained pathophysiological processes associated with type 1 diabetes is the seemingly contradictory secretion and production of glucose from multiple physiological mechanisms, such as gluconeogenesis, glycogenolysis and increased secretion of glucagon, which occur in the face of existing elevations in glucose. Despite the fact that relative or absolute insulin deficiency is considered to be the cause of increases in glucose associated with type 1 diabetes, lack of insulin does not account for this aspect of hyperglycemia.

Although peptides, neurotransmitters, and other nutrients affect insulin secretion, glucose is the key regulator. Glucose is the primary and preferred source of energy for the body and is the major and ultimate source for nerve cells, which do not require insulin for the utilization of glucose. Because glucose is so vital to the brain, and because the brain cannot store glucose, the nervous system is intricately geared to maintain a minimum critical level of glucose in the blood. While many hormones influence glucose levels and storage, glucose metabolism is ultimately regulated by the nervous system.

The nervous system regulates not only glucose activity but also interacts with and regulates the immune system. Although type 1 diabetes is described as resulting from an autoimmune process, it is also categorized as a disease of autonomic dysfunction because of the nature of many of the long-term complications.

Non-genetic factors such as stress influence nervous system activity, including the capacity to modulate the regulation of glucose metabolism. Environmental factors are believed to account for greater than 50% of the risk for type 1 diabetes and have been hypothesized to unmask the disease in individuals with a genetic predisposition. This article builds on research describing the influence of environmental factors on the nervous system and presents a new model for explaining the influence of non-genetic factors on the origins of type 1 diabetes. The model integrates neurophysiological findings from the developmental and psychophysiological literature, drawing from two relevant fields of study: 1) the experience-dependent maturation of the nervous system, in which the environment of early experience influences the structural and functional development of the nervous system, and 2) traumatic stress, which is increasingly understood to be capable of exerting complex and frequently long-lasting effects on activity of the autonomic nervous system (ANS). These fields of study have been reviewed elsewhere and important concepts are summarized below to provide a foundation for understanding current perspectives on factors known to influence states of autonomic dysfunction. These principles are then applied to provide a common denominator explaining a link between the varied and seemingly unrelated environmental risk factors for type 1 diabetes.
I. Non-genetic factors affecting ANS function

1. The experience-dependent maturation of the nervous system

Gene-environment interactions during development

The nervous system is immature at birth and maturation takes place in early life during relatively defined periods of time. Pruning of synapses is genetically timed and the number as well as strength of synapses is influenced by interactions with the environment. The contribution of environmental factors is referred to as experience-dependent maturation.

The process of experience-dependent maturation: 1) influences the density of synapses in different tissues as well as variations in density in the same tissues in different individuals, 2) can predispose to relative predominance of sympathetic or parasympathetic activity, and 3) fosters unique individual responses to different types of stress. This process promotes plasticity of the nervous system and facilitates human organisms' finely honed capacity for adaptation to their own unique environments.

Synapse development

Cortical synaptogenesis begins prenatally, peaks by approximately 1 to 2 years of age, and appears to be activity-dependent. Genetically timed apoptosis and elimination of synapses follows and is at least partly environmentally regulated. Timing of cortical synapse elimination varies in different areas, is most dramatic from one year of age through mid-adolescence, and continues at a slower rate in adulthood. Imaging studies used to evaluate growth rates of the developing nervous system have tracked patterns of glucose utilization as a measure of metabolism, synaptogenesis, and plasticity to demonstrate that growth is particularly active between 4 and 9 to 10 years of age, when glucose utilization is at its highest. Levels of growth then decline to reach adult values by the ages of 16 to 18.

During development, nerve pathways that are reinforced, such as through frequent utilization, are generally promoted through the stabilization and strengthening of synapses, while those that are underutilized are reduced through selective pruning. Gene-environment interactions contribute to individuality, take place both in prenatal and postnatal life, and are believed to influence risk for pathology and disease.

