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ORIGINAL PAPER

The hypothalamic-pituitary-adrenal axis and serotonin abnormalities: a selective overview for the implications of suicide prevention

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Abstract Suicidal behavior and mood disorders are one of the world's largest public health problems. The biological vulnerability for these problems includes genetic factors involved in the regulation of the serotonergic system and stress system. The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that regulates the body's response to stress and has complex interactions with brain serotonergic, noradrenergic and dopaminergic systems. Corticotropin-releasing hormone and vasopressin act synergistically to stimulate the secretion of ACTH that stimulates the biosynthesis of corticosteroids such as cortisol from cholesterol. Cortisol is a major stress hormone and has effects on many tissues, including on mineralocorticoid receptors and glucocorticoid receptors in the brain. Glucocorticoids produce behavioral changes, and one important target of glucocorticoids is the hypothalamus, which is a major controlling center of the HPA axis. Stress plays a major role in the various pathophysiological processes associated with mood disorders and suicidal behavior. Serotonergic dysfunction is a well-established substrate for mood disorders and suicidal behavior. Corticosteroids may play an important role in the relationship between stress, mood changes and perhaps suicidal behavior by interacting with 5-HT1A receptors. Abnormalities in the HPA axis in response to increased levels of stress are found to be associated with a dysregulation in the serotonergic system, both in subjects with mood disorders and those who engage in suicidal behavior. HPA over-activity may be a good predictor of mood disorders and perhaps suicidal behavior via abnormalities in the serotonergic system.

Keywords HPA-axis · Suicide behavior · Mood disorders · Stress · DST · 5-HT

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Introduction

Suicide has taken lives around the world and across the centuries, and it accounts for about one million deaths annually, with devastating socioeconomic costs and consequences [138]. It is one of the world's largest public health problems and has multiple causes in which, according to a stress diathesis model, both genetic make up and acquired susceptibility contribute to a person's predisposition to suicidal acts in stressful situations [138, 258].

Suicide is a complex phenomenon resulting from various factors, including psychiatric, biological and environmental factors. It is well established that there is a substantial genetic contribution to suicidal behavior involving serotonin transporter and 5-HT1A receptors [178]. Mental disorders (particularly depression and substance abuse) are associated with suicide, and over 90% of

suicide attempters and 60% of completed suicides have mood disorders [23, 224]. For example, childhood depression is associated with an increased risk of suicide [26, 65, 69, 136]. Suicide results in excessive mortality in those with mood, psychotic and substance use disorders—two to three times above that of the general population [2, 3, 58, 66, 79, 226, 248]. However, having a mental disorder is not a sufficient condition for increased suicide risk. Many studies measuring the incidence of psychiatric disorder in suicides employ after-the-fact diagnosis. Such studies are often criticized for lack of objectivity. The main argument is that a decision of the psychiatrist is biased if he believes that suicidal people must be mentally ill. This bias is indirectly confirmed by statistics: "the highest estimate of mental illness when a sample had been diagnosed before suicide was 22%. Afterward, the highest estimate was 90%" [242].

The aim of this broad overview is to shed light on some biological dysregulations that may increase suicide risk regardless of psychiatric disorders as well as that may lead to vulnerability for developing a psychiatric disorder. A further aim of this paper is to attempt at identify possible strategies to treat such abnormalities.

Circadian rhythms and the suprachiasmatic nucleus

The circadian system allows the organism to anticipate environmental changes and prepare itself to better fit into the environment. In mammals, including humans, the biological clock regulates most, if not all, circadian rhythms [249]. Circadian rhythms enable the organism to synchronize its activities to the periodic fluctuations in the external environment. The hypothalamic suprachiasmatic nucleus (SCN) is the main biological clock in mammals, while the pineal gland has that role in reptiles and birds (see Fig. 1). In most mammalian cells, a set of ''clock'' genes and proteins forms a regulatory network that produces oscillations with a circadian period (24 h) [200]. Molecular and physiological rhythms are coordinated with the daily changes in the environment by a dominant circadian pacemaker, the SCN. The SCN neurons endogenously generate the circadian rhythm and adapt that rhythm according to light–dark cycles of the environment (entrainment). The SCN influences the pineal gland secretion of melatonin and also many peripheral clocks[1] in tissues other than the brain. Thus, there is a hierarchy of interacting clocks. These clocks may themselves regulate the SCN through feedback or feed-forward effects. There may exist specialized groups of neurons within the SCN,

[1] Isolated cells from different tissues, kept in cultures, maintain a cyclical pattern of their biochemical activities.

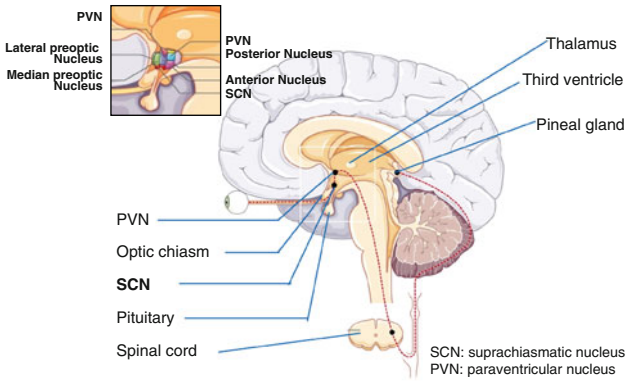

Fig. 1 Anatomy of SNC, in detail SCN and PVN

each group being aimed at the regulation of a given organ, targeting the pineal gland, the liver or other organs [25].

