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Hippocampal neuropathology in suicide: Gaps in our knowledge and opportunities for a breakthrough

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ABSTRACT

Suicide is a major global hazard. There is a need for increasing suicide awareness and effective and evidence-based interventions, targeting both suicidal ideation and conduct. However, anti-suicide pharmacological effects are unsatisfactory. The human hippocampus is vulnerable to neuropsychiatric damages and subsequently releases psychobiological signals. Human hippocampal studies of suicide completers have shown mechanistic changes in neurobiology, which, however, could not reflect the neuropathological 'fingerprints' of fatal suicide ideations and suicide attempts. In this review, we provide several leading theories of suicide, including the serotoninergic system, Wnt pathway and brain-derived neurotrophic factor/tropomyosin receptor kinase B signalling, and discuss the evidence for their roles in suicide and treatment. Moreover, the cognitive dysfunctions associated with suicide risk are discussed, as well as the novel evidence on cognitive therapies that decrease suicidal ideation. We highlight the need to apply multi-omics techniques (including single-nucleus RNA sequencing and mass spectrometry histochemistry) on hippocampal samples from donors who died by suicide or legal euthanasia, to clarify the aetiology of suicide and propose novel therapeutic strategies.

1. Introduction

Suicide is a worldwide major public health and societal problem that involves over 700,000 human lives lost every year (WHO, 2021), while twenty times more people attempt suicide. The suicide rate in European countries has been gradually rising. In the Netherlands, the number of suicides is increasing by between 3 and 6 % annually. Preventive measures are lacking efficacy (Zalsman et al., 2016), and almost half of the suicide cases in the Netherlands are conducted by individuals receiving psychotropic drugs. Suicide is also the fourth leading cause of death among teenagers and adolescents (WHO, 2021). Belgium has the highest suicide rates among the European countries, where almost a quarter of the young population has had suicidal thoughts or attempted suicide in the last 12 months (Belgium, 2021). Psychiatric disorders, such as mood disorder (MD) and repeated suicide attempts, are the main risk factors for suicide completion (Beghi et al., 2021; Turecki et al., 2019). While suicide is often considered the worst outcome or consequence of psychiatric disorders, little attention has been paid to its independent, and likely unique, molecular-genetic background (Wang et al., 2019).

The hippocampus (HC) is a subcortical brain region that is highly sensitive to stress and richly endowed with glucocorticoid receptors (GR) in humans (Wang et al., 2013). It is part of the limbic-cortical-hypothalamic circuit, which is implicated in the pathophysiology of suicide (Lutz et al., 2017; Mahar et al., 2017). Neuroimaging studies have discovered a smaller HC in suicide, along with significant histopathological changes. Hippocampal subregions were shown to be anatomically and functionally distinct, which was also reflected in suicide-specific changes. For example, fewer granular neurons and more glia with larger nuclei by age were reported in the dentate gyrus (DG), while more neurons but fewer astrocytes were found in the *Cornu Ammonis* (CA) 2/3 subareas of the HC in individuals with major depressive disorder (MDD) who died of suicide (Boldrini et al., 2019;

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Chen et al., 2020; Cobb et al., 2016, 2013), suggesting that components involved in the basic circuits of HC may perform functionally distinct roles in suicide development. In addition, antidepressants increased neural progenitor cells in the DG of subjects with MDD, which seems to be more specific to suicidal death than non-suicidal death (Boldrini et al., 2009; Lucassen et al., 2010).

While the neuropathology of suicidality was so far based upon HCs from subjects who had all completed suicide, a major problem for those studies is that it is hard to distinguish the molecular similarities and differences between suicide ideation, suicide attempts (single/repeated), and completed suicide. Strikingly, recent magneto-encephalographic studies showed that a specific type of electrophysiological connectivity and dynamics in the left HC was linked to suicidal thoughts in patients with MDD (Jiao et al., 2019; Nugent et al., 2020). While this novel finding points towards a putative neurobiological substrate and possible diagnostic marker for (the onset of) suicidality, it awaits future confirmation.

