Hypothalamic-pituitary-adrenal axis dysfunction as a neurobiological correlate of emotion dysregulation in adolescent suicide

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Background: **Biological markers of vulnerability for current or future risk of suicide in adolescents could be important adjuncts to the treatment and prevention of this phenomenon.**

Data sources: **We conducted a PubMed search of all English-language articles published between January 1990 and June 2011 using the following search terms: ("hypothalamic-pituitary-adrenal" OR "HPA") AND ("adolescence" OR "adolescent" OR "teenager") AND ("depression" OR "major depressive disorder" OR "suicidal behavior" OR "suicidal ideation" OR "suicidal thoughts" OR "deliberate self-harm" OR "suicidal attempt" OR "suicide").**

Results: **HPA axis activity can be examined using different methods that do not have the same biological interpretation. An abnormal HPA axis functioning together with an anomalous interaction between HPA mechanisms and other systems such as the serotonergic system may be one of the neurobiological correlates of emotion dysregulation (ED). ED may play an important role in adolescent suicidal behavior. Some psychopathological conditions such as depression or childhood psychological trauma that increase suicidal risk in adolescents are also associated with HPA axis dysregulation. ED, a personality trait, can also be viewed as a predisposing factor that augments the vulnerability to suffer from psychiatric conditions.**

Conclusions: **Correlating HPA axis dysfunction with psychological factors such as ED could lead to a better understanding of the role of HPA abnormalities in adolescent suicide and may enhance preventive and treatment strategies.**

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Key words: **adolescence; hypothalamic-pituitary-adrenal axis; suicide**

Review article

Introduction

Suicide is a complex human phenomenon. It is a leading cause of death in adolescents in post-industrialized societies.[1,2] The epidemiology of adolescent suicide in those societies has shown remarkable changes over the last 100 years. Since the beginning of the 20th century, there has been a steady increase in the incidence of suicide in young men interrupted by reported decreases during the 1st and 2nd World Wars. Two important peaks occurred in the 1960s and the middle of the 1990s.[3] However, since the 1990s, overall rates of suicide in young men started to decline progressively. By 2005 in Britain and 2003 in the USA, adolescent suicide was at their lowest level ever for almost 30 years.[3] This decline could be partly due to the reduction in poisoning from car exhaust gas as a result of the increased number of cars with catalytic converters and to some complex psychosocial factors.[4] Introduction of selective serotonin reuptake inhibitors (SSRIs) may have played a crucial role in the reduction of adolescent suicide rates since the 1990s.[5] In fact, between 2003 and 2005, youth suicide rates increased following the reduction of SSRIs prescription after issuing of public health warnings about the possible association between antidepressant use and suicide ideation.[6]

From a multi-level methodological perspective, adolescent suicide has been related different socio-cultural, psychological, psychopathological, and

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Table 1. Factors related to adolescent suicidal behavior

Socio-cultural factors	Parental separation or divorce
	Parental or other affectively significant losses
	Family discord or domestic violence
	Non-domestic violence exposure
	Affectionless parental bonding style
	Child physical, sexual, and/or emotional abuse
	Problems with friends
	Bullying
	Break-up of romantic relationships
	Binge drinking alcohol and substance use as a type of rite of passage
	High exigencies towards a culturally shaped bodily image
	Internet and mass media diffusion of suicidal behaviors
	Contagion
	Incarceration
	Early school drop-out
Psychological factors	A cognitive inability to retrieve specific autobiographical memories and to produce more general memories
	Poorer decision making abilities
	Higher impulsivity and impulsive aggressiveness
	High maladaptative and adaptative emotional responses
	A tendency to deeper insight
Psychopathological factors	Affective disorders
	Alcohol and other substance use disorders
	Personality disorders
	Posttraumatic stress disorder
	Eating disorders
	Other psychopathological conditions (e.g. conduct disorder, etc)
Biological factors	Hypothalamic-pituitary-adrenal axis hyperactivity
	Deficits in serotonin function

biological factors (Table 1).[1,3,7-13] Clinicians see many adolescents with suicidal thoughts or behaviors who are not all equally at risk for future lethal attempts. While demographic, diagnostic, and other clinical factors are helpful in identifying adolescents at risk for suicide, such factors are sometimes limited in their ability to identify individuals at greatest risk.[1] There is also a significant variation depending on the socio-cultural context where studies are conducted.