The SCN innervates brain areas in the human hypothalamic region [52–54], imposing its rhythm also into the body via (1) the secretion of hormones, (2) the parasympathetic autonomous nervous system, and (3) the sympathetic autonomous nervous system. The SCN uses separate connections via either the sympathetic or the parasympathetic system, not only to prepare the body for the impending change in the activity cycle, but also to sensitize the body and its organs for the hormones that are associated with such a change [35]. Bao et al. [19] and Bao and Swaab [21] have also found corticotropin-releasing hormone (CRH) fibers in the area of the SCN, which suggests the existence of a bi-directional direct anatomical connection, whose function is unclear, between the SCN and the paraventricular nuclei (PVN).

The SCN is responsible for the rhythmic changes in the stress system. Abnormal patterns of circadian rhythms in response to stress characterize a large variety of affective disorders, including unipolar and bipolar depression, mania, seasonal affective disorder and premenstrual dysphoric disorder [271], and dramatic improvements may be observed in some depressed patients in response to treatments involving manipulation of their circadian rhythms and/or sleep–wake cycle [253].

The hypothalamic-pituitary-adrenal (HPA) axis

Although the stress response of the body is meant to maintain stability or homeostasis, long-term activation of the stress system may have a hazardous or even lethal effect on the body, increasing the risk of obesity, heart disease, depression and a variety of other illnesses. The HPA axis is the neuroendocrine system that regulates the body's response to stress. CRH and vasopressin are released from neurosecretory nerve terminals at the median

eminence. They act synergistically to stimulate the secretion of stored ACTH from corticotroph cells. ACTH is released via different second messenger systems [272–274]. Both CRH and AVP are required for a normal pituitary and adrenal response to some acute stressful stimuli [125, 199]. In particular, AVP receptor up-regulation may be critical for sustaining the corticotrophic responsiveness in the presence of high circulating glucocorticoid levels during chronic stress or depression [1].

ACTH is transported to the adrenal cortex of the adrenal gland, where it rapidly stimulates biosynthesis of corticosteroids such as cortisol from cholesterol. Corticosteroids produce several behavioral changes [40]. Cortisol is a major stress hormone and has effects on many tissues in the body, including the brain [231]. Cortisol diffuses into the brain and binds with different affinities to two types of corticosteroid receptors: Type I or mineralocorticoid receptors (MR) and Type II or glucocorticoid receptors (GR). Both MR and GR are expressed in human brains [263, 266, 276] and monkey brains [184, 194, 216]. The hippocampus, amygdala and medial prefrontal cortex (mPFC) [60, 216] are mainly occupied during periods of stress [111, 115, 158, 232]. MR has a high binding affinity, is extensively occupied most of the time, and regulates the transcription of genes involved in tonic neurotrophic effects [74, 144, 213, 275]. MR and GR are in relative balance in brain regions that play a role in cognitive and neuroendocrine functions [55, 93, 127, 129].

Patel and colleagues [183] suggested that the relative distributions of MR and GR differ in hippocampal Cornu Ammonis (CA) regions. There are numerous studies in animals where it has been demonstrated that GR and MR expression was dysregulated or down-regulated in several cerebral areas such as hippocampal CA1, ventrolateral and dorsolateral prefrontal cortex, amygdala and locus coeruleus [12, 70, 113, 155, 180, 195, 208, 266, 281].

The GR cochaperone FKBP5 gene strongly affects HPA axis activity and may be involved in depression and stress. Szymańska et al. [238] observed at western blot that GR levels were significantly increased in the hippocampus and not in the frontal cortex of prenatally stressed rats. Concentration of cochaperone FKBP51 was decreased only in the hippocampus, and chronic administration of antidepressant drugs diminished the characteristics of this animal model of depression. These data strongly suggest that glucocorticoid action in depression was influenced by the rise in hippocampal GR levels and the lower concentration of FKBP51 in the frontal cortex.

The hypothalamus, the major controlling center of the HPA axis, is an important target of glucocorticoids. Inhibition of stress responsiveness is achieved partly (1) by the binding of circulating glucocorticoids to specific cytoplasmic receptors in the hypothalamus, where they inhibit CRH and then pituitary ACTH secretion, and (2) in limbic structures through neuronal connections that converge on the PVN, where the stress-responsive CRH and AVP neurons reside.

