

Toward a Biosignature for Suicide

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Objective: Suicide, a major cause of death worldwide, has distinct biological underpinnings. The authors review and synthesize the research literature on biomarkers of suicide, with the aim of using the findings of these studies to develop a coherent model for the biological diathesis for suicide.

Method: The authors examined studies covering a large range of neurobiological systems implicated in suicide. They provide succinct descriptions of each system to provide a context for interpreting the meaning of findings in suicide.

Results: Several lines of evidence implicate dysregulation in stress response systems, especially the hypothalamic-pituitary-adrenal axis, as a diathesis for suicide. Additional findings related to neuroinflammatory

indices, glutamatergic function, and neuronal plasticity at the cellular and circuitry level may reflect downstream effects of such dysregulation. Whether serotonergic abnormalities observed in individuals who have died by suicide are independent of stress response abnormalities is an unresolved question.

Conclusions: The most compelling biomarkers for suicide are linked to altered stress responses and their downstream effects, and to abnormalities in the serotonergic system. Studying these systems in parallel and in the same populations may elucidate the role of each and their interplay, possibly leading to identification of new treatment targets and biological predictors.

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In 2011, suicide claimed nearly 40,000 lives in the United States (1); worldwide, the number approached 1 million (2). In our model (3, 4), suicide is triggered by a life event or a psychiatric episode in an individual with a predisposing diathesis. The diathesis begins with the individual's genetic risk and develops further as the accumulation of traumatic events, mental and physical illnesses, and losses leads to neurobiological changes in the organism. We and others have proposed that a key component of the underlying diathesis is an altered stress response. In this review, we assess the evidence for this neurobiological mechanism and other related systems, as well as serotonergic function. These systems typically have been studied using biomarkers, as defined by the National Institutes of Health (5): "a characteristic that is objectively measured and evaluated as an indicator of ... pathogenic processes." We focus here on studies that distinguish biomarkers of suicide from those associated with co-occurring psychiatric disorders.

Suicidal behavior varies in degree of lethality and suicidal intent, and biomarkers will likely depend on these variables to some extent. To reduce this variance, we focus on the most serious manifestation of suicidal behavior, suicide itself. Because understanding the physiology of systems within which putative biomarkers fall is essential, we briefly review pertinent systems.

Stress Response and Its Modulation

Hypothalamic-Pituitary-Adrenal Axis and Locus Ceruleus-Norepinephrine System

Stress elicits a complex array of physiological and behavioral responses, which optimally are rapidly discontinued once the stressor is gone or the organism adapts to it (6). The main components of the stress response system are the corticotropin-releasing hormone/hypothalamic-pituitary-adrenal axis (CRH-HPA) system and the locus ceruleus-based norepinephrine (LC-NE) system (7).

Stress activates the CRH-HPA system via release of corticotropin-releasing hormone (CRH) and vasopressin from the hypothalamus into the portal circulation, which in turn activates CRH receptor 1 (CRHR1) and vasopressin receptors in the pituitary, leading to pituitary release of pro-opiomelanocortin (POMC), the precursor of β -endorphin and adrenocorticotrophic hormone (ACTH). Once in the main circulation, ACTH triggers cortisol release from the adrenal cortex, which mobilizes energy, potentiates some catecholamine actions, dampens inflammatory responses, and activates glucocorticoid receptors (GRs). GRs are ubiquitous lower-affinity receptors, binding cortisol when levels are high. GR stimulation increases glucose levels and lipolysis, mobilizing energy resources, and enhances memory storage and consolidation, preparing the organism for similar events in the future (6). Mineralocorticoid receptors (MRs) are higher affinity (~10 times the

affinity of GRs) and are occupied under basal conditions, thereby maintaining HPA axis tone. They are present in the hippocampus, the amygdala, the septum, and some cortical areas. When bound to corticosteroids, MRs and GRs regulate gene transcription (see Table 1 for a summary of gene expression findings in suicide), mediating later effects of stressors. They affect gene expression of G-protein coupled receptors, ion channels, and membrane proteins relevant to conductance and hence to cell activation. Downstream, they influence cell structure, metabolism, and synaptic transmission and may be central to apoptosis and neurogenesis in the hippocampus and other limbic and prefrontal areas (6), generating effects at both the neuronal and the neurocircuitry levels (8). Negative feedback commences when corticosteroids bind to MRs and GRs. GRs are also inhibited by the cochaperone, immunophilin FK506 binding protein 5 (FKBP5).

In parallel, activation of the LC-NE system leads to norepinephrine release from a dense network of neurons originating in the locus ceruleus and projecting widely to the forebrain, leading to enhanced arousal, vigilance, and anxiety. Several G-protein coupled subtypes of norepinephrine receptors are distributed throughout the neocortex, thalamus, hypothalamus, hippocampus, amygdala, and basal ganglia. Norepinephrine α and β receptors each have several subtypes. Norepinephrine α 1 receptors are postsynaptic, found mainly in the thalamus, hippocampus, basal ganglia, and cortical and cerebellar cortices. Norepinephrine α 2 receptors are mainly in the locus ceruleus and the cerebral cortex and are either postsynaptic or autoreceptors regulating norepinephrine release. Preclinical models suggest that further subcategories, norepinephrine α 2a and α 2c, are “stress promoting” and “stress protective,” respectively. Moreover, norepinephrine α 1 and α 2 have inhibitory and excitatory effects, respectively, on serotonergic function. β receptors found in the basal ganglia, subthalamic nuclei, and deep nuclei of the cerebellum are essential for memory consolidation. Norepinephrine neurotransmission is terminated by reuptake by norepinephrine transporters or catabolism by monoamine oxidase (MAO) or catechol *O*-methyltransferase (COMT).

Another, slower stress response system is regulated by urocortins II and III, acting mostly through CRH receptor 2 (CRHR2) and with anxiolytic properties, in contrast to the anxiogenic properties of norepinephrine. CRHR2 activation appears to dampen the stress response associated with CRHR1 activation. Of note, brain distributions of CRHR1 and CRHR2 overlap (6).

HPA axis in suicide. Studies comparing depressed individuals who have died by suicide to nonpsychiatric comparison subjects report elevated CRH (9–11) and vasopressin (11) levels in the forebrain, raphe, and locus ceruleus (11); fewer CRHR1s (but not CRHR2s) in the frontal cortex (12), presumably down-regulated in response to elevated CRH (13); increased POMC in the pituitary (14); decreased GR

expression (15) in the amygdala and prefrontal cortex, but not the hippocampus; and decreased hippocampal MR mRNA (16), a pattern similar to that observed in rodent models of chronic stress (17, 18). Of interest, one study noted decreased hippocampal GR expression only among suicide victims with childhood abuse (19). Basal cortisol levels are decreased in depressed suicide victims compared with depressed patients (20), implying that although data suggest HPA axis hyperreactivity to stimuli, basal HPA axis tone, generally modulated by MRs, may be lower. Studies showing adrenal cortex hypertrophy in violent suicides are also supportive (21–23) of an overactive HPA axis, although not all studies agree (24). Additionally, in a Japanese population, haplotype analysis of the FKBP5 gene (see Table 2 for a summary of genetic findings in suicide), which encodes a cochaperone that binds to cytosolic GR and inhibits its sensitivity, shows an association with suicide (25). The lack of psychiatric controls in these studies hampers interpretation.

Most data implicating the HPA axis come from studies examining the negative feedback system as tested by the dexamethasone suppression test (DST). In one study (26), depressed DST nonsuppressors were more likely to die by suicide and have higher-lethality attempts than DST suppressors, although a similar study did not confirm this (20). In depressed inpatients, although DST did not distinguish those at risk for suicide, suicide attempters with DST nonsuppression were more likely to die by suicide (27). Coryell and Schlessler (28), who followed a depressed cohort for 15 years, found that DST nonsuppression at baseline was associated with a 14-fold higher odds of eventual suicide. This finding was expanded by a meta-analysis of prospective studies of suicide, which generated a prediction model in which DST nonsuppression had a specificity of 55%, rising to 88% when a low CSF level of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, was included in the model; this, however, came at the expense of sensitivity, which declined to 38% (29).