At present, physician education in depression recognition and treatment as well as restricting access to lethal means are the two robust evidence-based strategies proven to be effective in preventing suicidal behavior.[14] However, some neurobiological research areas could improve the treatment and prevention of suicidal behavior in the future, including adolescent suicide.[15] A biological marker of current or future risk for suicide could be an important adjunct to the wider understanding by clinicians of this serious dilemma although biological findings will not be the unique clue to achieve a complete comprehension of this life-threatening phenomenon.

We propose that hypothalamic-pituitary-adrenal (HPA) axis dysregulation is a biological marker for emotion dysregulation, which in turn increases a vulnerability to psychiatric disorders and suicidal behavior in adolescents. In this paper, we will review the physiology and pathophysiology of the HPA system, and the role of the HPA axis in the stress response, in the pathophysiology of depression and suicidal behavior, and in some pathological changes associated with childhood abuse.

We conducted a PubMed search of all English-language articles published between January 1990 and June 2011 using the following search terms: ("hypothalamic-pituitary-adrenal" OR "HPA") AND ("adolescence" OR "adolescent" OR "teenager") AND ("depression" OR "major depressive disorder" OR "suicidal behavior" OR "suicidal ideation" OR "suicidal thoughts" OR "deliberate self-harm" OR "suicidal attempt" OR "suicide"). We decided on this time frame because we intended to focus on the recent literatures. Altogether 179 papers were identified. Where a title or abstract seemed to describe a study eligible for inclusion, the full article was obtained and examined to assess its relevance. Two independent researchers conducted the literature search. Any discrepancies between the two reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by consultations with a senior author.

Initially, we reviewed the role of the activity in the emotional regulation of humans. Then, we examined studies that associate HPA axis abnormalities with adolescent suicide. Finally, we analyzed current data about the role of HPA axis dysfunction in depressive disorders, childhood maltreatment, and suicidal behavior in adolescents. Our final aim is to see if the HPA axis irregular functioning could be one of the neurobiological correlates of emotion dysregulation (ED) that put

adolescents at higher risk for suicidal behavior. ED was defined as the deficit in the ability to regulate intense and shifting emotional states.[16]

The HPA axis and emotion regulation

Physiology of the HPA axis

Corticotrophin-releasing hormone (CRH) is the principal hypothalamic regulator of the pituitary-adrenal axis that stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn stimulates the secretion of glucocorticoids by the adrenal cortex.[1]

The amplitude of the CRH pulses augments early in the morning, resulting in increases in the amplitude of the pulsatile ACTH and cortisol secretion which are released episodically in pulses every 30-120 minutes.[17] Peak ACTH concentrations are usually observed at 4:00-6:00 a.m. and peak cortisol concentrations follow 30-45 minutes after awakening. Diurnal variations in the pulsatile secretion of ACTH and cortisol are often perturbed by changes in lighting, feeding schedules and activity, as well as following stress.[18] Therefore, cortisol is routinely assessed several times during the day or at least in a total 24-hour examination or in repetitive determinations (morning, afternoon and/or evening) in order to follow the diurnal variation of cortisol and to eliminate the fluctuations seen in serum samples as a result of the time of day or transient stress.

