Suicidal behavior (SB) is a major burden in most nations worldwide and a major public health concern [31]. According to estimates from the WHO based on reporting from 130 countries, approximately 1 million people commit suicide (SC) each year and 10–20 times more people attempt suicide. The causes of why certain people engage in SB are complex, involving for e.g., both environmental and genetic factors, and interactions in-between. Well-established environmental risk factors are events causing significant psychological stress, which are particularly difficult to cope with, e.g., exposure to physical and sexual abuse. Excessive stress have the potential to induce unfavorable effects in a variety of higher brain-functions, incurred as side-effects to maladaptive responses in the genetically controlled stress-responsive neurosystems, e.g. the hypothalamic-pituitary-adrenal (HPA) axis; a major and systemic stress-modulator, which is mainly controlled by the regulatory corticotrophin releasing hormone receptor 1 (CRHR1) gene. Variation in-between individuals in such stress-regulatory genes such as CRHR1, may underlie the causes of the increased susceptibility of certain individuals towards SB. Here we review some of the current knowledge on what is known about the roles of the HPA axis in SB, with a focus on CRHR1.

The ultimate consequence of mental ill-health, suicidal behavior (SB), is a significant problem in most societies of the world. Suicide causes about one million deaths worldwide each year, and 10–20 times more people attempt suicide. The causes of why certain people engage in SB are complex, involving for e.g., both environmental and genetic factors, and interactions in-between. Well-established environmental risk factors are events causing significant psychological stress, which are particularly difficult to cope with, e.g., exposure to physical and sexual abuse. Excessive stress have the potential to induce unfavorable effects in a variety of higher brain-functions, incurred as side-effects to maladaptive responses in the genetically controlled stress-responsive neurosystems, e.g. the hypothalamic-pituitary-adrenal (HPA) axis; a major and systemic stress-modulator, which is mainly controlled by the regulatory corticotrophin releasing hormone receptor 1 (CRHR1) gene. Variation in-between individuals in such stress-regulatory genes such as CRHR1, may underlie the causes of the increased susceptibility of certain individuals towards SB. Here we review some of the current knowledge on what is known about the roles of the HPA axis in SB, with a focus on CRHR1.

The biological response to environmental stress involves the hypothalamic-pituitary-adrenal axis (HPA), in partial overlap in time and neural substrates with the actions of monoaminergic systems and several other peptide systems [12]. Real or perceived alterations in environment which are judged by the individual to require adaptation (“stress”), induces (i) HPA activation by the release of corticotrophin releasing hormone (CRH) from the hypothalamus, acting at CRH receptor 1 (CRHR1) in the pituitary, to stimulate adrenocorticotropic hormone release and subsequent peripheral release of steroids/cortisol from the adrenal grand [9]. (ii) CRH also act in this initial phase on multiple central brains regions directly and within seconds [12], e.g. the amygdala [8]. A delayed resistance or adaptation response follows by action of cortisol, mainly initiated after 1–2 hours, and together with the CRH-effects, results in a range of behavioural, cognitive, autonomic, psychological and immunologic alterations [9]. This new homeostasis is normally reversed back to its “resting” state (partly