Together, these data implicate abnormalities in HPA axis function at several levels. Perhaps CRHR1 is down-regulated to compensate for higher CRH levels, but not enough to dampen the CRH-ACTH-cortisol pathway. Higher cortisol levels may also lead to low basal tone and DST nonsuppression, reflecting altered sensitivity of MRs and GRs, respectively, and potentially decreased GR sensitivity.

Noradrenergic-locus ceruleus system in suicide. Postmortem studies suggest alterations at several levels of the noradrenergic system in suicide, although the data are inconsistent. Higher locus ceruleus levels of tyrosine hydroxylase, the rate-limiting enzyme in norepinephrine synthesis, may reflect increased norepinephrine activity and/or effects of chronic stress. However, both higher (30) and lower (31) tyrosine hydroxylase immunocytochemical staining density have been reported in the locus ceruleus of suicide victims compared with matched comparison subjects.

TABLE 1. Gene Expression Findings in Suicide^a

System	Paper	mRNA	Brain Regions	Findings
CRH-HPA	Pandey et al. (15)	GR- α , GR- β , MR	Amygdala, PFC, hippocampus	In teenage suicide victims compared with deceased healthy controls: 1) GR- α mRNA levels reduced in amygdala and PFC, but not hippocampus, 2) no difference in PFC GR- β mRNA expression, 3) no difference in MR mRNA expression in all three brain regions
	López et al. (16)	GR, MR	Hippocampus	No difference in GR or MR mRNA levels in depressed suicide victims compared with deceased controls
	Labonte et al. (19)	GR, GR exon splice variants (1B, 1C, 1H)	Hippocampus, ACC	Hippocampus: decreased GR, GR1B, GR1C, and GR1H mRNA expression in suicide victims with abuse history compared with suicide victims without abuse history and controls; no difference between suicide victims without abuse and controls in GR1B, GR1C, and GR1H levels; ACC: no difference between groups in GR and variant expression
	López et al. (14)	POMC, GR	Pituitary	Increased POMC mRNA density in corticotropic cells of suicide victims compared with controls; no difference in GR mRNA expression
	Sequeira et al. (112)	MT	ACC, nucleus accumbens	Decreased mRNA expression of two MT families, MT-1 and MT-2, in both ACC and nucleus accumbens of depressed suicide victims compared with deceased controls; no difference in MT-3 mRNA expression
	Merali et al. (13)	CRH1, CRH2	FPC, DMPFC, VLPFC	In FPC, CRH1 mRNA expression lowered in suicide victims compared with controls, no difference in CRH2 mRNA levels; no differences in either CRH1 or CRH2 mRNA expression in DMPFC or VLPFC
NE-LC	Du et al. (51)	COMT	FPC, OFC	COMT mRNA expression elevated in depressed suicide victims compared with deceased controls in both the FPC and OFC; also, Met carriers who died of suicide showed elevated COMT mRNA levels in FPC compared with control Met carriers
	Escribá et al. (76)	α 2A-adrenoceptor	PFC	Increased mRNA expression levels found in suicide victims compared with controls
Cytokines	Tonelli et al. (61)	TNF- α , IL-1 β , IL-4, IL-5, IL-6, IL-13	BA 11	IL-4 mRNA expression was increased in female suicide victims compared with controls, whereas IL-13 mRNA expression was elevated in male suicide victims; no difference in the remaining factors
Endogenous opioids	Escribá et al. (76)	μ -opioid receptor	PFC	Increased mRNA expression found in suicide victims compared with controls
	Hurd et al. (77)	Prodynorphin	Caudate nucleus	Increased mRNA expression levels in suicide victims compared with patients with schizophrenia and controls
Serotonin	Bach-Mizrachi et al. (85)	TPH2	DRN, MRN	Higher mRNA expression in DRN (along entire rostrocaudal axis) and MRN of suicide victims compared with deceased nonpsychiatric controls
	Bach-Mizrachi et al. (88)	TPH2	DRN, MRN	Mean TPH2 mRNA expression levels per neuron in DRN and MRN greater in depressed suicide victims than deceased healthy controls; in DRN, expression levels different in caudal but not rostral regions
	De Luca et al. (87)	TPH2	DLPFC (BA 46)	No difference in mRNA expression between suicide victims and controls
	Perroud et al. (84)	TPH1, TPH2	VPFC	Increased TPH2 mRNA expression in suicide victims compared with controls; no difference in TPH1 expression
	López et al. (16)	5-HTR1A	Hippocampus	Decreased mRNA expression in depressed suicide victims compared with deceased controls
	Matthews and Harrison (89)	5-HTR1A	DRN	No difference in mRNA expression between suicide victims, three non-suicide groups (schizophrenia, bipolar disorder, depression) and controls
	Escribá et al. (76)	5-HTR1A, 5-HTR2A	PFC	Increased mRNA expression of both 5-HTR1A and 5-HTR2A in suicide victims compared with controls
	Sequeira et al. (112)	5-HTR2A, PER1, ADCY1	DLPFC	Decreased mRNA expression of 5-HTR2A, ADCY1 (adenylate cyclase gene) and PER1 (period homologue) in suicide victims compared with deceased controls

continued

TABLE 1. Gene Expression Findings in Suicide^a (continued)

System	Paper	mRNA	Brain Regions	Findings
	Pandey et al. (113)	5-HTR2C	Multiple brain regions	No difference in mRNA expression levels of 5-HTR2C between suicide victims and controls in any studied brain regions (PFC, hippocampus, choroid plexus, hypothalamus, nucleus accumbens, cerebellum)
GABA	Merali et al. (13)	GABA _A	FPC, DMPFC, VLPFC	In FPC, mRNA levels of GABA _A α1, α3, α4, and δ subunits, but not α2, α5, or λ, were lower in suicide victims compared with deceased controls; no difference in GABA _A expression between groups in DMPFC or VLPFC
	Poulter et al. (140)	GABA _A	OFC, LC, PVN, hippocampus, amygdala	Pattern of GABA _A subunit expression differed in suicide victims compared with controls; lowered subunit coordination in hippocampus and amygdala, increased coordination in OFC and PVN, unchanged in LC
	Sequeira et al. (139)	Multiple GABA-ergic genes	17 brain regions	Up-regulation in multiple GABA-ergic genes in depressed suicide victims, but no differences between nondepressed suicide victims and controls observed
	Klempan et al. (143)	Multiple GABA-ergic genes	VPFC (BA 44, 45, 46, 47), DPFC	Multiple GABA-ergic genes (GABA _A α5, β1, δ, γ1, and γ2, GABBR2, SLC6A1) differentially expressed in BA 46 of suicide victims compared with controls
	Choudary et al. (150)	Multiple GABA-ergic genes	ACC	GABA _A α1 and GABA _A β3 mRNA expression up-regulated in suicide victims with mood disorders compared with controls
Glutamate	Sequeira et al. (139)	Multiple glutamatergic genes	Multiple brain regions	GLUL down-regulated in PFC, amygdala of depressed suicide victims; AMPA up-regulated in amygdala, hippocampus, nucleus accumbens, and few cortical regions in depressed suicide victims; GRM3 down-regulated in PFC, parietal cortex of suicide victims (with and without depression) compared with controls
	Klempan et al. (143)	Multiple glutamatergic genes	VPFC (BA 44, 45, 46, 47), DPFC	Multiple glutamatergic genes (GRIA3, GRIN2A, SLC1A2) showed increased expression in BA 46 of suicide victims compared with controls
Neuronal plasticity	Pandey et al. (162)	BDNF, TrkB	PFC (BA 9), hippocampus	BDNF and TrkB mRNA levels lower in PFC and hippocampus of teenage suicide victims compared with deceased healthy controls
	Dwivedi et al. (164)	BDNF, TrkB	PFC (BA 9), hippocampus	BDNF and TrkB mRNA expression lower in PFC and hippocampus of suicide victims compared with deceased healthy controls
	Keller et al. (170)	BDNF promoter/exon IV	Wernicke area	Suicide victims with high BDNF promoter/exon IV methylation patterns showed decreased BDNF mRNA expression compared with intermediate and low methylation pattern groups (including suicide victims and controls)
	Keller et al. (169)	TrkB, TrkB-T1	Wernicke area	No differences in mRNA expression levels of either TrkB or TrkB-T1 in suicide victims compared with deceased controls
	Dwivedi et al. (166)	TrkA, TrkC, p75(NTR)	PFC, hippocampus	TrkA mRNA expression decreased, whereas p75 (NTR) expression increased, in both PFC and hippocampus of suicide victims compared with deceased nonpsychiatric controls; TrkC expression decreased in hippocampus
	Dwivedi et al. (167)	NGF, NT-3, NT-4/5, NSE	PFC, hippocampus	NGF, NT-3, NT-4/5, and NSE mRNA expression levels lower in hippocampus of suicide victims compared with deceased controls; in PFC, only NT-4/5 mRNA expression lowered in suicide victims
Methylation	Labonte et al. (19)	GR, GR exon splice variants (1B, 1C, 1H)	Hippocampus	GR1B: hypermethylation at CpG6 and CpG8, hypomethylation at CpG11 in suicide victims compared with controls; GR1C: hypermethylation at CpG9 and CpG12 (suicide victims), CpG8 (abused suicide victims), hypomethylation at CpG13 (abused suicide victims); GR1H: hypomethylation in abused suicide victims (CpG2, CpG5, CpG10) compared with suicide victims without abuse (CpG3, CpG7, CpG8, CpG12) and controls (CpG1)