Many factors affect the HPA axis basal and reactive functioning:[19] age, gender, endogenous and exogenous sex steroid levels, pregnancy, lactation, and breast-feeding, smoking, coffee and alcohol consumption, drug use, dietary energy supply, early life experiences, social factors, psychological interventions, personality, acute subjective-psychological stress responses, and, finally, states of chronic stress and psychopathology. In fact, "chronic" HPA axis activation seems to be more "neurotoxic" than "acute" HPA axis functioning.[17]

Moreover, prolonged activation of the HPA axis by stressors occurring during early prenatal and neonatal ontogeny influences the development of the central nervous system (CNS), thereby affecting epigenetically HPA adult functioning.[20] Excess of maternal CRH and/or cortisol has been associated with impaired fetal habituation to stimuli, and temperamental difficulties in infants[21] as well as prenatal anxiety influences cortisol responses in pre-adolescent children.[22] In addition, separation anxiety during childhood[23] as well as more serious adversities such as child abuse,[24] may finally result in a blunted cortisol response to diverse stimuli later in life. However, as not all individuals exposed to childhood adversities demonstrate altered HPA axis function, physiology, genetic and complex epigenetic variations may be crucial to explain variations in the consequences of trauma exposure.[24,25]

There have been relatively few investigations on the development of the HPA axis during childhood and adolescence, and normative data for cortisol in this population have not been established yet.[26] This fact may be explained by the high variability of the HPA axis functioning depending on a number of factors, including age, gender, duration of stress exposure, type of stressor, and time between stress exposure.[27] Indeed, the available studies indicate that the effects of stress exposure during adolescence differ from and may be longer-lasting than those of the same stress exposure in adulthood.[27,28] In addition, the effects of adolescent stress depend on the duration of stress exposure, type of stressor, and time between stress exposure and testing.[28]

The HPA axis and the stress response

Following the perception of an acute stressful event, there is a cascade of changes in the nervous, cardiovascular, endocrine, and immune systems.[29] The main neurobiological circuits involved in the stress response are the HPA and the sympathetic-adrenal-medullary (SAM) axes. In fact, the acute physiological response to stressors occurs in two temporally distinct waves. The immediate, 'first wave' response is initiated within seconds through activation of the SAM and results in rapid accumulation of circulating catecholamines that prepare the body for survival. The second wave or the endocrine response to stress involving the HPA axis is slower and results in the release of glucocorticoids (primarily cortisol in people, corticosterone in rodents), which play a critical role in long-lasting adaptations to stressors.[28] Glucocorticoids can either permit, stimulate and/or suppress ongoing stress responses and/or prepare for a subsequent stressor depending on the receptor they bind to.[17] The stress response mediated by the HPA axis activity has both CNS and peripheral components (Table 2).

As opposed to the response to physiological stimuli,

Table 2. Central and peripheral components of the hypothalamic-pituitary-adrenal axis

Central components	The parvocellular neurons of corticotropin-releasing hormone
	The arginine-vasopressin neurons of the paraventricular nuclei of the hypothalamus
	The CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla and the locus ceruleus
	Other mostly noradrenergic cell groups in the medulla and pons (locus ceruleus/NE system)
Peripheral components	The peripheral limbs of the hypothalamic-pituitary-adrenal axis
	The efferent sympatheticadrenomedullary system
	Components of the parasympathetic system

CRH: corticotrophin-releasing hormone; NE: norepinephrine.

the prefrontal cortex and limbic system play a modulatory role in the response of HPA and SAM axes to psychological stressors.[30,31] The hippocampus, which participates in cognitive processes, is also connected to the HPA axis and seems to be particularly vulnerable to stress.[9,28,30] In fact, with prolonged chronic stress, the HPA axis is hyper-activated, with the resulting release in adrenocorticotropin and cortisol, thus involving structural changes, cell atrophy and neuronal loss in the hippocampus.[30] Moreover, chronic stress (especially, but not only, during childhood) induces a dysregulation of the HPA balanced system that can result in the production of too much or too little cortisol.[32,33] Brain cells can respond to the abundance of a substance by "down-regulating" the number of receptors for that substance.[33] This could mean that the hypothalamus receives less negative feedback from the hippocampus, thus leading to more production of CRH and an exaggerated response to a stressful event.