This review discusses the clinical and neuropathological manifestations in the human HC in association with suicidality. We searched the PubMed database until November 2021 using the medical subject headings search terms of hippocampus and suicide. In addition, we discuss the current antidepressants, which are prescribed with the hope of reverting the hippocampal alterations found in suicide, and their adverse effects in suicide intervention. We further discuss the unique opportunity of the HC from brain donors who died of legal euthanasia, to study differences between suicide ideations and attempts. Finally, we propose the employment of single-nucleus RNA sequencing and mass spectrometry histochemistry (MSHC) as future key spatial '-omics' technologies to investigate the biomolecular fingerprints of different aspects of suicide severity. The objective is to obtain a better understanding of the cellular and molecular mechanisms that underlie suicide ideation and suicidal behaviour, and of potential novel targets for anti-suicidal therapies.

2. Suicide and hippocampal atrophy

Various structural and functional imaging studies have reported that the HC is dynamically and volumetrically disorganized in patients with psychiatric disorders and suicidality. Of note, MDD, as the condition most frequently linked to suicide, is associated with structural changes in the HC. Previous meta-analyses suggest a reduction in the hippocampal volume of subjects with MDD, which is absent in bipolar disorder (BD) (Campbell et al., 2004). Depressed patients with suicidal ideations show no volumetric alterations but do show a decreased dynamic activity in the HC compared to non-suicidal individuals with depression (Jiao et al., 2019; Lan et al., 2019). Different from suicide ideators, suicide attempters exhibit a regional asymmetry in their left HC, independent of their psychiatric disorder (Cao et al., 2015). For example, suicide attempters with MDD show evidence of higher hippocampal functional connectivity (Wagner et al., 2021; Weng et al., 2019).

MDD patients with repeated or acutely strong suicide attempts further show much smaller hippocampal volumes than patients with a first suicide attempt, non-suicidal patients, or healthy controls (Colle et al., 2015; Kang et al., 2020; Sarkinaite et al., 2021). Reversely, in adolescent and young populations, suicide attempters with MDD have larger white matter subfields than non-suicidal patients (Zhang et al., 2021b). Suicidal attempters with BD also appear to have significantly reduced grey matter volume in the HC as compared to non-suicidal BD patients (Johnston et al., 2017; Niu et al., 2019). Hippocampal volume is reduced in schizophrenia (SCZ) (Nelson et al., 1998), but suicidality-associated hippocampal atrophy does not appear in SCZ (Spoletini et al., 2011), suggesting that reduced hippocampal volume may be a promising selective neuroimaging marker to predict suicidality in MD.

3. Suicidality and cognitive impairment

Suicide is regarded to be a cognitive disorder because it strongly disturbs the mental processes involved in gaining knowledge and comprehension. The human HC is a crucial structure for such cognitive abilities and processing. Suicide-associated cognitive impairments have posited differences across ages. In psychiatrically hospitalized children, a sluggish cognitive tempo is associated with their increased suicide risk (Becker et al., 2016). These children also show decreases in episodic memory, which probably extends into adolescence and adulthood, where suicide attempts are also correlated with decreased memory performance (Huber et al., 2020). In adolescents, there is a significant association between specific cognitive characteristics and suicidal behaviours, with self-harm being among the strongest risk factors for eventual suicide death (Sinyor et al., 2020). Youths who attempt suicide are at high risk for repeated attempts and subsequently diagnosed mental health problems. They show general deficits in cognitive control towards emotional stimuli, a potential marker for adolescent suicide tendencies (Stewart et al., 2017). An increased risk for suicide completion in young males was associated with extreme cognitive abilities and poor social functioning (Weiser et al., 2017), while in young females, sleep disturbances are more likely linked to the onset of suicidal ideations (Bozzay et al., 2016).

Adults with suicide ideations can display social alienation due to perceived burdensomeness and thwarted belongingness, cognitive distortions, high reactivity to hopelessness, and aggression (Antypa et al., 2010; Fazakas-DeHoog et al., 2017; Jahn et al., 2015; Jankowski et al., 2020). In addition, susceptibility to suicidal thoughts seems to be induced via increasing anxiety sensitivity and rising cognitive concerns, robust predictors of suicide risk among patients with mental illnesses (Capron et al., 2013; Oglesby et al., 2015; Tucker et al., 2016). Compared to suicide ideators, people who have attempted suicide perform significantly worse on mental-state examinations including having a stronger self-blame, rumination, catastrophizing impulsiveness, and thus developing lethal behaviours (Abdollahpour Ranjbar et al., 2021; Gilbert et al., 2011). They also have less sense of acceptance, lower attention control, and hampered abilities of learning and memory (Abdollahpour Ranjbar et al., 2021; Alacreu-Crespo et al., 2020). In addition, relative to individuals who had either suicide ideations or undertook one single attempt, people who attempted suicide repeatedly showed worse neuropsychological performance (Delaney et al., 2012), suggesting that repeated suicidal behaviours might be related to impaired cognition. On the other hand, some studies seemed to show that the cognitive status of suicide attempters might not simply reflect a graver condition compared to the cognition of suicide ideators. For example, while cognitive inflexibility was prevalent among suicide ideators (Miranda et al., 2012; Roush et al., 2019), cognitive flexibility remained intact in suicide attempters (Brokke et al., 2020). Furthermore, regardless of their prior psychiatric disorder, suicide attempters have higher cognitive functions, such as normative planning and choice consistency (Alacreu-Crespo et al., 2020; Moniz et al., 2017). The above findings suggest that there might be distinct neurobiological mechanisms underlying suicidal ideations and suicide attempts, respectively.