Critical period programming

The timing of environmental events most strongly influences developing structures and has the highest impact on organ systems undergoing periods of rapid growth. Critical period programming occurs primarily in prenatal and early life. Adverse events occurring during these times may have long-term and irreversible effects on the developing organism.

Influence of the prenatal environment

Maternal-infant bonding & psychobiological regulation

The experience-dependent maturation of the nervous system is affected by interactions with the environment in general, and by the attachment bond between infant and primary caregiver(s) in particular.
The mother, who’s role has been the most frequently studied in the function of primary caregiver 11,12, serves as a “psychobiological regulator” 11 for her dependent and essentially helpless infant 12. In this capacity, she helps to modulate his or her levels of arousal to facilitate the establishment of self-regulation not only of behavioral rhythms, but also of physiological rhythms, including autonomic, neurochemical, and hormonal functions 11.

Many of the interactions that influence the ANS and the balance between parasympathetic and sympathetic activity occur at an unconscious nonverbal level 34 through a multitude of interactions inherent to parent-infant interactions, including holding, gazing, and soothing 11. The mother’s ability to respond to and to stimulate her infant at optimal levels is influenced by the degree of attunement with her infant, and serves to buffer his or her physiological 12,35 as well as emotional and behavioral responses to stress 11.

Attunement between mother and child is directly affected by the maternal-infant bond, which in turn is shaped by prenatal and perinatal events 11,36. Among the complex factors that influence bonding at birth are the mother’s attitude toward the pregnancy and her perception of available support systems 36,37, her experience of procedures such as amniocentesis 38,39, and her perception of stress during pregnancy 36,40,41.

The sensitive period
Among the most influential perinatal experiences affecting bonding are maternal-infant interactions in the hours and weeks following birth. Early contact during the first day in general, and the first hour postpartum in particular, appears to be of special importance 36,42. During the first hour the newborn exhibits qualities of alertness and exploratory behavior that do not occur again to the same extent for several weeks 36. Contact during this first hour has been found to increase the number of mothers that breastfeed, the duration of breastfeeding 43, or both 36,44-46. In addition, early contact also appears to improve the quality of future behavioral interactions between mother and infant 42,44,47-49 and to reduce the frequency of early infections in the baby during the first months of life 36. Measurable effects have been noted in the quality of maternal-infant interactions and infant development up to one 50 and three years 46 of age following early contact.

Bonding disruption
Separation in early life is associated with changes in hypothalamic-pituitary-adrenal (HPA) responses to stress 51, transient and long-term changes in immune competence in non-human primates 52, and reduced maternal-infant attunement 53. The impact of maternal-infant separation during the sensitive period may permanently alter affectional ties 36, and may consequently influence developing organ systems, including the nervous system 11. Events that affect the ability of the mother to attend to her infant shape the capacity of the newborn to tolerate stress, since the immature nervous system is unable to regulate states of high arousal. Events occurring during labor and delivery that may affect the mother or the infant’s ability to bond include early separation, pain in the mother or infant, the use of medication such as anesthesia, and anxiety, among others 36.

Whereas healthy newborns demonstrate more rapid returns to baseline cortisol following exposure to stress 54, babies born following mild obstetrical
complications have less optimal HPA responses as well as decreased habituation and sensitization to stressors. Maternal-infant separation following cesarean sections is common and appears to negatively impact quality of maternal-infant interactions as well as frequency of breastfeeding.

2. Traumatic Stress

Definition and physiology

The definition of traumatic stress has been summarized as the experience of an event that is perceived by a relatively helpless individual to be both life threatening and inescapable. Although the delineation between different types of stress has been difficult to fully elucidate, useful factors in the characterization of traumatic stress are that it is associated with extreme fear and high emotional charge.