continued

TABLE 1. Gene Expression Findings in Suicide^a (continued)

System	Paper	mRNA	Brain Regions	Findings
	Poulter et al. (142)	GABA _A α 1, DNMT	Multiple brain regions	DNMT-3B up-regulation associated with hypermethylation at three sites on GABA _A α 1 gene in FPC of depressed suicide victims compared with deceased controls
	Keller et al. (169)	TrkB, TrkB-T1, BDNF	Wernicke area	No differences in methylation patterns at any TrkB or TrkB-T1 CpG sites examined in suicide victims compared with deceased controls; hypermethylation of BDNF promoter IV present in suicide
	Keller et al. (170)	BDNF promoter/exon IV	Wernicke area	Significant hypermethylation at two CpG sites of BDNF promoter/exon IV in suicide victims compared with deceased controls

^a ACC=anterior cingulate cortex; BA=Brodmann's area; CRH-HPA=corticotropin-releasing hormone/hypothalamic-pituitary-adrenal axis system; DLPFC=dorsolateral prefrontal cortex; DMPFC=dorsomedial prefrontal cortex; DPFC=dorsal prefrontal cortex; DRN=dorsal raphe nucleus; DVC=dorsal vagal complex; FPC=frontopolar cortex; GR=glucocorticoid receptor; LC=locus ceruleus; LC-NE=locus ceruleus-based norepinephrine system; MR=mineralocorticoid receptor; MRN=median raphe nucleus; MT=metallothionein; OFC=orbitofrontal cortex; PFC=prefrontal cortex; PVN=paraventricular nucleus; VLPFC=ventrolateral prefrontal cortex; VPFC=ventral prefrontal cortex.

Findings regarding norepinephrine α 1 receptor binding abnormalities in suicide are inconsistent as well. Lower norepinephrine α 1 binding in the prefrontal cortex, temporal cortex, and head of caudate (32) has been reported in suicide compared with sudden death. However, Arango et al. (33) reported higher norepinephrine α 1 binding in the prefrontal cortex in suicide victims and higher norepinephrine levels. Of note, decreased norepinephrine α 1 binding in the lateral prefrontal cortex has been reported in alcohol-dependent suicide victims (34). The discrepancies in the aforementioned studies do not appear to be simply due to the use of different ligands.

Presynaptic norepinephrine α 2 binding is reportedly higher (35) or similar (36) in hippocampal and frontal regions in suicide victims relative to comparison subjects. Of note, a polymorphism in the α 2 norepinephrine receptor gene promoter region of unknown functional significance was more common in Japanese female but not male suicide victims relative to live healthy comparison subjects (37). Thus, whether norepinephrine α 2 receptor binding is altered in suicide remains unknown.

Some studies have reported higher norepinephrine β receptors in the frontal (38–40) and temporal (39) cortex of suicide victims, although subjects who died by suicide and comparison subjects were not matched by diagnosis. However, when a suicide group with diverse diagnoses was compared with a non-suicide group matched partly based on diagnosis, decreased norepinephrine β receptor binding was observed in the suicide group (41). Additionally, fewer norepinephrine β receptor binding sites have been reported in the temporal cortex (Brodmann's area [BA] 38) of depressed suicide victims with no antidepressant treatment in the previous 3 months (42) and in depressed suicide victims with antidepressant treatment (43), compared with nonpsychiatric comparison subjects. Moreover, suicide victims who used violent methods had fewer norepinephrine β receptors compared with those using nonviolent methods (42). Antidepressant-treated depressed suicide

victims also had lower norepinephrine β receptor binding in the thalamus compared with nonpsychiatric comparison subjects (43), consistent with animal studies in which antidepressants were found to down-regulate β receptor binding (44). Clearly, reconciling findings regarding norepinephrine β receptors in suicide is challenging.

Molecular abnormalities in the norepinephrine transporter, in related enzymes, and in neuron number also have been reported. Lower norepinephrine transporter binding has been observed in the locus ceruleus but not the hypothalamus in depressed suicide victims relative to nonpsychiatric comparison subjects (45). A monoamine oxidase A (MAO-A) gene polymorphism leading to high activity was found to be more prevalent in male but not female suicide victims with mood disorders compared with nonpsychiatric comparison subjects (46), although MAO-A and MAO-B activity does not seem altered in suicide victims (47). In a study of Japanese suicide victims, the Val/Val genotype of COMT, which renders COMT more efficient at catabolizing norepinephrine, was more prevalent in healthy live male comparison subjects than in suicide victims (48), but this was not observed in females. However, an opposite, protective effect of the Met/Met genotype was found in a sample of Caucasians who died from other causes compared with those who died by suicide, only among males (49). Moreover, in suicide victims compared with nonpsychiatric comparison subjects, decreased density and fewer norepinephrine neurons were observed in the rostral two-thirds of the locus ceruleus (50), as were higher concentrations of COMT in the prefrontal cortex and orbitofrontal cortex (51). Thus, some evidence suggests lower norepinephrine function in suicide, which, if true, could be secondary to down-regulation in response to chronic stress. The lack of psychopathological comparison subjects renders interpretation difficult.

Neuroinflammation

Cytokines. Cytokines are intracellular mediator proteins that act in a paracrine manner on secretion by inflammatory