The cortisol response to current stressor paradigms in children and adolescents (public speaking, negative emotion, relationship disruption/threatening, novelty, handling, and mild pain paradigms) varies according to several factors such as the availability of coping resources and the extent to which in older children the task threatens the society.[34] Gender-specific association patterns should also be considered as there is a gender differential sensitivity to stressful life events.[35] (i.e. increased sensitivity to stressors, mainly interpersonal, in females) that could be explained by the modulation of HPA axis system activity by sexual hormones.

In summary, HPA axis plays a major role not only in the maintenance of basal and stress related homeostasis but also in emotional regulation and cognitive processes. Moreover, the HPA axis intimately interacts with other biological systems in the brain.

The HPA axis and the serotonin system

Although noradrenergic, dopaminergic, glutamatergic, and gamma-aminobutyric acid (GABA) systems interact with the HPA axis stress response at different levels,[30] the relationship between the serotonergic and HPA systems seems to be crucial in understanding the neurobiological underpinnings of ED.

The serotonin system is a stress response system that activates both anxiogenic and anxiolytic pathways, and serotonin is regarded as a master control neurotransmitter of the complex neuronal communication.[36-39] In conditions of moderate stress, serotonin is released into the frontal cortex, acting to calm and diminish dysphoria and anxiety.[40,41] However, severe stress or trauma can lead to excessive serotonin activation in many regions of the brain.[42] Excessive elevation in serotonin levels appears to eventually result in serotonin depletion and "down-regulation" of its receptors if trauma is chronic or persistent.[43] Reduced availability of serotonin leads to less ability of the central nervous system to dampen emotional responses to later stressors, increasing one's proneness to dysphoric states and hyperarousal symptoms after trauma exposure.

The HPA axis interacts with serotonergic mechanisms[44,45] and serotonergic systems modulate both the HPA axis and hypothalamic-spinal-adrenal (HSA) axis activity, which converge at the level of the adrenal cortex to regulate glucocorticoid secretion. Paradoxically, serotonin can either facilitate or inhibit HPA axis activity and stress-related physiological or behavioural responses. Detailed analysis of the brainstem raphe complex and its ascending projections reveals facilitatory and inhibitory effects of serotonergic systems on glucocorticoid secretion in two distinct neurophysiological pathways: 1) a serotonergic system arising from the middle and caudal dorsal raphe nucleus and projecting to a distributed central autonomic control system and a lateral "emotional motor system". Serotonin would sensitize this subcortical circuit associated with autonomic arousal, anxiety, and conditioned fear; and 2) a serotonergic system arising from the median raphe nucleus with selective and extensive projections to the ventral subiculum system.

Hippocampal function is also modulated by serotonergic projections mostly from the dorsal raphe nucleus in the midbrain.[44] Glucocorticoids modulate the activity of this raphe-hippocampal system in various ways. These effects are mediated via central corticosteroid receptors which include glucocorticoid and mineralocorticoid receptors located in the hippocampus and in other cortical structures.[44,45] Evidence suggests that serotonin facilitates this limbic circuit associated with inhibition of ultradian, circadian and stress-induced activity of both the HPA axis and HSA axis.

CRH is the stress neurotransmitter that plays a crucial role in the activation of the central sympathetic and serotonergic systems. The activity of CRH is expressed through specific receptors (CRH 1 and 2) that are extensively distributed in the limbic regions of the brain, in the hypothalamus, and on immune cells.[46,47] The mechanism whereby chronic stress, via the CRH, induces the activation of the dorsal raphe nucleus, can lead to a change in the serotonergic system activity, through an increase in the $5HT_{2A}$ and a decrease in the $5HT_{1A}$ receptor mediated function.[46]