Medication may impact on HPA axis activity as suggested by McKay and Zakzanis [145] in a recent meta-analysis (including 34 studies and a total of 1,049 depressed patients). They reported that, before and after treatment, the subtype of depressive illness and length of treatment may contribute to the changes in cortisol levels, but no significant differences in the mean effect size of pre–post cortisol levels based on type of treatment (e.g., antidepressant vs. ECT) were found. Schüle and colleagues [221] observed a significant reduction in HPA axis activity as measured by the DEX/CRH test after 5 weeks of reboxetine treatment. They found, as demonstrated in a previous study [219], that mirtazapine significantly reduced cortisol and ACTH concentrations (presumably via direct pharmacoendocrinological effects although this is not necessarily related to clinical improvement) after 1 week, but after 5 weeks mirtazapine only partially increased the cortisol and ACTH responses in both responders and non-responders. Moreover, it was suggested that, in major depression, performance of a single DEX/CRH test does not predict the therapeutic response. It would appear that the best predictor for response seems to be an early attenuation of HPA axis activity within 1 or 2 weeks. However, early improvement on HPA system dysfunction is not a sufficient condition for a favorable response. Since a substantial proportion of depressive patients display a persistence of HPA axis hyperactivity at discharge, down-regulation of HPA system function is not a necessary condition for acute clinical improvement either [220].

Additionally, Ising et al. [98] suggested that the combined DEX/CRH test, which reflects changes in HPA system regulation, could be a good biomarker as a predictor of clinical outcome at follow-up. The initial increased ACTH and cortisol responses to the first DEX/CRH test producing a down-regulation of HPA system is not a necessary condition for the clinical improvement. Improved HPA system regulation in 50 inpatients with severe major depression in the second DEX/CRH test was associated with a beneficial treatment response after 5 weeks and a higher remission rate at the end of hospitalization. Early improvement on HPA axis function may be not followed by a persistent beneficial treatment outcome, although this was the best predictor for immediate response [220].

The HPA-axis has complex interactions with brain serotonergic, noradrenergic, and dopaminergic systems.

The HPA axis and serotonin in suicidal behavior

Serotonergic dysfunction is a well-established substrate for suicidal behavior, a relationship apparently mediated by increased aggressivity in mood disorders as initially suggested by van Praag [251], Traskman-Bendz [245], and others [42, 78, 80, 139, 142, 173]. There is an association between aggressive behavior and serotonergic dysfunction both in suicidal patients with Axis-I disorders with relatively milder forms of aggressive behavior and in suicidal patients with a low concentration of CSF 5-HIAA which is related to aggressive behavior [233]. The first research into CSF 5-HIAA in relation to suicidal behavior was by Asberg [10].

Low plasma concentrations of cholesterol [22, 229], low plasma serotonin concentrations [22, 84], and blunted neuroendocrine responses to 1-(3-chlorophenyl) piperazine (MCPP) [243] or fenfluramine [43, 159] have all been associated with low platelet 5-HT concentrations. One of the major biochemical serotonin abnormalities associated with suicidal behavior is a lowered concentration of 5-hydroxyindoleacetic acid (5-H1AA), the major degradation product of serotonin (5-HT), in the cerebrospinal fluid (CSF). Also, lower plasma neurosteroids levels, such as essential fatty acids (EFAs) which are formed by cholesterol, were involved in depression, impulsivity, and suicidal intent [72]. However, despite previous findings, plasma levels of cholesterol were not related to a history of suicide attempts among affective disorder patients in a study by Pompili et al. [188].

Low CSF 5-HIAA has been reported primarily in MDD, both melancholic and delusional [252]. Meta-analysis of 27 reports, both prospective and retrospective, found that suicide attempters, particularly those who use violent methods, when compared to psychiatric controls had low CSF 5-HIAA [117], contributing a 4.5-fold increased suicide risk [141]. Furthermore, Carroll and Curtis [36] and Banki et al. [16, 17] found a positive correlation between increased levels of post-dexamethasone cortisol and low 5-HIAA.

In the stress diathesis model, Mann et al. [138] focused on two candidate biomarkers for suicidal behavior: low CSF 5-HIAA and non-suppression in the dexamethasone suppression test (DST) (a marker of HPA axis dysfunction). The question is whether CSF 5-HIAA and non-suppression in DST are associated or dependent risk factors.

Mann and colleagues [141] suggested that non-suppressors in the DST have more than a fourfold increased risk of suicide compared with suppressors. Although in a recent study, the DST did not prove to be a useful predictor for mood disorder outpatients or for those with no clinical evidence of suicidality [48], the majority of studies find non-suppressors to be at higher risk for future suicide regardless of CSF-5-HIAA levels and DSM diagnoses [270]. Both Jokinen et al. [101], in a sample of hospitalized mood disorder patients, and Fawcett et al. [67] found a positive correlation between low CSF 5-HIAA and DST non-suppression and considered them as relatively independent biomarkers of suicide risk in suicide attempters. The absence of reports of negative correlations between the two markers suggests that they both may be associated with suicide, but through different and independent mechanisms.

Jokinen et al. [102] investigated the association between low CSF 5-HIAA and DST non-suppression in completed suicides with mood disorder and found in 6 male suicide victims that the serum cortisol level at 4:00 p.m. was significantly associated with CSF 5-HIAA. Low CSF 5-HIAA was a predictor of short-term suicide risk (within 1 year) and DST non-suppression was a long-term (after 1 year) suicide predictor.

What is the relationship between serotonin and the HPA-axis?