TABLE 2. Genetic Findings in Suicide

System ^a	Genes	Paper	Sample	Findings
CRH-HPA	FKBP5	Supriyanto et al. (25)	Japanese	Higher frequency of TC haplotype associated with higher transcription of FKBP5 in suicide victims compared with live nonpsychiatric controls
NE-LC	ADRA2	Fukutake et al. (37)	Japanese	C-allele of C-1291G SNP (unknown function) more prevalent in female suicide victims than in live female nonpsychiatric controls
	MAO-A	Du et al. (46)	Hungarian	High activity-related allele of EcoRV polymorphism differed in depressed male but not female suicide victims compared with deceased nonpsychiatric controls
	COMT	Ono et al. (48)	Japanese	High activity Val/Val genotype of 158Val/Met polymorphism found less prevalent and Val/Met genotype more prevalent in male but not female suicide victims compared with living nonpsychiatric controls
	COMT	Du et al. (51)	Hungarian	No difference in allele frequency or genotypic distribution in depressed suicide victims compared with deceased nonpsychiatric controls
	COMT	Pivac et al. (49)	Slovenian	Val/Val and Val/Met genotypes of 158Val/Met polymorphism more prevalent in male but not female suicide victims, as compared with deceased controls
	Endogenous opioid	OPRM1	Hishimoto et al. (71)	Japanese
Serotonin	TPH2	Zill et al. (91)	German	SNP rs1386494 (located between exon 5 and exon 7) associated with suicide in a sample of suicide victims compared with live healthy controls
	TPH2	Lopez de Lara et al. (92)	French-Canadian	T allele of SNP rs4448731 and G allele of rs6582071 in upstream region, G allele of rs4641527 in intron 1, and C allele of rs1386497 in intron 8 more prevalent in depressed suicide victims compared with live depressed patients
	TPH2	Stefulj et al. (93)	Croatian	No difference in genotype or allele frequency of G-703T SNP in sample of suicide victims compared with controls
	TPH2	Mouri et al. (94)	Japanese	No difference in genotype or allele frequency of 15 tagging SNPs in suicide victims compared with live healthy controls
	TPH1, TPH2, SLC6A4	Buttenschön et al. (102)	Danish	No significant association of either TPH1, TPH2, or 5-HTTLPR with suicide in a sample of suicide victims compared with living controls
	TPH, 5-HTT	Jernej et al. (103)	Croatian	Co-occurrence of 5-HTT intron 2 VNTR 10 allele and CC variant of TPH intron 7 A218C SNP more frequent in suicide victims than in live healthy controls
	5-HTT	Bondy et al. (171)	German	S allele and homozygous SS genotype of 5-HTTLPR more prevalent in suicide victims than in healthy living controls
	5-HTT	Lopez de Lara et al. (101)	French-Canadian	VNTR STin2 allele 10 more frequent in depressed suicide victims compared with depressed controls; no significant genotypic or allelic differences noted at 5-HTTLPR locus
	5-HTT	Hranilovic et al. (105)	Croatian	No difference in allele and genotype frequency in either 5-HTTLPR or VNTR intron 2 polymorphisms in suicide victims compared with live healthy controls
	5-HTR1A	Videtic et al. (172)	Slovenian	No difference in C-1019G allele or genotype distributions between suicide victims and deceased controls
	5-HTR1B	Zouk et al. (114)	French-Canadian	Higher frequency of T allele at A-161T locus in suicide victims compared with live nonpsychiatric controls; no differences at T-261G, C129T, G861C, or A1180G loci
	5-HTR1B, 5-HTR1D α , 5-HTR1E, 5-HTR1F, 5-HTR2C, 5-HTR5A, 5-HTR6	Turecki et al. (117)	French-Canadian	No difference in allele or genotype frequencies in any loci examined (G861C of 5-HTR1B, T1350C of 5-HTR1D α , C117T of 5-HTR1E, C-78T and C528T of 5-HTR1F, G-995A of 5-HTR2C, G-19C of 5-HTR5A, and C267T of 5-HTR6) in suicide victims compared with live healthy controls

continued

TABLE 2. Genetic Findings in Suicide (continued)

System ^a	Genes	Paper	Sample	Findings
	5-HTR2A	Ono et al. (119)	Japanese	No association between 5-HTR2A A-1438G SNP and suicide
	5-HTR2A	Turecki et al. (111)	French-Canadian	No difference in T102C or A-1438G SNP allele or genotype distribution in suicide victims compared with deceased controls
	5-HTR2C	Videtic et al. (116)	Slovenian	Increased frequency of G68C G-allele and GG genotype in suicide victims compared with controls; relationship also significant in females but not males; no association between G-995A and suicide
	5-HTR6	Azenha et al. (115)	Portuguese	Difference in C267T genotype distribution in male suicide victims compared with deceased nonpsychiatric controls; no association present when females included
Neuronal plasticity	BDNF	Pregelj et al. (168)	Slovenian	No difference in Val66Met variant distribution in suicide victims compared with deceased controls; in females, more likely to have Met alleles associated with low activity
	DISC1	Ratta-apha et al. (173)	Japanese	Allele frequency and genotype distribution of Ser704Cys variant differ in suicide victims and live healthy controls

^a CRH-HPA=corticotropin-releasing hormone/hypothalamic-pituitary-adrenal axis system; LC-NE=locus ceruleus-based norepinephrine system.

leukocytes and some non-leukocyte cells. Although cortisol inhibits cytokine secretion during acute stress (52), inflammatory cytokines also modulate HPA axis function in a complex manner, activating the CRH-ACTH-cortisol cascade and down-regulating GRs (53). Thus, inflammation may induce a functional glucocorticoid insufficiency, contributing to the blunted responsiveness of the negative feedback loop to glucocorticoids, as measured by the DST (54).

The observation that cytokine therapies such as β -interferon can induce suicidal ideation and behaviors (55) as well as depression has led to work to uncover the mechanism. One pathway may be via influences on the serotonin system. In cell culture, serotonin transporter activity is stimulated by the proinflammatory cytokines interleukin [IL]-1 β (56, 57) and tumor necrosis factor (56, 58), enhancing reuptake of intrasynaptic serotonin and reducing signaling. Conversely, the anti-inflammatory cytokine IL-4 induces a dose-dependent decrease in serotonin uptake by the transporter (59).

Cytokine abnormalities in suicide. Suicide victims with a variety of diagnoses exhibit altered levels of cytokines, including increased frontopolar cortex levels of IL-1, IL-6, and tumor necrosis factor alpha (TNF- α) in teen suicide victims (60), increased orbitofrontal cortex levels of IL-4 mRNA in female and IL-13 in male suicide victims (61), and microgliosis (62), another marker of neuroinflammation, compared with nonpsychiatric comparison subjects. Because these study samples had relatively few depressed subjects, cytokine elevations in suicide victims are unlikely to be explained by depression.

Polyunsaturated fatty acids. Another potential path to an inflammatory role in suicide is an imbalance of proinflammatory omega-6 (primarily arachidonic acid) and anti-inflammatory omega-3 (primarily docosahexaenoic acid

[DHA] and eicosapentaenoic acid [EPA]) polyunsaturated fatty acids. Omega-3 fatty acids reduce proinflammatory eicosanoids, cytokines, reactive oxygen species, and adhesion molecules via several mechanisms, including competitive inhibition of omega-6, influencing inflammatory gene transcription factors, and through anti-inflammatory effects of their own metabolic products, the resolvins (63). Low omega-3 fatty acid levels are associated with suicide attempts (64) or predicted future attempts (65), suggesting a role in suicide risk.

Polyunsaturated fatty acid status in suicide. A single large retrospective case-control study of deceased U.S. military personnel who had died by suicide and by non-suicide causes found that the suicide group had lower serum concentrations of omega-3 DHA as a percentage of total fatty acids (66). Suicide risk increased 14% with each standard deviation of decrease in DHA concentration. Two other postmortem samples (67, 68) showed no differences between suicide deaths and non-suicide deaths in brain fatty acid composition; however, sample sizes were small, and only one included psychiatric comparison subjects (68). A large population study using dietary questionnaires did not find a link between EPA consumption and suicide either (69).

Endogenous Opioid System

The opioid system plays a key role in stress response and interacts with both the HPA axis and the LC-NE system. Stress causes pituitary release of POMC, the precursor of ACTH and β -endorphin and a major endogenous opioid (70). Endogenous opioids reduce the emotional component of pain, but not pain perception per se. As such, these peptides may attenuate stress effects, and their alteration may contribute to suicide risk.

The opioid system in suicide. Eight studies have examined the opioid system's role in suicide (71–78). Six of them (71–76) focused on the mu receptor, with inconclusive results. Three suggest higher mu receptor binding in suicide victims compared with dead or live comparison subjects (72, 75, 76); however, they focused on different brain areas (the caudate and frontal cortex, the frontal and temporal cortex, and BA 9 and the prefrontal cortex, respectively), or analyzed only young suicide victims (75). In contrast, Zalsman et al. (74) and González-Maeso et al. (73) found no differences in mu receptor distribution despite examining similar brain regions (the prefrontal cortex and BA 9, and the dorsolateral prefrontal cortex, respectively). Studies of endogenous opioids in suicide are few and difficult to interpret, with one study of prodynorphin showing higher levels in the caudate but not the putamen or nucleus accumbens (77), and one of beta endorphin showing lower levels in the caudate and temporal and frontal cortex (78). Unfortunately, most of these studies had small samples, ranging from 10 or fewer cases to 28 cases per cell. One genetic study (71) comparing suicide victims and comparison subjects found a single-nucleotide polymorphism (SNP) in the mu receptor gene associated with suicide. Drawbacks include the lack of matched psychiatric comparison subjects, variable postmortem intervals, and a variable toxicology status among subjects.