In the aged population, people diagnosed with a recent mild cognitive impairment or dementia are at an increased risk of attempting suicide (Günak et al., 2021), when suicide attempters demonstrate a pattern of deficits involving poorer abstract thinking and conceptual reasoning (McGirr et al., 2012; Olsson et al., 2016). Of note, suicide-associated cognitive dysfunction, such as decision-making impairments, were also apparent in healthy first-degree relatives of suicide completers (Hoehne et al., 2015). This may be related to the observation that individuals with relatives who completed suicide are more likely to attempt suicide (Qin et al., 2002). Thus, for every age group, the profiling of molecular patterns in association with the monitoring of cognitive performance and the pertinent brain morphology in the HC will be critical in a better understanding of the pathological mechanisms

of suicide, as well as in improving the diagnosis and treatments.

Importantly, the cognitive deficits we summarized above were more prominently connected with the HC in structure and function (Brambilla et al., 2013; Chung et al., 2021; Hanseeuw et al., 2016; Khoury et al., 2019; Tang et al., 2021; Wixted et al., 2014) as compared to the other brain regions that were also reactive to (the early phase of) suicidality, such as the dorsolateral prefrontal cortex and insula (Nugent et al., 2020). In addition to the neuroimaging observations, HC-associated cognitive manifestations in clinical practice could be more sensitive in predicting an early phase of suicidality, suggesting that the HC might be a pertinent and regionally-specific target for suicide-related cognition repair and early prevention.

4. Biological mechanisms in the hippocampus that are associated with suicide

4.1. Epigenetic marks of suicide in the hippocampus

As one of the main mechanisms through which environmental and genetic factors interact with each other, epigenetic modifications in the HC are assumed to contribute to the development of suicidal behaviours (Kouter et al., 2019). Heritable phenotypic alterations, e.g. via DNA methylation and histone modification, reflect the multifactorial and polygenic state of suicide. A genome-wide methylation study on hippocampal tissue comparing suicide completers with non-psychiatric control subjects revealed a series of methylated DNA promoters that were functionally involved in learning and memory, and neuronal communication, such as synaptic transmission (Labonté et al., 2013). In addition, risk factors of suicide can alter the epigenetic status of specific genes. A specific genotype of the somatostatin receptor 4, a receptor that is predominantly found in the CA1, is involved in memory formation and related to an increased risk of suicide in individuals with alcohol dependence (Berent et al., 2017). Moreover, early life adversity is known as a relationship-associated suicidality factor, increasing the risk for various psychiatric disorders and posing a significant risk for attempting suicide. In particular, decreased levels of several human GR variants were found in the HC of suicide completers with a history of childhood abuse versus suicides without such history (Labonté et al., 2012). Also, hypermethylation of the ribosomal RNA gene promoter U13369 was consistent with reduced ribosome RNA expression in suicide subjects with a history of early childhood neglect/abuse (McGowan et al., 2008).

4.2. Gene expression and signal pathways concerning suicide

4.2.1. Serotonin receptor 2A (5-HT2AR)

The human HC has a particular role in regulating the serotonergic system. Serotonin (5-hydroxytryptamine, 5-HT) is involved in various mental processes such as cognition, memory, anxiety and mood by activating its specific receptors that are regionally distributed throughout the brain. Both depression and suicide are accompanied by modulation of distinct 5-HT receptor subtypes in the human HC. It is widely accepted that an overall downregulation of the 5-HT1A system is characteristic for depression (Yohn et al., 2017), without an influence of suicide (López et al., 1998). Where the concentrations of 5-HT and its turnover and transporter were not altered by suicidality (Anisman et al., 2008; Cheetham et al., 1989; Little et al., 1997), its main metabolite, i.e. 5-hydroxyindoleacetic acid, was increased in the HC of depressed patients who died by suicide (Cheetham et al., 1989; Owen et al., 1986).