Highly emotional experiences promote the imprinting of an event, along with associated contextual environmental and physiologic cues, into procedural (unconscious) memory. In comparison with other types of conditioning, fear conditioning can occur following one trial and can be extremely long-lasting. The imprinting of highly charged experiences creates conditioned responses that even when extinguished remain stored in memory and available for activation following exposure to an environmental trigger. These characteristics of the nervous system represent innate survival strategies that serve as internal references to promote survival by enabling the organism to respond to future experiences with enhanced rapidity and efficiency.

Traumatic stress is capable of reprogramming the HPA axis and affects ANS regulatory function, resulting in states of exaggerated autonomic cycling and arousal, especially in response to stress. Traumatic stress can also result in states of prolonged sympathetic arousal as well as disruption in the interdependence between the two branches of the ANS.

Risk for ANS dysfunction

Kindling

The term kindling dates from studies of rats in which the repeated use of low intensity electrical stimulus produces or kindles seizures that become self-perpetuating and that require no further stimulus for seizure activity to occur. The seizures are the result of new circuits that are activated and kindled by physiologic and psychological responses to internal and external cues increasingly distinct from the original learned trigger or conditioned stimulus. The conditioned responses that imprint during traumatic stress appear to be mediated by changes in the hippocampus occurring at the time of high arousal. They may also take place through the creation of new cell assemblies, in which neurons that initially fire spontaneously together in response to certain stimuli are more likely to eventually fire without obvious stimulation, a Hebbian model referred to by Ledoux. The concept of kindling is utilized in the neurological literature and in models of traumatic stress.

Reinstatement

Conditioned responses occurring as a consequence of traumatic stress may be quiescent or inaccessible for long periods of time, but appear to remain in procedural memory. Following exposure to an
event similar to the original stimulus 71 or to some unrelated stressful experience 63,64 these memories can be kindled and the conditioned responses “reinstated”. Conditioned responses associated with PTSD such as hyperarousal become activated with increasing ease following exposure to adverse environmental cues. The effects of traumatic stress are consequently considered to be intrinsically self-perpetuating 15,70.

**The role of perception**

Although certain types of events such as earthquakes or the witnessed murder of a loved one are more likely to be experienced as traumatic because of their overwhelming nature, it is the perception of an event rather than the specific nature of an event that influences kindling, reinstatement, and risk for ANS dysregulation 15,60. Risk is influenced by a number of factors, including intensity 72 and degree of life threat perceived during the original traumatic stressor 73, previous experience of trauma 74, and subsequent exposure to seemingly irrelevant as well as related stressors 61. ANS function is also affected by the perceived availability and quality of social supports 61,75 and buffers 61, history of bonding and attachment 15,61,73, and stage of emotional and physiological development, all of which influence the capacity to regulate arousal and to cope with stress 76. Because experiences are unique to each individual, the determination of whether an event is experienced as traumatic, as well as risk for kindling, reinstatement, symptomatology, and disease 11,77 appears to be idiosyncratic 15.

**Risk in early life**

Stress in early life influences the immune and nervous systems, among others 78. Children are at increased risk of perceiving stressful events as intense and life threatening because of their inherent dependence and relative helplessness 14, and are consequently particularly vulnerable to PTSD 15. Risk for adverse physiologic consequences is believed to be due to the high degree of nervous system development 20 that occurs during childhood and to the fact that immature nervous systems are incapable of regulating states of high arousal 11. A strong bond has been found to promote while a disrupted bond to interfere with the ability of a child to regulate arousal 79 and early separation from parents has been identified as an important risk factor for PTSD 80. The experience of traumatic stress in the context of relationship with another human being is one of the most influential risk factors for ANS dysregulation and PTSD 15,61. Secure attachment, on the other hand, is one of the most protective factors against the development of symptoms following exposure to traumatic stress 14.