Neurotransmitter Systems Implicated in Suicide

See Table 3 for a summary.

Serotonin

Cell bodies in the dorsal and median raphe nuclei provide extensive serotonergic innervation throughout the brain. Seven serotonin (5-hydroxytryptamine [5-HT]) receptor families exist, many with several subtypes. All but one (5-HT₃, a ligand-gated ion channel) are G-protein coupled receptors (79). The presynaptic serotonin transporter (5-HTT) removes serotonin from the synaptic cleft. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in 5-HT synthesis (80, 81), and two isoforms, TPH1 and TPH2, are present in humans. TPH1, found primarily in the periphery after birth, is implicated in intrauterine neurodevelopment (82, 83). TPH2 is specific to brain (82). Serotonin breakdown involves oxidation of 5-HT by MAO-A and aldehyde dehydrogenase to produce 5-HIAA. Given the serotonergic system's involvement in regulation of sleep, appetite, anxiety, mood, cognition, aggression, and memory, all of which have a role among the clinical features associated with suicide, it is a key candidate for study.

Tryptophan hydroxylase and serotonin synthesis in suicide. Elevated TPH2 levels have been reported in the ventral prefrontal cortex of suicide victims (84) relative to comparison subjects, even controlling for psychopathology; this elevation is more pronounced in subjects who died in

nonviolent suicides (84). Additionally, increased TPH2 expression and protein have been noted in suicide victims in the dorsal (85, 86) and median raphe nucleus (85) and along the entire rostrocaudal axis of the dorsal raphe nucleus (85), but not in the dorsolateral prefrontal cortex (87). Whether these elevations reflect a compensation for decreased serotonin availability (85, 86) is unknown. In addition to increased expression of TPH2, the presence of more serotonin neurons in the raphe nuclei of suicide victims (88, 89) indicates that serotonin synthesis capacity is enhanced, perhaps in response to decreased serotonergic tone. Indeed, Bach et al. (90) recently reported more serotonin in the raphe nuclei of suicide victims. In addition, links have been reported between suicide and SNPs located between TPH2 exons 5 and 7 (91), in intron 1, intron 8, and the 5' upstream region (92). However, no link was found between suicide and the G703T SNP (93) or multiple other TPH2 polymorphisms (94).

Serotonin transporter in suicide. Most studies report a decrease (95–98) or no change (99) in 5-HTT binding affinity in the hippocampus and prefrontal cortex, although an increase has also been reported (100). Fewer neurons express the serotonin transporter in the raphe nuclei of suicide victims. The deficit in transporter binding has been shown to differ from that seen in major depression, where it extends over most of the prefrontal cortex, whereas in suicide it is restricted to the ventromedial prefrontal cortex and anterior cingulate regions (95), which are implicated in decision making and willed action. Of note, a serotonin transporter intron 2-variable nucleotide tandem repeat (STin2-VNTR) 10-allele was more common in depressed Canadians who died by suicide compared with depressed live comparison subjects (101), but no other 5-HTT polymorphisms have been shown to confer risk, including promoter (5-HTTLPR) alleles in the Canadian study (101) and a more recent one (102) examining the SCL6A4 site. One study (103) examining the co-occurrence of the 10-allele of the STin2-VNTR polymorphism and the CC variant of the TPH A218C polymorphism in suicide found that concurrent presence of these genotypes increased suicide risk, but a study of alcohol-dependent suicide victims (104) did not find effects for them, either separately or together. Not all studies concur (105), but most data suggest fewer serotonin transporters in suicide victims, possibly as a homeostatic adaptation to low serotonergic tone, particularly in the ventral prefrontal cortex and anterior cingulate.

Serotonin receptors in suicide. Higher rostral dorsal raphe nucleus 5-HT_{1A} binding has been identified in depressed suicide victims (106–108), although a study of 5-HT_{1A} gene expression (89) did not find an abundance of mRNA. Suicide victims also appear to have more prefrontal cortex 5-HT_{2A} receptors and gene expression relative to nonpsychiatric comparison subjects (38, 109–112), even after accounting for the sex effect on 5-HT_{2A} binding sites (males >

TABLE 3. Neurochemical, Autoradiographic, Morphological, and Other Findings in Suicide^a

System ^a	Focus of Findings	Findings in Suicide	Location ^b	Samples ^c	
Neurochemical findings					
System	Compound	Findings in suicide	Location	Samples	
CRH-HPA	CRH	Elevated concentration	CSF (9), LC (10, 11), caudal raphe nucleus (10), DLPFC, VMPFC (11), FPPFC (11, 13), DMPFC (13)	DS v. NC	
		Reduced concentration	DVC (11)	DS v. NC	
	Vasopressin	Elevated concentration	LC, DMPFC, paraventricular hypothalamic nucleus (11)	DS v. NC	
		Reduced concentration	DVC (11)	DS v. NC	
NE-LC	CRHR1	Reduction in number of binding sites	Frontal cortex (12)	DS v. NC	
	Cortisol	Reduced baseline levels	Plasma (20)	MDS v. PC	
	Tyrosine hydroxylase	Reduced stain density	LC (31)		
	NE	Elevated concentration	Temporal cortex (33)		
Cytokines	MAO-A, MAO-B	No difference	Frontal cortex (47)		
	MHPG	Reduced concentration	CSF (20)	MDS v. PC	
	IL-1 β , IL-6, TNF α	Elevated expression	BA 10 (60)		
Fatty acids	Microglia	Elevated density	DLPFC, ACC, MDT (62)		
	DHA	Reduced concentration	Serum (66)		
Endogenous opioids	DHA, MUFA, saturated FA	No difference	BA 10 (67)		
	FAs	No difference	OFC, VPFC (68)	S v. DS v. PC	
	β -endorphin	Reduced concentration	Temporal cortex, frontal cortex, caudate nucleus (78)		
Serotonin	TPH	Elevated concentration	DRN (86)		
		No difference	MRN (86)		
	5-HT	Elevated concentration	Brainstem (90)		
	5-HIAA	Reduced concentration	CSF (121–124)	S v. SA (121); MDS v. PC (122, 124)	
Dopamine	HVA/5-HIAA	Elevated concentration	Hippocampus (125), amygdala (126)	DS v. NC (126)	
		Higher ratio	Frontal cortex (134)		
	DOPAC	Reduced concentration	Caudate, putamen (AFS), nucleus accumbens (AFS) (135)	AFS v. ATS v. NC	
Glutamate/GABA Neuronal plasticity	Glutamine	Reduced concentration	Hypothalamus (146)		
	BDNF	Reduced concentration	PFC, hippocampus (165)		
	NT-3	Reduced concentration	Hippocampus (165)		
Autoradiographic findings					
System	Receptor	Ligand	Findings in suicide	Location	Samples
NE-LC	α 1-adrenoceptor	³ H]Prazosin	Decreased binding	Caudate nucleus, PFC, frontoparietal and temporal cortical regions (32)	
			Increased binding	PFC (33)	
			No difference in number of receptors	PFC, hippocampus, hypothalamus, thalamus, caudate, putamen (36)	ATS v. NC; AFS v. NC
	α 2-adrenoceptor	p-[¹²⁵ I]Iodoclonidine	Increased binding	LC (30)	
			Increased binding	Hippocampus (CA1), frontal cortex (35)	
		³ H]Rauwolscine	Decreased binding	Occipital cortex, hippocampus (36)	ATS v. NC
			No difference	PFC (33)	
	³ H]Aminoclonidine	³ H]Rauwolscine	No difference	PFC (33)	
			Increased binding	Temporal cortex (BA 21/22) (36)	AFS v. NC

continued

TABLE 3. Neurochemical, Autoradiographic, Morphological, and Other Findings in Suicide^a (continued)