Under physiological conditions, transiently increased concentrations of corticosteroids, as induced by stress, result in occupation of corticosteroid receptors most commonly glucocorticoid receptor, and allow

increased activity of the raphe-hippocampal system.[44] Stimulatory actions of corticosteroids include increased responsiveness of hippocampal neurons to 5-HT_{1A} receptor stimulation, attenuated autoinhibition of 5-HT, and a permissive effect on stress-induced increases in 5-HT release. Acutely, glucocorticoids regulate neuronal excitability and alter hippocampal-dependent behaviors, such as spatial memory. Chronically elevated corticosteroid concentrations, however, impair serotonergic neurotransmission. A possible causal relationship between HPA axis disturbances and reduced 5-HT_{1A} receptor expression is suggested by the modulatory effect of glucocorticoids on 5-HT_{1A} receptor number and function, which has been demonstrated repeatedly in animal studies.[44,45] A persistent pathologically hyperactive HPA axis in major depression could decrease 5-HT_{1A} receptor binding, partly by a reduction in gene expression. 5-HT_{1A} mRNA is reduced in the hippocampus of depressed suicides. In fact, single-prolonged stress has been seen to increase expression of glucocorticoid receptor and CRH in rats which were treated with 5-HT_{1A} receptor antagonists.[48] With respect to humans, newborns with the "S/S" specific functional polymorphism in the 5'flanking region of the serotonin transporter gene (17q11.2, 5-HTTLPR) of the 5-HT transporter gene have been seen to develop a significantly higher endocrine response to stress in comparison to newborns with "L/L" or "S/L" genotype.[49]

In conclusion, after chronic stress exposure the HPA axis and the serotonergic systems seem to be both altered in part because of their close interactions. The dysfunction of both systems may partly explain the neurobiology of ED in individuals who have been exposed to early and continuous adverse stimuli.

Assessing HPA axis function

The most common, non-equivalent ways of examining the HPA axis function are as follows:[9,18,50]

1. Single and/or repeated cortisol and ACTH blood assessments with or without previous psychological specific stressors;
2. Single and/or repeated cortisol salivary assessments with or without previous psychological specific stressors;
3. Hair cortisol concentrations;
4. ACTH response to the insulin tolerance test, the insulin-induced hypoglycemia test, which is widely regarded as a good dynamic test to evaluate the HPA function;
5. Standard dose and short-synacthen test for measurement of cortisol blood levels after ACTH administration. During the test, ACTH is injected, and the amount of cortisol the adrenals produce in response is measured;
6. Twenty-four hour urine cortisol profile;
7. Dexamethasone suppression test (DST) has had unprecedented attention among biological tests proposed for clinical use in psychiatry. This neuroendocrine test consists of the administration of a low dose of dexamethasone at 11 pm and the measurement of cortisol levels at one or more time points on the following day;
8. Combined dexamethasone-CRH suppression test (DST-CRH). After CRH became available for clinical studies, the DST was combined with CRH administration. In this test, patients are pretreated with a single dose of dexamethasone at 11 pm and receive human CRH intravenously at 3 pm the following day.

These methodological evaluations vary in their discriminative power[51] and there may be a large intra- and inter-individual variability.[19] Therefore, there is a recent serious concern in choosing the highest sensitive and specific HPA axis assessing method.[50-52] Research findings on the HPA axis reflect a variety of methodological approaches that reflect different facets of HPA-axis functions. Besides, some methods are designed to assess basal HPA axis activity and others evaluate the HPA axis response to different stressors. Partly owing to the methodological heterogeneity of those studies, descriptive reviews of this area may produce inconsistent conclusions.[52]

Intrinsic and methodological variations of studies on HPA axis activity should be taken into account when analyzing studies on HPA axis and adolescent suicide. The complexity of the HPA axis acute and chronic response to stressors poses doubts on the unequivocal biological significance of those measures. Therefore, although most studies have found a correlation between HPA axis dysfunction and suicidal behavior, caution is required to elucidate the theoretical relevance and clinical significance of those findings. Hence, we will further discuss the relationships between the HPA axis abnormalities and suicidal behaviour.