**Prenatal stress**

Early exposure to non-genetic factors such as stress in prenatal life stimulates the fetal HPA axis 81, can permanently affect the number and sensitivity of glucocorticoid receptors, and can program the HPA axis for life 31,81. Number of glucocorticoid receptors has been found to be proportional to the severity of symptoms of PTSD 82. Maternal exposure to prenatal stress has also been found to predict birth size and gestational age independent of biomedical risk 83,85, and to influence physiological as well as psychological development postpartum 37. Size at birth appears to be influenced by the timing 83 and quality 81,83 of emotional stress experienced by the mother during
pregnancy, as well as by her perceived availability of social support.

**Rate of progression**

The rate at which reinstatement occurs following traumatic stress is idiosyncratic and symptoms of PTSD can occur weeks, months or years following the original event. High intensity initial and subsequent exposure to relevant stressors promotes a more rapid response of neurophysiological hyperreactivity and increases the rate with which reinstatement can occur. Exposure to insufficient stimuli may allow symptoms to resolve after reinstatement or enable a dormant conditioned response to remain inaccessible. Although the development, progression, and resolution of symptoms of PTSD are variable and occur in relatively few individuals following traumatic stress, symptoms are often remarkably refractory to treatment once they develop.

**III. A Model of Autonomic Dysfunction**

The model proposes that dysfunction of the sympathetic nervous system associated with type 1 diabetes is at least partly influenced by exposure to adverse events, including traumatic stress, during the experience-dependent maturation of the nervous system. Initial exposure to such events is suggested to occur during critical period programming of structures relevant to glucose and insulin regulation, such as the nervous system. Kindling and reinstatement of SNS patterns of dysfunction are proposed to occur following sufficient exposure to relevant stressors during periods of programmed synapse pruning and growth, which predominates during preschool age and adolescence. At-risk individuals may fail to develop diabetes or may do so at later ages if they are not exposed to relevant types, number, or intensities of stressors. This is hypothesized to occur because the predisposing conditioned responses of autonomic SNS dysfunction fail to kindle or kindle more slowly.

**IV. Relevance of the model to non-genetic risk for type 1 diabetes**

**Stress, traumatic stress & type 1 diabetes**

Stress has long been suggested, and recently confirmed as a risk factor for type 1 diabetes. Many reports exist describing the onset of diabetes within days or weeks of intense emotional events and traumatic stress was believed by many to be an important risk factor for type 1 diabetes in the first half of the twentieth century. One means by which traumatic stress was believed to cause diabetes was by reactivation of infantile neuroses that were indirectly expressed through the vegetative (autonomic)
nervous system. Models of traumatic stress as a cause of diabetes fell into disfavor, however, when a smaller number of soldiers than anticipated developed the disease following service in World War I and II and direct causal links with psychogenic factors could not be made.

The proposed model provides a framework for explaining the role of stress and trauma in the etiology of type 1 diabetes and suggests that individuals who develop the disease are those who have been exposed to traumatic stress during a specific time in early life and who have experienced appropriate intensity and frequency of subsequent stressors sufficient to promote kindling and reinstatement. From this perspective, the small number of soldiers who developed diabetes would have been the few who had experienced both relevant traumatic experiences during critical period programming in early life so as to be predisposed to patterns of SNS dysfunction and who were also subsequently exposed to sufficient and appropriately timed relevant idiosyncratic stressors.

Stress occurring in the year before diagnosis has been found to be the only variable affecting age of onset in humans in one large study and has been proposed to precipitate rather than initiate the disease. Stress has also been found to reduce the age of onset of diabetes in BB rats.

**Risk factors preceding diagnosis**

A variety of factors occurring in the years preceding diagnosis of type 1 diabetes have been proposed to influence risk. In addition to stress and trauma, risk factors include infection, a cold environment, and seasonality, to name a few. Studies attempting to clarify the relationship between identified factors and type 1 diabetes have frequently demonstrated conflicting results, however. For example, infection is associated with increased risk for type 1 diabetes in some studies, but has been found to be unassociated or even protective in others.