System ^a	Focus of Findings		Findings in Suicide	Location ^b	Samples ^c	
System	Receptor	Ligand	Findings in suicide	Location	Samples	
	β-adrenoceptor	[³ H]DHA	Increased binding	Frontal cortex (38), PFC (40)	VS v. NC (38)	
		[¹²⁵ I]PIN	Increased binding	PFC (39)		
		[¹²⁵ I]PIN	Decreased binding	Frontal cortex (41)		
		[³ H]CGP 12177	Decreased binding	Temporal cortex (42, 43), thalamus (43)	DS v. NC (42); ATS v. NC (43)	
Endogenous opioids	NET	[³ H]Nisoxetine	Decreased binding	LC (45)	DS v. NC	
	μ-opioid receptor	[³ H]DAGO	Higher density	Frontal cortex (72, 75), caudate (72); temporal cortex (75)	Young S v. NC (75)	
Serotonin	5-HTT	[³ H]DAGO	No difference	PFC, PPCG (74)		
		DAMGO	No difference	PFC (BA 9) (73)	MDS v. NC	
		[³ H]CN-IMI	Decreased binding	VLPFC (95), VPFC (96)		
		[³ H]CN-IMI	No difference	DRN, MRN (99)	DS v. NC	
		[³ H]Imipramine	Decreased binding	Frontal cortex (97); hippocampus (98); claustrum, insular cortex, PCCG (100)	DS v. NC (98)	
Dopamine	5-HTR1A	[³ H]Imipramine	Increased binding	Hippocampus (100)		
		[³ H]8-OH-DPAT	Increased binding	VLPFC (95), DRN (106)	DS v. NC (106)	
	5-HTR2	[³ H]8-OH-DPAT	Decreased binding	DRN (99, 107), MRN (99)	DS v. NC	
		[³ H]Spiroperidol	Increased density	Frontal cortex (110)		
		[³ H]Spiroperidol	Increased binding	Frontal cortex (38)		
D ₁ receptors	[³ H]Spiperone	Increased binding	Frontal cortex (109)			
	[³ H]SCH23390	No difference	Caudate nucleus, putamen, and nucleus accumbens (133)	DS v. NC		
	D ₂ receptors	[³ H]Raclopride	No difference	Caudate nucleus (132, 133), putamen, nucleus accumbens (133)	DS v. NC	
GABA	Dopamine reuptake sites	[³ H]WIN 35428	No difference	Caudate nucleus (131)	DS v. NC	
	GABAA receptors	[³ H]-Flunitrazepam	No difference	LC (141)	DS v. NC	
	GABAB receptors	[³ H]GABA	No difference	Frontal cortex, temporal cortex, hippocampus (144)	DS v. NC	
Glutamate	NMDA	[³ H]Dizocilpine	No difference	Frontal cortex (148, 151, 152), parietal cortex (148), temporal and occipital cortices, hippocampus, thalamus (152), putamen, caudate nucleus (147, 152), nucleus accumbens (147)	DS v. NC (152); S v. PC, S v. NC (147)	
		AMPA	[³ H]CGP-39653	Decreased binding	Frontal cortex (151)	
			[³ H]AMPA	Increased binding	Caudate nucleus (149)	
		[³ H]CNQX	Increased binding	Caudate nucleus (147)	S v. PC, S v. NC	
Morphological findings						
System	Structure		Findings in suicide	Samples		
CRH-HPA	Adrenal glands		Increased adrenal weight (21–23)	VS v. C (21)		
NE-LC	Locus ceruleus		No difference in adrenal weight (24)			
			Decreased number of neurons, decreased neuron density (50)			
Serotonin	DRN		Increase in DRN area, decrease in 5-HT neuron size, increased 5-HT neuron density (89)	S v. PC		

continued

TABLE 3. Neurochemical, Autoradiographic, Morphological, and Other Findings in Suicide^a (continued)

System ^a	Focus of Findings	Findings in Suicide	Location ^b	Samples ^c
System	Structure	Findings in suicide		Samples
Neuronal plasticity	Hippocampus	Decreased number of dentate gyrus granule neurons; increased anterior and mid granule cell layer volume (160)		AFS v. NC
		No difference (161)		SS v. NC
	Parahippocampus	Decreased right parahippocampal volume (161)		SS v. NC
	PFC	Reduction in cortical and laminar thickness (159)		S v. PC
Other findings				
System	Test	Findings in suicide		Samples
CRH-HPA	Dexamethasone suppression test (DST)	DST nonsuppressors more likely to die by suicide (26–28)		MDP DST suppressors v. nonsuppressors (26, 28) MDS DST suppressors v. nonsuppressors (27)
Dopamine	Apomorphine challenge	Decreased growth hormone response to apomorphine (129)		DS v. DP

^a CRH-HPA=corticotropin-releasing hormone/hypothalamic-pituitary-adrenal axis system; LC-NE=locus ceruleus-based norepinephrine system.
^b Numbers in parentheses are reference numbers. ACC=anterior cingulate cortex; BA=Brodmann's area; CSF=cerebrospinal fluid; DLPFC=dorsolateral prefrontal cortex; DMPFC=dorsomedial prefrontal cortex; DRN=dorsal raphe nucleus; DVC=dorsovaginal complex; FPPFC=frontopolar prefrontal cortex; LC=locus ceruleus; MDT=mediodorsal thalamus; MRN=median raphe nucleus; OFC=orbitofrontal cortex; PCCG=postcentral cortical gyrus; PFC=prefrontal cortex; PPCG=pre- and postcentral gyri; VLPFC=ventrolateral prefrontal cortex; VMPFC=ventromedial prefrontal cortex; VPFC=ventral prefrontal cortex.
^c Numbers in parentheses are reference numbers. The samples cited consist of nonspecific suicide victims compared with comparison subjects, unless otherwise specified. AFS=antidepressant-free suicide victims; ATS=antidepressant-treated suicide victims; DP=depressed patients; DS=depressed suicide victims; MDP=patients with mood disorders; MDS=suicide victims with mood disorders; NC=nonpsychiatric comparison subjects; PC=psychiatric comparison subjects; S=suicide victims; SA=suicide attempters; SS=suicide victims with schizophrenia; VS=violent suicides.

females) (109), although one study (108) detected no difference. Similarly, 5-HT_{2C} is reported to be more abundant in the prefrontal cortex of suicide victims relative to comparison subjects (113). No relationship to the violence of the suicide method has been noted for 5-HT₂ binding (109).

Genetic association studies of 5-HT receptors have yielded disappointing results. One study examining polymorphisms at five 5-HTR1B loci found an association between the A161T promoter variant and suicide (114). Individuals who died by suicide were more likely to have homozygous TT genotype and score higher on aggression and impulsivity measures (114). Another study investigating the 267C/T SNP of 5-HTR6 found a significant association between this SNP and suicide in males only (115). However, other studies found no association between suicide and genetic variants of the 5-HTR1B, 5-HTR1D, 5-HTR1E, 5-HTR1F, 5-HT2A, 5-HTR5A, 5-HTR6, or 5-HTR2C genes (112, 116–119). Genome-wide association studies have used larger samples, although these have still been insufficient to detect small effects and have not detected any serotonin receptor associations (120).