Also, 5-HT2AR is abundant in the HC of patients who completed suicide. Previous studies have associated polymorphisms of the 5-HT2AR gene with a biological susceptibility to suicide attempts (Vaquero-Lorenzo et al., 2008). The expression of 5-HT2AR is also higher in the HC of suicide victims, while its binding potential, combining receptor density and the affinity of serotonin, was not altered (Pandey et al., 2002; Roth et al., 1990; Soloff et al., 2007). Others showed that the binding sites of 5-HT2 receptors in the HC were diminished in antidepressant-free individuals who died by suicide compared to control subjects (Cheetham et al., 1988). This is likely due to a reduction of 5-HT2A binding sites accompanied by higher serotonin affinity (Rosel et al., 2004, 1998). Moreover, while the presynaptic uptake of serotonin was decreased in suicide cases as compared to the controls, the 5-HT2A postsynaptic receptor was hypersensitive in line with a high affinity of this receptor subtype (Rosel et al., 2000, 1997).

Taken together, the above evidence indicates that suicide may possibly trigger a synaptopathy in hippocampal cells. Functionally, a microarray analysis has revealed alterations of synaptic neurotransmission in the hippocampus of subjects who died by suicide (Sequeira et al., 2009). In synaptic structures, decreases of synapsin/synaptophysin ratio and postsynaptic density protein 95 have been found in the hippocampus of suicide victims (Sowa-Kućma et al., 2013; Vawter et al., 2002), suggesting that suicide may have affected synaptic components and plasticity. One of the major results is 5-HT2AR-mediated postsynaptic hyper-excitability during serotonin transmission. Downstream of the 5-HT receptors, a decreased activity of protein kinase B (PKB or Akt) has been reported in the HC of suicide victims with depression compared to non-psychiatric control subjects (Fig. 1) (Dwivedi et al., 2010). In addition, 5-HT receptor ligands and purine nucleotides were shown to have molecular similarities in terms of their receptor regulatory properties, such as crosstalk between the 5-HT2A receptor and P2Y purinoceptor 12 in 5-HT storage during platelet aggregation, and in suicide as well (Vaquero-Lorenzo et al., 2008; Zhang et al., 2020a, b; Zhang et al., 2021a). Other depression-associated receptors, such as 5-HT1A, 5-HT1C, 5-HT2C, and 5-HT4 did not display alterations in the HC of suicide completers (López et al., 1998; Lowther et al., 1997; Pandey et al., 2006; Rosel et al., 2004; Roth et al., 1990). Of note, the above findings were derived from suicide victims who had suffered from depression as well and were analyzed by comparing them to non-psychiatric controls, indicating that the possible influence of the psychiatric disorders could have been overlooked (Zhao et al., 2019).

4.2.2. Brain-derived neurotrophic factor system

The brain-derived neurotrophic factor (BDNF) is highly expressed in the human HC and it is a critical mediator of physical activities. Among others, BDNF supports neuronal survival and promotes the growth and differentiation of immature neurons and synapses (Duman et al., 2021; Marlatt et al., 2012; Notaras and van den Buuse, 2020). As a well-known genetic locus of risk for mental disorders, BDNF is associated with stress and stress-related disorders (Castrén and Rantamäki, 2010; Molendijk et al., 2014; Shirayama et al., 2002). The presence of BDNF Val66Met polymorphism is even proposed as an independent predictor of high lethality in suicide attempts of depressed patients (Schenkel et al., 2010).

In conditions of prolonged stress, the influx of increased glucocorticoids into the HC activates the mitogen-activated protein kinase (MAPK) pathway via phosphorylation of its receptor tropomyosin-related kinases B (TrkB), and thereby enhances negative memory formation (Notaras and van den Buuse, 2020). Dysfunctional BDNF in depression and suicide probably share common pathways and may procure similar hippocampal malfunctions (Fig. 1). Previous studies have reported an overall breakdown of BDNF as well as the downstream-regulated molecules in the HC of depressed patients (Molendijk et al., 2014). At the extracellular and membrane levels, reduced BDNF results in lower levels of the transmembrane receptor TrkB, its activation resulting in decreased intracellular signalling among the phosphatidylinositol-3-kinase/Akt and MAPK-ERK kinase/MAPK pathways (Banerjee et al., 2013; Dwivedi et al., 2001, 2006; Dwivedi et al., 2003b, 2008; Dwivedi et al., 2009a,b, 2010; Karege et al., 2005; Pandey et al., 2008). Consequently, intra-nuclear expression and functional characteristics of cyclic adenosine monophosphate response element-binding protein, a transcription factor that triggers expression of various genes involved in neurogenesis and mood regulation, has