The HPA axis and suicidal behavior

Suicidal behavior has been related to a dysfunction of the HPA axis.[53-55] Dysfunctions in the HPA axis have been related to violence of attempts and eventual suicide completion during adulthood.[53,54,56-61] Abnormal HPA axis responses to increased levels of stress are found to be associated with a dysregulation in the serotonergic system, both in subjects with mood disorders and in those who engage in suicidal behavior.[62]

Most prospective studies of HPA-axis function have found that DST non-suppressors are more likely to commit suicide during follow-up.[57] Completed suicides are reported to have higher cortisol levels after being

administered dexamethasone than non-suicides, and HPA axis hyperactivity at baseline may increase the odds of an eventual suicide as much as 14 folds.[53,54] Patients with a history of violent suicide attempt are reported to have higher levels of urinary free cortisol, and serum cortisol in response to 5-hydroxytryptophan (5HTP) and DST non-suppression compared with patients without such history.[53-56] Moreover, a meta-analysis of studies on the association between non-suppression on the DST and suicidal behavior showed that non-suppression was associated with subsequent completed suicide consistently but had no constant association with prior attempted suicide.[53] Some studies suggest that there is no difference in the DST test results between low lethality suicide attempters and non-attempters.[53,56] However, in a follow-up study with suicide attempters,[58] evening salivary cortisol levels were lower in adult suicide attempters compared to controls but were associated with more severe psychiatric symptoms during follow-up. Vreeburg et al[63] have seen that unaffected individuals with parental history of depression or anxiety show a higher cortisol awakening curve, similar to that of the participants with depression or anxiety disorders. This finding suggests that a higher cortisol awakening curve reflects a trait marker, indicating an underlying biological vulnerability for the development of depressive and anxiety disorders.

With regard to adolescents, Robbins and Alessi[56] demonstrated a highly significant association of DST non-suppression with lethal or potentially lethal suicidal behavior. Exposure to adversities combined with genetic and epigenetic vulnerabilities may lead to a chronic impairment of HPA axis normal functioning, a neurobiological correlate of emotion dysregulation. Variations between individuals in stress-regulatory genes such as *CRHR1* have been said to increase the susceptibility towards suicidal behavior.[60] In fact, changes in the *CRHR1* gene expression moderate the effect of childhood maltreatment on cortisol responses to the DST-CRH test.[61] Variations in the *CRHR2* gene expression are also associated with suicidal behavior in bipolar patients.[47] Other HPA-axis regulating genes such as the *FKBP5*[64] put adolescents and adults exposed to childhood trauma at higher risk for attempting suicide. Young et al[65] have recently reported that, except in relation to conduct symptoms, awakening salivary cortisol levels is unrelated to any psychiatric disorders or symptoms in adolescents. However, they found that the relationship between cortisol and conduct symptoms is moderated by both gender and mood symptoms.

In summary, suicidal behavior is related to HPA axis abnormal functioning both in adolescents and adults. ED, a putative consequence of child maltreatment, is associated with an increased risk for depression, substance use disorders, and suicidal behaviors during adulthood.[16] We hypothesize that ED, correlated with HPA dysfunction (e.g. after exposure to chronic adverse conditions, such as child maltreatment), could be one of the factors that augment the risk of suicidal behavior in adolescents. It also may increase the risk of comorbid conditions such as depression which is associated with high risk of suicide.[1,15] In both psychopathological conditions, the HPA axis system also seems to be acutely altered, thus closing a pathological loop (Fig.). Therefore, HPA axis dysregulation may be one of the common neurobiological underpinnings of depression and suicidality in adolescents.

Adolescent depression, HPA axis, and suicidal behavior

Depression has been neurobiologically correlated with combined hypercortisolism and an apparent hypoactivity of serotonergic transmission.[43,52,66-69] Hypercortisolism in depressed patients may be related to emotion dysregulation but HPA axis dysfunction in depression could also be interpreted as a transient state more than as a stable biological trait as most studies are conducted during the course of depressive episodes.