Roy et al. [210] suggested that serotonin plays an excitatory role in the regulation of the release of CRH. CRH is carried from the hypothalamus via the portal system to the anterior pituitary where it stimulates the secretion of ACTH into the blood. CRH neurons of the central amygdala are directly and indirectly connected to brain nuclei such as the locus coeruleus and raphe nuclei [88, 89, 147], the major source of serotonergic projections which are involved in the stress response [177]. The hippocampus is important for HPA feedback mechanisms as demonstrated in rats, where hippocampal lesions result in increased circulating corticosterone [90]. In addition, animal studies have shown that corticosteroids may alter several elements of serotonergic neurotransmission.

How do steroids regulate 5-HT1A receptors? What are the roles of MR and GR in mediating hippocampal 5-HT1A receptor regulation? Do 5-HT1A receptors react to chronic stress? Removal of circulating corticosteroids by adrenalectomy (ADX) results in anatomically specific decreases in indices of serotonin metabolism and in a significant increase in 5-HT1A receptor binding and mRNA in the rat hippocampus [83]. This increase was prevented by the administration of a low dose of corticosterone, probably selectively occupying the MR. After ADX, dexamethasone, primarily a GR agonist, was only partially effective in reversing the ADX-induced up-regulation of 5-HTl-A. The MR could have an important role in modulating hippocampal 5-HT1A under basal conditions, and 5-HT1A hippocampal receptors could be under tonic inhibition by corticosteroids, an effect selectively mediated by the MR [127, 148].

5-HT1A receptor mRNA levels and 5-HT1A-binding densities were significantly reduced in the hippocampus after 2 weeks of chronic stress produced by persistent elevation of circulating corticosteroids probably occupying both MR and GR simultaneously [127]. Imipramine, probably reducing HPA hyperactivity, prevents both the down-regulation of hippocampal 5-HT1A receptors and the stress-induced increase in plasma corticosteroids [29]. When imipramine is unable to decrease corticosterone levels, it is also unable to prevent 5-HT1A down-regulation after chronic stimulation.

Meltzer et al. [149] studied 5-hydroxytryptophan, which induces the release of cortisol and tryptophan hydroxylase, the rate limiting serotonin biosynthetic enzyme that appears to be sensitive to circulating corticosteroid levels, and their results strongly suggested a functional connection between the serotonin system and the HPA axis. Maes et al. [134], investigating the seasonal variation in levels of plasma L-tryptophan in healthy humans in relation to climatic variables, total serum protein levels, and violent suicide occurrence in twenty-six healthy volunteers, found a bimodal seasonal pattern in the availability of plasma L-tryptophan that matches seasonal patterns in the prevalence of violent suicide in the local population and depression in other studies. Plasma L-tryptophan and the L-tryptophan/CAA ratio were significantly lower in spring than in other seasons. A significant time relationship was noted between the seasonal variation in L-tryptophan availability and the occurrence of violent suicide. Therefore, the hypothesized functional connection between the serotonin system and the HPA axis may be affected by seasonal fluctuations.

Maes et al. [133] stated that there was also a significant seasonality for violent suicide which is determined by different circannual rhythms in young and elderly persons. Therefore, corticosteroids, by interacting with the 5-HT1A receptors, may play an important role in the relationship among stress, mood changes, and perhaps suicide [39, 189].

The role of 5-HT transporter and 5-HT1A receptors

According to recent imaging studies, alterations in the function and density of brain 5-HT transporters and receptors have been associated with MDD and suicide and may impact treatment outcomes [51, 62, 172, 182]. Malison et al. [137] were the first to find a significant reduction in the density of 5-HT transporter-binding sites in the brainstems of living patients with MDD compared with healthy controls. This reduction may be an adaptive response by the brain to increase 5-HT availability, and the findings provide support for the critical link between alterations in serotonergic neurons and the pathophysiology of depression.

Interactions between 5-HT transporter genotype and exposure to stress may also impact vulnerability to depression and suicide [247]. In a prospective longitudinal study of a representative birth cohort, Caspi and colleagues [38] examined the association between the number of stressful life events and depression outcomes as a function of 5-HT transporter genotype. A functional polymorphism in the promoter region of the 5-HT transporter gene was found to mediate the effects of life stress on depression. Individuals carrying one or two copies of the short allele of the 5-HT transporter promoter polymorphism had more depressive symptoms and diagnosable depression, as well as an increased probability of suicide ideation or attempt, compared with individuals homozygous for the long form of the 5-HT transporter genotype. Thus, the long form of the 5-HT transporter genotype may confer protection, possibly decreasing the probability of MDD episodes. In a double-blinded, randomized, 8-week study of elderly patients with MDD, Murphy et al. [161] found that the short form of the 5-HT transporter gene was associated with adverse events and modest reductions in efficacy among patients treated with paroxetine.

In 88 drug-naive healthy individuals, Praschak-Rieder et al. [191] investigated seasonal variations in serotonin transporter levels and found that serotonin transporter levels were significantly higher in the fall and winter compared with those in spring and summer. Higher serotonin transporter density is associated with lower synaptic serotonin levels. They concluded that serotonin transporter levels vary during the year with the seasons, and there may be lower synaptic serotonin levels in the fall and winter. Therefore, polymorphisms in the promoter region of the 5-HT transporter gene also influence antidepressant efficacy and tolerability, and abnormalities in 5-HT1A may play an important role in suicide.