According to the model, it is not the specific nature of an event that represents risk for diabetes, but the idiosyncratic nature in which events are perceived. Such a perspective is consistent with the proposal that stress is the common link between perinatal risk factors for type 1 diabetes as well as risk factors in the period preceding diagnosis. This model predicts contradictions in the identification of risk factors.

Seasonal risk for type 1 diabetes, which is increased in fall and winter in certain age groups, may represent a stressful event and result from increased workload on beta cells. Physiologic increases in SNS activity occur in mammals prior to and during cold seasons as a result of changing energy needs, glucose utilization and storage, and immune activity. Changes in sympathetic activity associated with seasonal variation may promote kindling and reinstatement in individuals predisposed to states of increased sympathetic tone.
Perinatal risk factors

Early separation and stress represent common denominators linking perinatal risk factors

Important environmental risk factors for type 1 diabetes appear to originate during a limited period of exposure in early life and are proposed to be factors to which only children are exposed. These environmental risk factors probably occur during prenatal life and include maternal-related events. Perinatal risk factors proposed for type 1 diabetes include maternal infection, respiratory disease in the newborn, preeclampsia, cesarean section, maternal-child blood group incompatibility and jaundice, amniocentesis and labor complications, shorter gestational age and larger birth size, and certain patterns of intrauterine growth, among others. According to the proposed model, early events affect risk for type 1 diabetes through complex interactions between protective and adverse events that influence experience-dependent maturation of the nervous system. A common denominator among perinatal risk factors for type 1 diabetes is an increased risk for disruptions in maternal-infant bonding, such as occur following stress and early separation.

Intrauterine growth patterns, larger size at birth, and shorter gestation have been proposed to reflect prenatal exposure to non-genetic events such as stress. Prenatal stress in the mother and prenatally for example, may be experienced during many of the identified perinatal risk factors for type 1 diabetes, including procedures such as amniocentesis. The experience of stress may precede the procedure, vary according to the reasons for the test, and last until results have been received. Positive results may be reassuring to the mother and may facilitate bonding whereas abnormal results may impact stress levels as well as bonding.

Early separation was found to be the only factor identified with risk for type 1 diabetes in an animal study evaluating risk associated with jaundice with or without phototherapy. Other identified perinatal risk factors also appear to increase risk for early maternal-infant separation, particularly during the sensitive period immediately following birth. As previously discussed, even brief early separation influences bonding, capacity for physiological self-regulation in the infant, and experience-dependent maturation, and may be perceived as traumatic by the newborn.

Exposure to maternal states of sympathetic arousal during experience-dependent maturation in the first three years of life contributes to predisposition for states of increased sympathetic tone in the infant and in the growing child. Such effects may last into adulthood. Risk factors such as preeclampsia, which has been associated with states of increased sympathetic activity in the mother, may have similar effects, as may cesarean sections, which can be associated with maternal postpartum traumatic stress.

Early life events involve complex idiosyncratic interactions and predict variability in perinatal risk factors rather than strict consistency. The apparent lack of risk associated with some measures of perinatal distress such as reduced Apgar scores may represent contributions from protective factors such as bonding.
Breastfeeding and cow’s milk

Breastfeeding may be protective from risk for type 1 diabetes and shorter duration, as well as lack of breastfeeding are associated with increased risk in most studies. Contradictory findings, however, exist regarding a role for cow’s milk in risk for type 1 diabetes.

Higher rates of separation in early life are associated with decreases in the frequency and duration of breastfeeding. Decreases in duration of breastfeeding can reduce physiological and social bonding and may interfere with protective factors that reduce risk for type 1 diabetes. The idiosyncratic nature of experience and complex interactions between risk and protective factors is consistent with contradictory findings regarding the role of cow’s milk and breastfeeding in risk for type 1 diabetes. According to the model, decreases in breastfeeding and the early introduction of cow’s milk may represent disruptions in maternal-infant bonding.

Timing of diagnosis
Age of onset

Incidence of type 1 diabetes is highest in children and adolescents, and peaks at 2, 3 to 6, and 10 to 14 years of age. Only 25% of individuals develop type 1 diabetes after the age of 21.