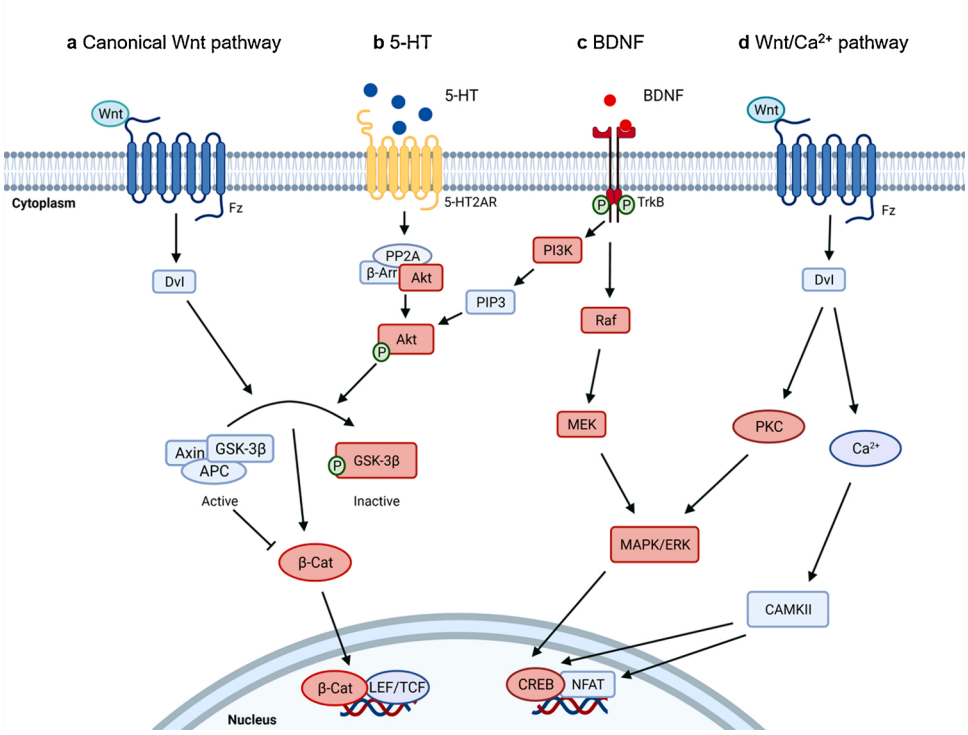

Fig. 1. Schematic illustration of altered molecules in 5-HT, BDNF and Wnt pathways in the homogenate HC of depressed suicide. Molecules in red show down-regulation. Molecules in blue show, so far to our knowledge, no alterations have been reported. The molecule in yellow reveals up-regulation in signal cascades. By summing up this review, we considered that an excessive release of intracellular neuronal inhibitor dopamine may trigger a hyperpolarization of the postsynaptic membrane and thus activate postsynaptic 5-HT2AR, which produces a long-lasting depression to the downstream molecules. The figure is based on the literature of the present review and partly on modified figures by Voleti and Duman (Voleti and Duman, 2012). Abbreviations: Akt, protein kinase B; APC, adenomatosis polyposis coli; β-Cat, β-catenin; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding; Dvl, Disheveled; ERK; extracellular signal-regulated kinase; 5-HT, serotonin; 5-HT2AR; serotonin receptor 2A; Fz, frizzled; GSK-3β, glycogen synthase kinase β; HC, hippocampus; LEF, lymphoid enhancer-binding factor; MAPK, mitogen-activated protein kinase; MEK, MAPK-ERK kinase; NFAT, nuclear factor of activated T-cells; p, phosphorylation; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PP2A, protein phosphatase; TCF, T-cell factor; TrkB, tyrosine kinase receptor B. (Fig. 1 is created with BioRender.com. Agreement number: QO22Q3OPVD).

been found decreased in the HC (Dwivedi et al., 2003a). Decreased histone acetylation and increased levels of factors related to de-acetylation and methylation processes also have been reported to lower BDNF, which may trigger subsequent alterations (Misztak et al., 2020).