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by the negative feedback regulation by cortisol on its receptor NC3R1, and CRH on CRHR2), as the stressor have been coped with. However, when adequate coping/adaptation is not achieved and stress continues, (iii) an “exhaustion” stage can follow, possibly inflicting lifelong changes (epigenomic and neurostructural) [9,12,16]. Such changes can be marked by altered HPA-activity (i.e., low or high cortisol levels) and -reactivity (i.e. reduced or increased “efficiency” in feedback regulation of cortisol levels), both of which can be driven into opposite directions in e.g. posttraumatic disorder (decreases, “hyper”) versus and melancholic types of MD (increases, “hyper”) [10,25]. Interestingly, these HPA-disturbances are also partially predictive of SB [5,18] and regarded as an endophenotype of SB [17]. However, the interindividual variation in the psychological effects of these disruptions and how they arise, are much more diverse, as they involve many brain regions and other neurosystems (limbic and prefrontal). One inroad to further understanding is to investigate how variation in the HPA regulatory genes affects the mechanisms of activation of such central neurons in response to psychological stress, influencing the interaction of circuits of emotional processing (e.g., amygdala and prefrontal cortex), learning and memory (hippocampus), decision-making (prefrontal cortex) and reward circuits, by study of, for e.g., the major “activation” receptor CRHR1 [11]. The functions and interplay between these brain functions are likely altered in SB, leading to e.g. endophenotypes of SB [17]. This is in contrast to physical stress, which primarily engages the more peripheral hypothalamic and brain stem regions in the adaptive response [12]. Furthermore, some central CRH-activities may also partly decouple from the peripheral HPA neuroendocrine activities (e.g., hyperactivating the amygdala) [12], whereby the study of solely HPA activity/reactivity (at the level of cortisol) may not properly reflect the reduced resilience and maladaptation to psychological stressors.

The central effects of CRHR1 on neuron firing patterns, gene expression and behaviour are both CRH dose- and brain region-dependent [12]. Specifically demonstrated examples of CRHR1 direct actions are multiple (and also often involve also cortisol- and monoaminergic receptors on the same neurons) [12]. Examples are interaction with dopamine receptors 1 and 5 in the basolateral amygdala, in controlling glutamate transmission to medial prefrontal cortex [22], one of the routes important for emotional regulation and decision-making (both critically altered in SB) [17]. Likewise, dense CRH-innervations in/to the dorsal raphe nucleus control output of serotonin to the forebrain, by actions of CRHR1 and CRHR2 [28], another route of altering limbic–prefrontal functions, of importance for e.g. in choosing coping strategies. CRH projections from central amygdala to CRHR1 in the locus coeruleus, mediates shift in noradrenergic LC neuron firing [29], e.g. affecting hippocampus and amygdala function in the linking of emotions to memories. Indeed, antagonists active against CRHR1 may be effective as a new type of treatment-option for affective disorders and anxiety [11], and possibly in related conditions such as SB. In summary, various suicide- indicated psychopathological states are often concordant with direct or downstream actions by CRHR1, and CRH-alterations are found in suicide victims [19–21].

Thus, investigating CRH-effects by actions through the gene CRHR1, may have major implications for the ongoing research in this area. Furthermore, the (pathological) effects mediated from CRHR1 seem to be complexly related to varying changes in expression of the gene [1], in addition to any changes in receptor sensitivity/activity, which can only be properly understood by invoking a genetic perspective. But, in contrast to the broad panel of CRHR1 gene studies in animal models, showing roles of broad CRHR1 in, for e.g. depression, anxiety and alcohol intake [11], fewer studies exist about the influence of genetic variation in the human CRHR1 gene. Recently, it is now becoming clearer that the variation also in the human CRHR1 gene may be of importance, for e.g., as mediator of childhood abuse (CA) through G × E. Polymorphisms in human CRHR1 have now been associated with depression, treatment efficiency of depression and levels of alcohol intake [3,4,13–15,23,24,26,30]. Recently, it was further shown that CRHR1 SNPs rs110402/rs242924 showed significant G × E with CA on development of elevated HPA-reactivity per se in the adult [27]. To this, we can now further add examples of studies of variation in other, CRHR1-related and HPA regulatory genes, with associations in relation to SB as a secondary phenotype to schizophrenia, bipolar disorder and major depression; the FKBP5 gene (modulator of cortisol receptor NC3R1), CRHR2 (the second CRH-receptor, often displaying opposite functions to CRHR1) and CRH binding protein (CRHBP, modulator of CRH receptor activities) together with CRHR1 (by gene–gene interaction) [6,7,23,33]. Only our group has so far investigated the CRHR1 gene in relation to SB as the primary phenotype [30,32], while others have associated variation in CRHR1 with SB as a secondary phenotype [7,23]. We used a family-based sample, in which all offspring had performed medically serious SA (n = 672 trios), and this combination of sample-structure and large number of suicidal individuals, still remains unique in the field of suicidology. The initial study [30] demonstrated association and linkage of an intronic SNP to suicide attempt (rs4792887), among whom most males were depressed. The finding was interestingly confined to individuals who had been exposed to low levels of lifetime stress, and it was proposed that these individuals may carry CRHR1-variants that are more prone to produce a dysregulated HPA-/CRH-system [30]. Our subsequent follow-up investigation, with more SNPs in the CRHR1-gene, confirmed and expanded these findings, associating three non-correlated, but proximally located SNPs residing in the 5′-region of CRHR1, with increasing depression intensity among SA-males [32]; the previous intronic rs4792887, an exonic SNP rs12936511, as well as the aforementioned SNP rs110402. Interestingly, there is evidence of both alternative splicing and an alternative transcription start-site in this region of CRHR1, according to public databases. We have not yet investigated G × Es with CA specifically, and our results appear as main genetic effects acting among these depressed, SA-males. The plausibility of no/minimal G × Es in this context among certain individuals, is supported by recent results from animal selective breeding, clearly demonstrating the possibility of a preexisting alteration in psychological stress resilience by HPA (hypo-/hyper-) dysregulation, that is completely heritable and thus formed with minimal environmental inference, i.e. a predisposition mostly under genetic control already from birth [25].