Multiple lines of evidence point to abnormalities of the HPA system in depression.[52,66-68] Elevated CRH concentrations in cerebrospinal fluid (CSF), blunted ACTH and β-endorphin responses after intravenous CRH administration, lower CRH binding in the frontal cortex, pituitary gland enlargement, adrenal gland enlargement, hypercortisolemia and elevated CSF cortisol concentrations, plasma glucocorticoid, ACTH and β-endorphin non-suppression after dexamethasone administration, higher urinary free cortisol concentrations, elevated 5-hydroxytryptophan-induced cortisol secretion, higher ACTH-induced cortisol secretion and higher ACTH and cortisol responses to CRH after dexamethasone pretreatment have been observed in patients with major depression.

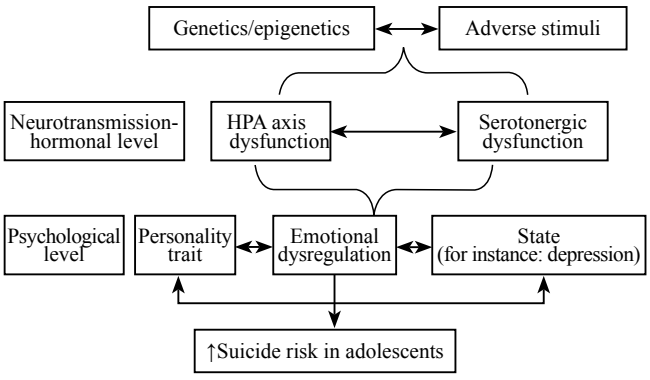

Fig. Emotional dysregulation, hypothalamic-pituitary-adrenal axis dysfunction, and suicide risks in adolescents.

[66-68] Attempts to identify subgroups suggest that 60%-90% of depressed patients with melancholic features and/or psychosis may demonstrate DST abnormalities.[70] One research group observed non-suppression to dexamethasone in 81% of patients with psychotic depression compared to 37% of patients with non-psychotic depression.[70] HPA axis hyperactivity in depressed patients can be explained by hypersecretion of CRH and secondary pituitary and adrenal gland hypertrophy, although impaired negative feedback at various CNS sites including the hippocampus and the pituitary are also likely to contribute.[52,66-68] Both the volume and function of the hippocampus are reduced in adult patients with major depression.[71] This reduction, which appears to be greatest in patients with the longest duration of illness, may be partially mediated by hypercortisolism.

Adolescent suicidal behavior is frequently associated with depression.[1] A recent meta-analysis[52] has shown an association between HPA-axis dysregulation and youth depression. Specifically, as compared with control peers, depressed youth tended to have an altered response to dexamethasone and moderately higher cortisol levels throughout the day. However, there was no evidence of a dysregulated response to CRH in depressed pediatric samples. Data on HPA axis response to psychological stressors in this clinical population were also limited. Surprisingly, group differences in high baseline cortisol levels did not appear to be a function of sex, age, type of control group or time of sample collection but were related to anomalies within circadian systems. Atypical HPA axis functioning preceded the emergence of clinical levels of depression, and the HPA axis became increasingly dysregulated from child to adult manifestations of depression.[72] Depressed adolescents as well as adults demonstrated a significantly higher non-DST suppression rate than controls. About 50% of depressed patients were non-suppressors.[66,68,70]

Although HPA axis dysfunction could be understood as a state biological marker of depression, it could also be seen as a diathesis trait that increases the risk of suicide through the life-span and that worsens during the acute episode of depression. Childhood adversities may be neurobiologically correlated with HPA axis abnormalities and become of the neurobiological findings of suicidal behavior in teenagers.

Childhood trauma, HPA axis, and adolescent suicidal behavior

Prolonged and severe trauma, particularly trauma that occurs early in the life cycle, tends to result in a chronic inability to modulate emotions, thus augmenting the risk of getting involved in indiscriminate relationships with others in which old traumas are, somehow, re-enacted[73-79] or, in some cases, leading to the loss of social bonds.[80] It may also lead to new traumas as a result of psychiatric pathology, maladaptive personality features, impulsive behavior, alcohol, substance abuse, and other factors.