Serotonin turnover in suicide. Several studies have shown that low CSF levels of 5-HIAA, an index of 5-HT turnover

(121), predict suicide (122–124), although one study found this to be true only for males (124). Similarly, most studies of brainstem 5-HT or 5-HIAA in suicide victims report low 5-HIAA levels. Interestingly, Bach et al. (90) reported higher 5-HIAA levels in the brainstem in a pilot study that sampled the raphe nuclei systematically, from rostral to caudal, identifying differences in the ratio of 5-HT to 5-HIAA based on the anatomical level of the raphe. Yet, no such differences were detected in the prefrontal cortex. Because the study excluded subjects exposed to long-term use of antidepressants, which tends to increase 5-HIAA, and found increases in 5-HT or 5-HIAA along the length of the raphe nuclei but not in the prefrontal cortex, it suggests that the impairment is in serotonergic neurotransmission rather than synthesis. In fact, other studies of depressed suicide victims and comparison subjects have found that suicide victims have increased 5-HIAA levels in the hippocampus (125) and amygdala (126) and no differences in 5-HT levels in the cortex or amygdala (126). One study reported that drug-free nonviolent suicide victims had significantly lower 5-HIAA and 5-HT concentrations in the hippocampus than did violent suicide victims (121, 126).

Thus, the most extensive corpus of work in suicide is focused on the serotonergic system, and many studies link altered serotonin transmission to suicide risk, with the most compelling case being made by follow-up studies of individuals with low 5-HIAA.

Norepinephrine

See the section “Noradrenergic-locus ceruleus system in suicide,” above.

Dopamine

Dopamine is synthesized from L-dopa in the ventral tegmental area and substantia nigra (127). Dopamine binds to five receptor subtypes, D₁, D₂, D₃, D₄, and D₅, each belonging to one of two metabotropic G-protein coupled receptor families, the D₁-like and the D₂-like families (128), activated by apomorphine, a dopamine agonist (129). Dopamine, when metabolized via MAO, yields 3,4-dihydroxyphenylacetic acid (DOPAC), which COMT then breaks down to homovanillic acid (HVA) (130). In noradrenergic and adrenergic neurons, dopamine β-hydroxylase metabolizes dopamine to norepinephrine (130). Dopamine is implicated in mood, motivation, aggression, reward, working memory, and attention, making it a prime candidate for study.

Dopamine in suicide. Suicide studies have examined dopamine receptors (131–133) and metabolites (134, 135) and growth hormone (GH) response to apomorphine (129), but only some found any association (129, 134, 135). A retrospective study of GH response to apomorphine in depressed inpatients found that suicide victims had lower mean GH peak responses compared with depressed patients who did not die by suicide, suggesting a potential role of the D₂ receptor (129). However, studies using [³H]raclopride found no differences in the number or binding affinity of D₁ or D₂ receptors in the nucleus accumbens, putamen, and caudate nucleus of depressed suicide victims relative to comparison subjects (132, 133). Dopamine transporter availability in the caudate nucleus does not differ either (131). Data regarding dopamine turnover is scant. Compared with persons who died of physical diseases, those who died by suicide have higher cortical HVA concentrations, unrelated to violence of method, an observation also reported for homicide victims (134). Nonviolent depressed suicide victims appear to have lower DOPAC concentrations in the nucleus accumbens, caudate, and putamen, but not in the amygdala or the hippocampus (135). Unfortunately, comparison subjects in these studies were often psychopathology free, so interpretation is challenging. The paucity and inconsistency of results preclude identifying dopaminergic function as a marker of suicide risk.

GABA

GABA inhibition is mediated by two receptor types: GABA_A, the ligand-gated ion channel, and GABA_B, the

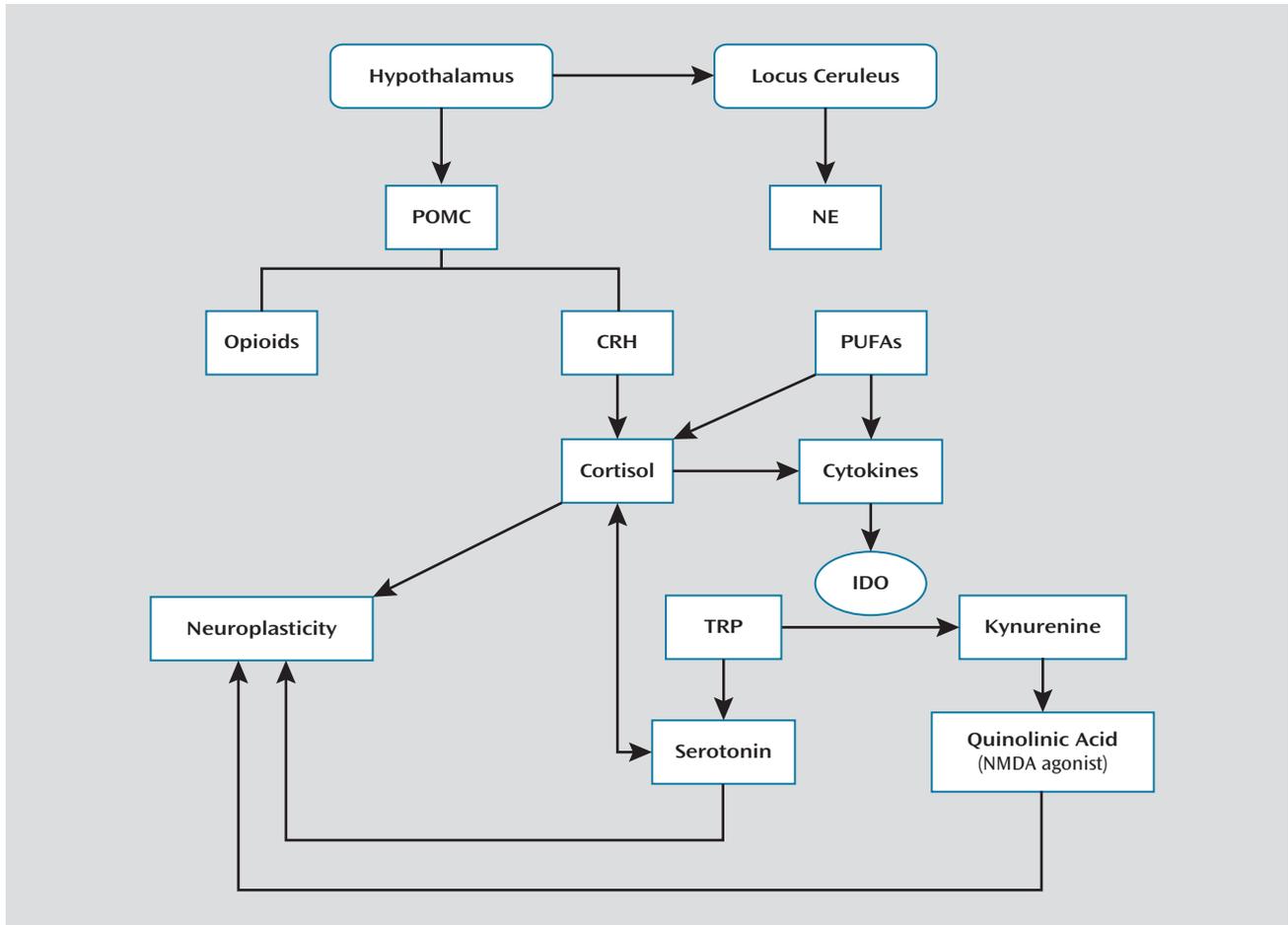
metabotropic G-protein coupled receptor (136). GABA_A has multiple isoforms based on subunit combinations (137). GABA_B has only two subtypes: GABA_{B1} and GABA_{B2} (138). It is implicated in anxiety, addictive, and convulsive disorders.

GABA in suicide. Few suicide studies have focused on GABA_A receptors (13, 139–141). One study comparing GABA_A α1, α2, α3, α4, α5, δ, and γ2 subunit mRNA expression in the frontopolar cortex of suicide victims and comparison subjects found decreased expression of α1, α3, α4, and δ mRNA in suicide victims (13), possibly linked to methylation patterns (142). Furthermore, among suicide victims, the coordination of GABA_A subunit expression seen in comparison subjects was not present, presumably hindering configuration of subunits into a functional receptor (140). Whether these findings relate to depression or suicide cannot be determined. Of interest, a gene expression study compared nonpsychiatric comparison subjects and both depressed and nondepressed suicide victims and found no differences between nondepressed suicide victims and comparison subjects in GABA receptors, subunits, or receptor-linked protein genes across several brain regions (139, 143). However, greater gene expression or binding in the hippocampus and prefrontal cortex of the depressed group (139, 141) suggests a potential role of GABA in depression. Two neuroreceptor binding studies did not confirm abnormalities in GABA_A or GABA_B in either suicide or depression compared with nonpsychiatric comparison subjects (141, 144). Together, these findings do not suggest GABA-ergic dysfunction in suicide.