HPA axis activity and suicide

Prospective biological studies suggest that dysfunctions in the HPA axis have some predictive power for suicide in mood disorders [41, 100, 109, 118, 138, 140, 141, 179, 185, 187]. Convergent findings showed that HPA axis hyperactivity may be a relevant risk factor for suicide both in subjects with MDD (for more details, see Table 1) and those without a clear psychiatric diagnosis [128, 166, 198, 237]. HPA hyperactivity is associated both with non-fatal suicidal behavior [126, 270] and completed suicide [48, 100, 277]. In addition, higher cortisol levels after DST (a clinical measure of HPA axis hyperactivity) may

Table 1 Findings supporting the involvement of the stress system in depression and suicide (modified by Bao et al. [20])

System	Hypothesis	Studies
CRH	Increased CRH neuron in PVN	Raadsheer et al. [196], Bao et al. [19]
	Increased CRH mRNA in PVN	Raadsheer et al. [197]
	Increased CRH in CSF	Banki et al. [18]
	CRH-R1 SNP	Liu et al. [124]
	Antidepressants decrease CSF CRH	Heuser et al. [91]
	Antidepressants as antagonists of CRH-R1	O'Brien et al. [169], Keck and Holsboer [108]
	Symptoms in rats induced by CRH i.c.v.	Holsboer [94]
	Transgenic mouse with increased CRH were anxious	Stenzel-Poore et al. [234]
	Combined DST-CRH as a useful tool for evaluating patients with depression, alcoholism and suicidal behavior, suicide attempts and suicidal ideation	Sher [227], Pfennig et al. [186]
	Alcoholism is associated with abnormalities in HPA function detected by the modified DST-CRH	Sher et al. [228]
	Hypothalamic peptidergic systems (HPA-axis, SCN, SON and HPT-axis) have many interactions with aminergic systems that are implicated in depression	Swaab et al. [236]
Glucocorticoid	Increased corticosteroids and decreased CRH in atypical depression	Gold et al. [77], Gold and Chrousos [76]
	Depression as a side effect of glucocorticoid treatment	Mitchell and O'Keane [153]
	Atypical depression in the majority of subjects with Cushing's syndrome	Gold et al. [77], Dorn et al. [61]
	SNPs GR gene NR3C1	Van West et al. [254]
	Metyrapone, aminoglutethamide, ketoconazole are both inhibitors of cortisol and antidepressants	Reus et al. [201], Murphy [160]
	Mifepristone (RU486) is a GR-antagonist used for psychotic depression	Gold et al. [76], Belanoff et al. [24]

CRH corticotropin-releasing hormone, *CRH-R* CRH receptor, *CSF* cerebral spinal fluid, *GR* glucocorticoid receptor, *NR3C1* Nuclear Receptor Subfamily 3, Group C, Member 1, *OXT* oxytocin, *PVN* paraventricular nucleus, *SNPs* single-nucleotide polymorphisms, *SON* supraoptic nucleus, *HPT* hypothalamo-pituitary thyroid

indicate an increased risk of suicide by as much as 14-fold [32, 46], and an elevated cortisol response to the DEX/CRH test is associated with a 4- to 6-fold higher risk for depressive relapse [282].

Increased pituitary gland volume [73, 112, 131, 181, 217], a measure of HPA axis activation, is associated (in animal studies) with increased levels of CRH, subsequent increased size and number of pituitary corticotrophs (ACTH-producing cells) [75, 268], and circulating cortisol levels [13]. Further evidence is provided by the association of suicide with larger adrenal glands and less prefrontal cortical CRH binding [138].

However, studies in high-risk patients with MDD have shown that abnormalities in HPA-axis function already exist prior to the onset of the clinical symptoms. These abnormalities may merely precipitate depressive episodes [93]. There is also evidence of HPA-axis hypoactivity in the pathophysiology of stress-related and fatigue-related disorders [88].

The dexamethasone suppression test

Disturbances in the HPA system measured with the DST test and dexamethasone/CRH test [95, 96] have been associated with increased risk of suicide in depressed patients in several prospective studies [28, 46, 47, 168, 210, 240, 277, 278], with relapse of MDD [6] and worse treatment outcome [31] (for more details, see Tables 2 and 3).

Jokinen et al. [104] found that, in young inpatients with mood disorders, with and without a history of a suicide attempt, the DST non-suppressor rate was significantly higher in suicide attempters compared to non-attempters. Birmaher et al. [26] reported that an estimated 50–70% of depressed children were considered to be DST non-suppressors, and higher rates of non-suppression are also noted in patients with endogenous and psychotic symptoms, a prior history of MDD and a family loading of depression.