Early stressful life events are associated with higher salivary cortisol levels, DST non-suppression, and approximately the same subset of symptoms (mainly, depressive and psychotic symptoms) in moderate to severe psychiatric out-patients.[81] Their abnormal HPA axis response may be triggered after exposure to new stressful events.[81] In fact, Bevans et al[82] clarified that exposure of children (mean age: 10.7 years) to high stress within the past 12 months was related to higher afternoon cortisol levels but if the levels of trauma were high in combination with frequent exposure to trauma earlier in life, the pattern of HPA axis response corresponded to lower morning cortisol levels and higher afternoon cortisol levels.

Chronic exposure to adverse stimuli during childhood is associated with an impairment of the HPA axis normal functioning. For instance, parental loss during childhood is associated with DST increased cortisol responses.[83] Childhood trauma is also related to lower morning ACTH and increased cortisol during withdrawal in alcohol-dependent patients.[84] Moreover, dampened cortisol reactivity to dexamethasone-CRH challenge has been postulated as a consequence of childhood emotional abuse that is cumulative over time.[85] Cichetti and Rogosch[86] underlined that cortisol dysregulation patterns were specific to the type of maltreatment experienced. Maltreated children who had been physically and sexually abused exhibited higher morning cortisol levels, whereas children who had only been physically abused showed a lower level of morning cortisol and had a smaller decrease from morning to afternoon cortisol level. A decrease in hippocampal volume has been described as a major biological consequence of exposure to trauma.[40,87] Some critical periods such as peripuberty seem to be especially detrimental to hippocampal volume, and the damage is also modulated by the gender factor as the window of vulnerability for reduced myelination is earlier for boys and later for girls.[88] However, other factors, such as the effect of alcohol and substance abuse, may also affect hippocampal size as some studies have failed to show a reduce hippocampal volume if children and adults are exposed exclusively to traumatic events.[89,90]

In summary, a persistent abnormal functioning of the HPA axis and its interactions with the serotonergic system may be one of the neurobiolocial consequences of child maltreatment and may contribute to an increased

risk of suicidal behavior in adolescents. Assessment of HPA axis functioning could become a powerful biomarker of suicidal risk in this group of patients. Some abnormalities in HPA axis activity may become persistent, and certain state-dependent adverse circumstances such as major depression could be worsened.

Limitations

There are some limitations to the present review. First, we did not carry out a meta-analysis because data from most of the studies focused on the main topic did not allow us to conduct this kind of study. Specifically, this is related to the fact that studies used different measurements and outcomes as they assessed patients at different time points. Another limitation, which is inherent in this type of studies, is that the inclusion and exclusion of papers may reflect the authors' choice on the basis of their expertise.

Conclusion

A biological marker of current or future risk for youth suicide could be seen as a valuable tool from the clinical point of view as it could help to identify patients at higher risk for suicidal behavior. Despite methodological discrepancies in the assessment of HPA axis functioning, its dysfunction can be postulated as a putative universal biomarker related to ED when confronting adverse psychosocial stimuli. Those "perceived adversities" may vary from one individual to another and from one cultural setting to another. However, ED is deeply related to chronic adverse stimuli such as child maltreatment and some dysfunctional models of parenting. In any case, ED can be seen as a psychological trait that may place adolescents at risk for suicidal behavior. It could also augment the individual vulnerability to suffer from psychopathological conditions such as depression. Moreover, those mental illnesses have been seen to affect HPA axis activity regardless of its previous normal functioning. Attempts at correlating HPA axis dysfunction with psychological factors such as ED in a comprehensive temporal framework will lead to a wider understanding of its role in adolescent suicide and may enhance preventive and treatment strategies for this life-threatening condition in the future.

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