Glutamate

The role of glutamate in the CNS is generally excitatory, with receptors falling into three major categories: metabotropic, ionotropic, and transporters. The metabotropic receptor family comprises at least eight different receptor subtypes (mGluR1–mGluR8, encoded by genes GRM1–GRM8). The ionotropic receptor family is more complex, with three subgroups, each with several subtypes: α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) sensitive receptors (GluR1–GluR4, encoded by genes GRIA1–GRIA4); kainate-sensitive receptors (GluR5–GluR7, KA1, and KA2, encoded by GRIK1–GRIK5); and N-methyl-D-aspartate (NMDA) sensitive (NR1, NR2A–NR2D, NR3A, and NR3B, encoded by genes GRIN1–GRIN3B). Two major glial high-affinity transporters, SLC1A2 and SLC1A3, have been identified. They regulate glutamate reuptake, affecting synaptic activation (145).

Glutamate in suicide. Few, mostly small (<15 suicide victims) studies have been conducted (146–150). We could find none with samples larger than 26 (139). In all but two studies (139, 149), suicide victims were not matched to comparison subjects on diagnosis. All studies included individuals exposed to various drugs at the time of death. One reported fewer metabotropic (GRM3) receptors in the prefrontal cortex (139) in suicide victims relative to nonpsychiatric comparison subjects. Higher AMPA binding in the caudate

FIGURE 1. A Model for Relationships Between Putative Suicide Biomarkers^a

^a CRH=corticotropin releasing hormone; IDO=2,3-iodo-deoxygenase; NE=norepinephrine; NMDA=N-methyl D-aspartate receptor; POMC=pro-opiomelanocortin; PUFAs=polyunsaturated fatty acids; TRP=tryptophan.

has been observed (147, 149), but lower GRIA3 binding in the prefrontal cortex (139) has also been found. Studies of NMDA binding in the prefrontal cortex in suicide report decreases (151) or no difference (148, 152). Glutamate levels measured by high-performance liquid chromatography in eight brain regions (146) and in homogenized frontal and parietal cortex (148) appear no different between suicide victims and comparison subjects. Thus, the role of glutamatergic alterations in suicide is unclear, but it may, given ketamine's putative antisuicidal properties, be a potential subject for further study.

Molecular Markers of Neuronal Plasticity in Suicide

Structural and functional adaptation to environmental demands occurs through synaptic plasticity and neurogenesis, processes regulated by neurotrophins (153, 154). Of four identified neurotrophin classes, brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-receptor kinase B (TrkB), are critical mediators of plasticity (155, 156). Besides BDNF, compounds such as

adenosine, pituitary adenylate cyclase-activating polypeptide (PACAP), anandamide (an endocannabinoid), kainate, glucocorticoids, and dopamine also activate TrkB receptors (157). Putative rapid antidepressant and antisuicidal actions of compounds like ketamine, proposed to act through NMDA receptor antagonism and AMPA/kainate receptor activation, may ultimately be attributable to AMPA/kainate receptor effects increasing TrkB gene expression (158).

Neuronal Plasticity in Suicide

Findings in suicide include cortical thinning in dorso-lateral prefrontal cortex neurons (159), fewer dentate gyrus granule neurons in depressed suicide victims (160), and smaller right parahippocampal volume (161), although in the latter study, the finding was attributed to depression rather than suicide. Nonetheless, volume loss suggests reduced neurogenesis, accelerated neuron loss due to apoptosis, or loss of neuropil. Teenage suicide victims with diverse diagnoses have been reported to have lower BDNF protein expression in the prefrontal cortex, fewer TrkB full-length receptors in the prefrontal cortex and hippocampus,

and less BDNF and TrkB mRNA (162), possibly linked to microRNA interference with gene transcription (163). Similar findings have been reported in adult suicide victims with diverse diagnoses (164). Another study demonstrated less BDNF and neurotrophin-3 in the hippocampus and ventral prefrontal cortex, but not the entorhinal cortex, in both depressed and nondepressed suicide victims (165) compared with nonpsychiatric comparison subjects, suggesting that alterations are not due to depression. Of note, BDNF levels were similar between antidepressant-treated suicide victims and nonpsychiatric comparison subjects, suggesting normalization of neurotrophin levels with antidepressants (165). Expression of neurotrophins and proteins in the neurotrophin cascades in the prefrontal cortex and hippocampus of suicide victims is altered (166, 167), indicating impairments in neurogenesis. Furthermore, female suicide victims have been reported to be more likely to carry the BDNF Val66Met (Val/Met or Met/Met) polymorphism, a gene variant associated with lower activity-dependent secretion of BDNF (168). Epigenetic changes, possibly reflective of early-life adversity, may also be relevant to BDNF-TrkB system dysfunction, as suicide victims have been reported to have higher BDNF-gene DNA methylation (169) and, correspondingly, lower BDNF mRNA relative to non-suicide comparison subjects (170). Thus, this small literature supports a potential role of neuroplasticity in suicide, independent of its role in depression.

Conclusions

Biological systems implicated in suicide are interrelated (Figure 1), suggesting that a coherent model can be built. However, its components require further development. Currently, data demonstrating multilevel HPA axis dysfunction make this a top candidate biomarker. Some abnormalities, such as high CRH levels, appear to be primary and may result in downstream compensatory changes, such as DST nonsuppression. Abnormalities in the LC-NE stress response system require further elucidation, although some findings suggest lower norepinephrine function, which, if confirmed, could be secondary to norepinephrine depletion due to excessive response to stress. Linked to stress response through POMC release is the opioid system. Although postmortem evidence for opioid involvement is currently weak, its role in pain alleviation in the context of stress may be relevant. The serotonergic system, so extensively studied in suicide, exhibits changes at several levels, with the most compelling data being the prediction of suicide by low CSF levels of 5-HIAA. The serotonergic system has a close, bidirectional relationship to the HPA axis and is linked to inflammatory processes. Indeed, the small but convincing cytokine and suicide literature helps collate data implicating the HPA axis and polyunsaturated fatty acids and provides a basis for connections between these systems and their effects on

suicide. In contrast, scant work examining GABA, dopamine, and glutamate appears negative. Yet, despite less-than-compelling data about glutamate's role, emerging data regarding "antisuicidal effects" of ketamine suggest that more studies are needed. Furthermore, the glutamatergic and serotonergic system and cytokines have a role in neuroplasticity and neurotoxicity, which is key to suicide independent of their role in depression, thus also supporting a role for these systems in suicide.

Future work on the neurobiology of suicide must overcome challenges such as use of small samples; examination of different brain regions; use of agonists, antagonists, and partial antagonists in neuroreceptor assays; confounding due to damage to the brain; presence of psychotropics that potentially affect biomarkers; variable postmortem intervals; lack of well-matched cases including psychiatric controls; and predominantly male samples. Another key issue is that there are likely differing biological pathways to suicide, and the lack of studies delineating suicide subtypes remains an issue for data interpretation. Thus, defining a precise mechanism underlying suicide is beyond available methodology, and we lack biomarkers with diagnostic utility, let alone treatment targets. The few biomarkers measurable in vivo, such as DST or CSF 5-HIAA level, lack the positive predictive value essential for clinical use.

In summary, a dysregulated CRH-HPA axis is linked to other systems implicated in suicide: the serotonin, opioid, and glutamate systems, inflammatory pathways, lipid status, and neuroplasticity or neurogenesis. Therefore, a battery of biomarkers, rather than a single one, will likely be needed to identify individuals at risk. The silo approach to biomarkers should be phased out in favor of the study of multiple systems in parallel and in the same populations. Only in that way will the role of each and their interplay be clarified, with the goal of identifying new treatment targets and improving suicide risk prediction.

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