In a prospective follow-up study of inpatients with major or schizoaffective depressive disorders, Coryell and

Table 2 DST result and risk for later suicide among inpatients with depressive disorders

Authors (years)	Number followed	Mean follow-up length (years)	Number of suicides (% of those followed)	% suicide by DST result	
				S	NS
Carroll et al. [37]	250	–	4 (1.6)	0	3.3
Roy et al. [211]	27	1	4 (14.8)	7.6	21.4
Boza et al. [28]	13	1	2 (5.4)	0	50
Coryell and Schlesser [47]	205	1.5	4 (1.9)	0	4.2
Norman et al. [168]	66	8	13 (19.7)	12.2	41.2
Coryell and Schlesser [46]	78	10	8 (10.3)	2.2	21.9
Nielsen et al. [167]	120	14	6 (5)	0	10.3
Yerevanian et al. [277]	101	2	3 (3)	0	8.8
Coryell et al. [48]	189	21	9 (4.8)	2.6	8.3
Jokinen et al. [100]	382	18	36	16	20
Fontoulakis et al. [68]	50	–	–	34	16
Jokinen and Nordström [105]	99	–	–	48	51
Jokinen et al. [103]	106	17	25	62	44
Jokinen et al. [101]	58	–	–	37	21
Jokinen et al. [102]	58	21	11	–	–
Jokinen and Nordström [104]	36	–	–	27	9

Suicides were matched to two no-completor groups. *DST* dexamethasone suppression test, *S* suppressors, *NS* non-suppressors (adapted in part from Coryell [49])

Table 3 DST result and sex as additive risk factors for suicide in depressed inpatients

	n	*n* (%) dead by suicide
Female		
Suppressors	80	0 (0)
Non-suppressors	51	3 (5.9)
Males		
Suppressors	37	3 (8.1)
Non-suppressors	21	3 (14.3)

DST dexamethasone suppression test, *S* suppressors, *NS* = non-suppressors (from Coryell [49])

Schlesser [45] found that patients who had an abnormal DST result were significantly more likely to commit suicide during the follow-up. Additionally, a recent meta-analysis of seven studies concluded that DST non-suppression increases the risk of suicide by a factor of 4.6 [141]. Jokinen and Nordstrom [105], in a sample of depressed elderly inpatients, found that elderly mood disorder inpatients who fail to suppress cortisol in DST have a higher risk of suicide. DST non-suppression distinguished between suicides and survivors in elderly depressed inpatients and had higher specificity and predictive value in the suicide attempter group. However, Coryell et al. [48] have suggested that DST non-suppression may not be a useful predictor for mood disorder outpatients or for those without a clinical history of a suicide attempt [100].

Aging increases the cortisol response to a pharmacological challenge with CRH, and increasing insensitivity of the HPA axis to the feedback of cortisol may be another factor involved in the activation of the HPA axis during aging [92, 101]. In a recent meta-analysis of 45 studies (including both pharmacological and non-pharmacological challenges (e.g., psychosocial stress and both challenge and suppression procedures), an increased cortisol response to challenge in older compared to young subjects was demonstrated, as well as a threefold stronger effect of aging on cortisol responses to challenge in women compared with men [176].

Heuser et al. [92] demonstrated higher peak cortisol levels at baseline and after DST in females compared with males and suggested that age-associated alterations in HPA function in healthy volunteers are more prominent in women. Many diseases that increase in prevalence with aging have been associated with an elevated cortisol response to pharmacological challenge, including depression [76, 94].

One important issue is the possible effect of geographic latitude. Rihmer [204] investigated this variable among participants in a recent WHO multicenter collaborative study on the DST in depression. It was shown that, overall, 46% of the 543 patients with major depressive disorder showed abnormal DST results, but different rates were found in different centers. Rihmer found that patients living in cities closer to the equator

showed less frequent abnormality in their cortisol secretion patterns.

CRH and cortisol levels

CRH has been implicated as an important factor in clinical depression and suicide [154, 165]. CRH levels were increased in the hypothalamus of completed suicides [11, 27, 196]. Suicide attempt and suicidal ideation in depressed patients is associated with lower ACTH levels and cortisol levels [186]. Patients who make repeated suicide attempts have lower CSF-CRH than non-repeaters which remains unchanged and low for 7 months [269]. Traskman-Bendz et al. [246] reported lower levels of CRH in the CSF of suicide attempters with MDD compared to non-MDD suicide attempters.

There are two G protein-coupled CRH receptors in rat models, CRHR1 and CRHR2 [121]. The role of CRHR2 is less well established [15, 87]. Wasserman et al. [261] reported the association between neurotic personality traits, suicidality and the TBX19 gene was initially found by Wasserman et al. [259], which has been shown to be regulated by CRH [135] and to act as a transcriptional activator of the ACTH gene [114, 123]. They identified the allele rs4792887 in a large sample of families which may represent a part of the genetic susceptibility for suicidality by increasing HPA axis activity upon exposure to low levels of stress.

De Luca et al. [56] typed three polymorphisms of the CRHR2 gene, CRHR2(CA), CRHR2(GT), and CRHR2 (GAT), in 312 families where at least one subject had a DSM-IV bipolar disorder. Quantitative measures showed an association between suicide-related traits haplotype 5-2-3 and higher severity, and haplotype variation at the CRHR2 locus is associated with suicidal behavior. In addition, genetic variation at the CRHR2 locus was an important regulator of the HPA axis. The human CRH-binding protein (CRHBP) has been characterized [190] and inactivates CRH circulation in the plasma. Nemeroff et al. [166] found a marked reduction in CRH-binding sites in the frontal cortex of completed suicides. However, Hucks et al. [97] were unable to replicate this. More recently, Merali et al. [150] found that CRHR1, but not CRHR2 or CRHBP, mRNA expression was changed in the frontal cortex of completed suicides. Coste et al. [50] showed that CRHR2 performs regulatory functions of the HPA axis stress response, indicated by early termination of ACTH release in $Crhr2^{-/-}$ mice. Furthermore, Crhr2-deficient mice display stress-sensitive and anxiety-like behavior in the elevated plus maze and open-field test [14]. In contrast, the deletion of the highly homologous crhr1 receptor results in a decreased anxiety in stressed animals [230, 244].