Two other groups have also performed certain investigations of human CRHR1 in relation to SB [7,23]. Papiol et al. showed association with the major A-allele of rs110402 with age of onset and seasonal pattern of MD, among non-suicidal females [23]. In comparison, we found the A-allele more frequently among depressed SA-males [32], while similarly to Papiol et al., we also observed an increase in BDI-scores among non-SA female AA-carriers (unpublished data). Together, the results suggested that the A-allele of rs110402 is indicative of increased risk of non-suicidal depression in females, while being associated with suicidal depression among the males [32]. De Luca et al. indicated suicidality with another, more 3′-located CRHR1-SNP (rs16940665) in context of a G × G interaction, together with an SNP in CRHBP, in a sample with schizophrenics [7]. This CRHR1-SNP was also been investigated by us [32], but not in context of this G × G, which may partly explain our negative results. It is highly likely that variation in CRHR1 will interact with variants in other genes on the same biological pathways, for e.g. the HPA axis, as being parts of a complex stress–modulatory system, which can manifest into SB.
On a final note, there is a high degree of gender dimorphism in both suicidality, depression/anxiety [31], as well as in the biological stress-response functions [16]. In certain cases, it may even be that factors, e.g. certain CRHR1-alleles or specific G × Es, which increase suicide risk in males, may reduce the risk in females, comparable to observations with genes MAOA and SLC6A4. Our CRHR1-studies of SB were the only to invoke a clearly gender-stratified approach, showing dimorphic relationships between depression, suicidality and CRHR1 polymorphisms, likely reflecting the higher likelihood that depressed males may die by suicide, compared to depressed females [31]. There is also an interesting link between reduced antidepressant treatment response, suicidality and HPA axis reactivity [31], and the association results with certain polymorphism in CRHR1 and FKBP5 may further reflect the genetics of this aspect. In line with these results, it was recently also shown that HPA-dysregulation predicts a non-response to antidepressant treatment, particularly among males [2].

Summary

The understanding of the link between actions of genes and environment on various behavioural outcomes can be better understood by studies of stress-response systems. Many neurobiological aspects and endophenotypes of SB are reciprocity interconnected with the function of HPA axis, for e.g., of central CRH acting on CRHR1. Slight changes in one system affect the other, and these interactions will likely be better accounted for, also, in the future suicide research. One road ahead is thus to follow the context- and time-dependent functions of, for e.g. CRHR1, and the subsequent mechanisms of interactions with genes from “other” systems (e.g., monoaminergic), influencing events in specific neurocircuits, ranging from molecular-cellular to behavioural levels. This may achieve a further increased understanding of suicidal causality, which is much needed for additional improvement of suicide prevention and intervention tools, in the form of better risk-assessment and treatment opportunities, at both the population-wide and individual levels.

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