The model suggests that life events associated with risk prior to the diagnosis of type 1 diabetes represent idiosyncratic stressors that kindle and reinstate existing conditioned responses of chronic sympathetic arousal. Risk factors are proposed to induce reinstatement during periods of genetically programmed synapse development, which predominate during experience-dependent maturation in early childhood and adolescence.

The preclinical phase

The preclinical phase leading to diabetes is frequently lengthy, lasting up to 10 years or longer. This period has been documented through the presence of autoantibodies as well as through changes in insulin levels, which have been shown to decline up to 11 years prior to the onset of diabetes. The existence of a preclinical phase in diabetes has similarities with the latency period that frequently precedes onset of symptoms of PTSD. This pattern is consistent with the model, in which conditioned responses kindle during latency periods and are reinstated following exposure to sufficient idiosyncratic stressors in conjunction with synapse loss or proliferation.

Rate of progression

Although type 1 diabetes is commonly proposed to occur following exposure to certain environmental events preceding diagnosis, some investigators have proposed that predisposition occurs early in life and that variation in age of onset reflects different rates of disease progression rather than different ages of exposure to critical environmental events. The model supports the latter hypothesis.

Autoimmune activity

It has been proposed that non-genetic risk factors in early life initiate autoimmunity leading to type 1 diabetes while factors preceding diagnosis unmask or accelerate the disease process. The presence of autoantibodies to islet cells, insulin, and glutamate acid decarboxylase (GAD or GAA) is associated with increased risk for type 1 diabetes even though none of these
antibodies are specific for beta cells $^{1,154}$ and 10% of individuals have no detectable autoantibodies at diagnosis $^{10}$.

Autoantibodies can be acquired early in life and develop over a period of months to years $^{155}$. They can fluctuate $^{10}$, exhibit transiency $^{156,157}$, and have been found to remit in 10 to 78% of individuals, perhaps because the offending factor has been removed $^{10}$. Only a small number of individuals with autoantibodies develop type 1 diabetes and highest risk is associated with early expression of IAA $^{158}$. Increased risk is also associated with persistence $^{156}$, sequential progression $^{155}$, and presence of multiple antibodies $^{158}$. The incidence of autoantibodies appears to decrease with age $^{10}$ and conversion to autoantibody positivity is rare over the age of 10 years $^{10,148,153}$.

Although the mechanisms by which autoimmunity plays a role in type 1 diabetes remain unclear, the patterns of incidence, transience, and persistence of autoantibodies in relationship to risk for disease are consistent with models of experience-dependent maturation and traumatic stress. Activation and specificity of autoimmune processes may be regulated by ANS activity and promoted by states of dominant sympathetic activity, which persistently promotes inhibition of insulin and in some states also promotes increases in immune activity $^{159}$. Similarly, fluctuations in autoantibody levels may represent varying stages of kindling influenced by the frequency and quality of exposure to idiosyncratic stressors and buffers. It has been suggested that islet cell autoantibodies (ICAs) may represent secondary markers of islet cell destruction $^{160}$. Progression to disease in individuals who are autoantibody positive has been proposed to depend on sufficient exposure to environmental pathogens or “multiple hits” $^{161}$, a concept also consistent with kindling $^{162}$.

**CONCLUDING REMARKS**

Our growing understanding of the interaction between environmental factors and human physiology provides powerful new perspectives from which to consider the origins of chronic physical disease such as type 1 diabetes. Such a model may be applicable to a developing a better understanding of the origins of other chronic diseases, ranging from type 2 diabetes, to multiple sclerosis and rheumatoid arthritis, to chronic fatigue, fibromyalgia, and multiple chemical sensitivity. The integration of concepts from multiple disciplines represents an exciting frontier that may contribute to identification of increasingly effective prevention and treatment strategies, and concepts presented in this model warrant further study.

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