Therefore, genetic variations in CRH receptors may represent a relevant part of the genetic susceptibility for suicidality by increasing HPA axis activity.

HPA axis hyperactivity

Considerable evidence suggests that hypercortisolemia is a frequent finding in depressed patients and persists between episodes [82, 86, 107, 203, 264, 280].

Roy et al. [212] and Norman et al. [168] found that violent suicide attempters had higher cortisol levels than those who made non-violent suicide attempts. Asberg and colleagues [9] also suggested that HPA axis activation is a consistent finding in patients with depressive disorder with melancholia and reflected a disturbed secretion pattern of cortisol, high urinary output of cortisol and its metabolites, high CSF concentrations of cortisol, and a reduced ability to suppress cortisol secretion after dexamethasone administration. Virkkunen [255] studied groups of male offenders and male controls for their excretion of urinary free cortisol. Habitually violent offenders with an antisocial personality disorder had a significantly lower excretion rate of urinary free cortisol than did all the other groups of offenders or the control subjects.

Post-mortem studies have found evidence of chronic HPA activation in completed suicides, such as adrenal hyperplasia, increased the CRH content in the CSF [7], down-regulated the CRF1 receptors by CRH and induced the CRF1 expression in hippocampal and cortical regions of the immature rat brain [34].

There are also six reports of a significant association between HPA-axis hyperactivity and completed suicide in mood disorder [37, 46, 47, 168, 240, 277]. Two other studies found the relationship to be confined to depressed patients who had attempted or seriously contemplated suicide [48, 100]. In a sample of borderline personality disorder (BPD) patients with minimal exposure to treatment, Jovev et al. [106] found that parasuicidal behavior might be associated with greater activation of the HPA axis.

However, despite the correlation of depressive symptoms and suicidal behavior with increased HPA-axis activity, HPA activity may be only one of the various risk factors involved in these complex phenomena [44].

Seasonality and risk of suicide in affective disorders

The association between seasonal variations and suicide was first investigated by Morselli in 1881 when he described "Spring-fever," noting marked seasonal variations in the frequency of suicide with a peak in late spring

(June) [157]. Durkheim [63] also reported a marked peak in the frequency of suicides in June. He associated the temporal fluctuations in suicidal behavior with temporal or cyclical aspects of social interaction.

More recent research has documented a spring and an autumn peak [110, 143]. Some studies have reported a spring peak for males but spring and autumn peaks for females [119, 120, 151, 152, 163, 164, 257].

Seasonal variations have also been reported for major affective disorders, with the peaks of depressive episodes generally in winter and in the early spring [192, 267]. Unipolar affective disorders peak in spring, while bipolar affective disorders peak in the spring and autumn peaks [209].

Since affective disorders are prevalent in suicidal individuals [239], it has been suggested that the seasonal variation in affective disorders leads to a parallel seasonal variation in suicidality [81, 133, 192, 267].

A study [8] has reported a significant seasonal fluctuation in the DST findings which were different from the seasonal variations in unipolar and bipolar II disorders. However, Harris et al. [86], van Bemmel et al. [250], and Deshauer et al. [59] found no evidence of significant seasonal variation post-DST cortisol values in acute psychiatric patients or in depressed patients.

Rybakowski and Twardowska [215] found a sex difference in this. During the winter months, female depressive patients had lower DST non-suppression rates and lower concentrations of post-dexamethasone plasma cortisol, compared to the March–October period. Male depressed patients had lower pre-dexamethasone cortisol levels during the winter months, suggesting less abnormality of HPA axis in winter months.

Reutfors et al. [202] found that suicide seasonality was more evident in violent than in non-violent suicide methods, and, furthermore, the seasonality of suicide was stronger in suicides with a history of inpatient psychiatric care.

Some studies have reported an increase in suicide seasonality [30, 162, 207], others have reported a decreasing trend [4, 205, 279], while still others have found no time-trend [162, 256]. These differences by nation may be a result of changing socio-economic conditions and medicine-related factors [174, 175]. In addition, several studies have found that the time-related trends in seasonality of suicide are associated with how hot the summers are [33, 193, 206, 218]. Thus, weather may play a role here [57, 85, 99, 116, 130, 146, 192].

Pituitary abnormalities

Pituitary microadenomas and adrenal enlargement, clinical as well as subclinical, are relatively frequent in completed suicides [71, 93, 112, 132, 156, 170, 214, 222, 265]. In a retrospective study, Furgal-Borzych et al. [71] found pituitary microadenomas in 47.7% of completed suicides compared to only 18.3% of the non-suicidal group. Logistic regression analysis in a model controlling for age and sex showed that microadenomas constituted a unique risk factor. The immunohistochemical phenotyping revealed a higher percentage of immunopositive (secreting) microadenomas in the non-suicidal group compared to the suicidal group (80.0% vs. 59.4%) and a predominance of growth hormone-secreting microadenomas in both groups. Some post-mortem changes, such as the precursor molecule for ACTH (POMC), were found in the pituitaries of the completed suicides, both as mRNA and peptide content, and as an indication of chronic activation of the HPA axis.

Hypocortisolism

Several studies have found evidence of HPA-axis hypoactivity in stress-related disorders [88]. Low HPA-axis activity has been documented in depression with atypical features [5], as well as in multiepisodic and chronic depressive disorders [64, 171, 225, 262]. Among suicide attempters, patients with Axis II personality disorders display lower cortisol levels than those without such a diagnosis [270].

Lindqvist et al. [122] followed up attempted suicides and non-suicidal controls for 12 years and found that evening salivary cortisol was lower in the suicide attempters compared to the controls. Low cortisol levels at follow-up were associated with severe psychiatric symptoms. They also found a negative correlation between suicidal intent and post-dexamethasone serum cortisol levels among suicide attempters with MDD, indicating an inverse relationship between suicidality and HPA-axis activation. Low 24-h urinary cortisol is associated with adverse events during the early life of similar patients [235]. In line with these results, other studies have also demonstrated that suicidal patients may show decreased levels of cortisol [186, 223].

These results indicate an association between low HPA-axis activity and suicidal behavior and are probably due to long-lasting and severe psychiatric morbidity, which in turn has exhausted the HPA-axis. However, more attention should be given to the potential role of hypocortisolism.

Conclusion

There might be an interplay between underlying biological factors and psychosocial factors leading to suicidal

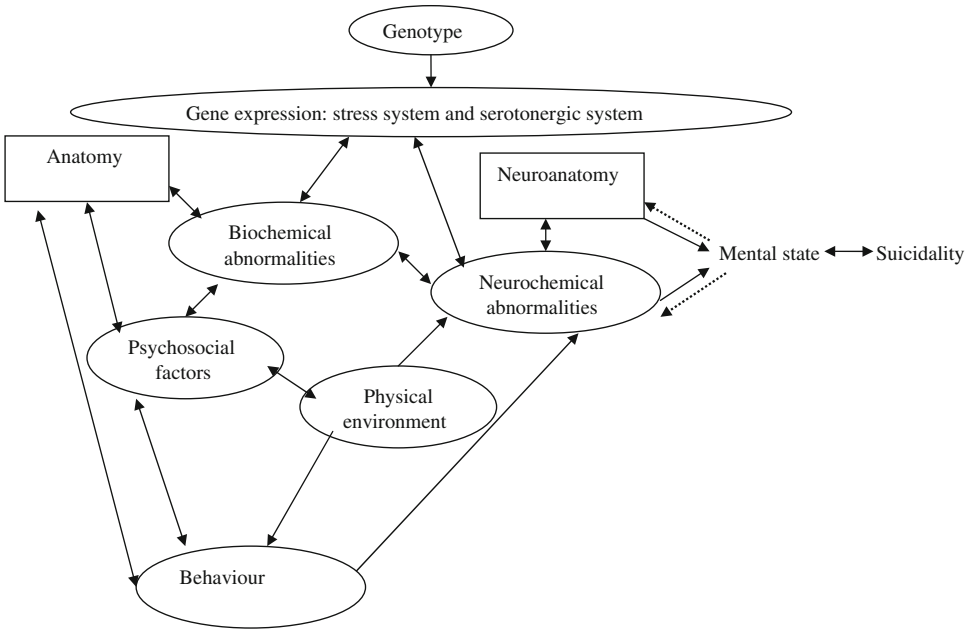

Fig. 2 The complex network of gene–environment interactions and a model for suicidality. Relatively stable and constant parameters are encircled. Arrows outline the relationships between the various parameters; solid arrows show well-established interactions, whereas dotted arrows show hypothesized interactions (modified from Wasserman et al. [260])

behavior in vulnerable patients with psychiatric disorders. The biological vulnerability is probably reflected in genetic factors and physiological abnormalities that involve the serotonergic system as well as the stress system (see Fig. 2). The psychosocial factors may involve early childhood experiences [241]. Both factors may influence neuroendocrine (the HPA axis), neurochemical (particularly serotonin), and clinical (aggression/impulsivity, pessimism, neuroticism, and hopelessness) endophenotypes of suicidal behavior.

Stress plays a major role in various (patho)physiological processes associated with mood disorders. HPA-axis hyperactivity is probably present in a large subpopulation of depressed subjects. CRH and cortisol seem to be causally involved in the development of depression and suicidal behavior. A crucial factor seems to be time. Effects that are beneficial to an organism in the short term may have detrimental effects in the long term.

An important question is whether the biological abnormalities found in completed suicides are characteristic of a sub-population, particularly of patients affected by affective disorders, or whether there are neurobiological precursors common to all suicides. Disturbances in the 5-HT and HPA systems have been identified both in completed suicides and in affective disorders without suicidal behavior. The answer is particularly relevant, because 40–60% of suicide victims have a history of affective disorders.

In summary, the HPA axis may exert an important modulatory influence on some components of the serotonin system. Thus, HPA over-activity is not merely an epiphenomenon of the suicidal state, but may be responsible for (or worsen) some of the 5-HT abnormalities found in mood disorders and suicide.

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