Of note, the above-mentioned studies all were performed on hippocampal tissue from patients who died by suicide. The data were compared to healthy controls, and, thus, the contribution of the underlying psychiatric disorders themselves was not considered as a putative confounder (Zhao et al., 2019).

4.2.3. *Wnt signalling*

A role for the Wnt pathway in suicidal behaviours has been reported in several studies on the human postmortem HC. Generally, Wnt signalling is a pivotal regulator of cell proliferation, specification and migration. Molecules activated by the BDNF pathway are also involved in the modulation of Wnt signalling (Fig. 1). Three different Wnt signalling pathways have been described: a canonical pathway and two non-canonical ones. In the canonical pathway, the activity of Akt is influenced by serotonergic and BDNF systems. Both Wnt and BDNF signalling are coupled to activation of intracellular signalling cascades that involve phosphorylation of glycogen synthase kinase β (GSK-3β) (Voleti and Duman, 2012). This key downstream enzyme controls the translocation of β-catenin to the nucleus and activates the transcription of Wnt target genes. In the HC of suicide victims, pGSK-3β-ser^{9}, the phosphorylated isoform of Ser9 that exhibits a reduced activity, and β-catenin, both showed decreased expression relative to the controls (Pandey et al., 2009). This indicates aberrations in the downstream cascades of the Wnt signalling pathway, whereas GSK-3β itself does not show marked changes in expression (Ren et al., 2013).

On the other hand, reduced activity of protein kinase C (PKC) levels has been reported in the HC of suicide cases compared to non-psychiatric control subjects. PKC is a midstream molecule involved in the non-canonical Wnt pathway that downregulates the MAPK/ERK signals and subsequent cascades (Dwivedi et al., 2003a; Voleti and Duman, 2012). This is in accordance with a decreased phosphorylation of its substrate in the HC (Pandey et al., 2003). It also supports the synergistic effect between BDNF and non-canonical Wnt pathways (Fig. 1). Taken together, this evidence emphasizes that data obtained after mixing suicide and depression in the same comparison may be interpreted with more prudence.

4.2.4. *Glucocorticoid receptor*

Long-term, stress-induced glucocorticoid elevation impairs hippocampal neuroplasticity and neurogenesis, and is involved in functional (feedback) abnormalities of the hypothalamus-pituitary-adrenal (HPA) axis that can, to some extent, be normalized by antidepressant drugs (Anacker et al., 2018; Brummelte and Galea, 2010; Lucassen et al., 2013, 2015; Snyder et al., 2011; Surget et al., 2011). A recent retrospective analysis has shown that oral glucocorticoids were associated with a robust increased risk of suicide in a dose-dependent manner (Laugesen et al., 2021). Although previous findings did not reveal obvious alterations in the cellular integrity or total transcripts of the human HC in relation to depression or glucocorticoid treatment, we later observed an increased expression of the GR in hippocampal CA1 of MDD patients, which interestingly, appeared higher in females than in males (Klok et al., 2011; Müller et al., 2001; Wang et al., 2012). In addition, glucocorticoid stress hormones that act on the GR have been proven to interact with the BDNF Val66Met polymorphism to determine hippocampus-gated fear and spatial memory (Notaras et al., 2016). In contrast, current studies did not reveal changes in the HC in molecules involved in the HPA circuitry in relation to suicide, including corticotropin-releasing hormone, its receptors and binding protein, or GR (isoforms) (Medina et al., 2013; Pandey et al., 2019, 2013). Other studies hypothesize that early life adversity, but not suicide, was the primary cause of subfield volume and plasticity changes, and

dysregulation of the GR gene in the HC (Alt et al., 2010; Boldrini et al., 2019; Labonté et al., 2012; McGowan et al., 2009; Teicher et al., 2012; Youssef et al., 2019). However, these hippocampal measurements were performed in bulk hippocampal preparations, which might preclude the profiling of the unique effects of glucocorticoids on specific cell populations in the hippocampus.

4.2.5. Androgen receptor

Androgens are steroid hormones involved in adult hippocampal neurogenesis and mood regulation by selectively binding to androgen receptor (AR) subtypes (Hamson et al., 2013; Zhang et al., 2010). Circulating levels of testosterone have been positively associated with suicidal behaviours in patients with depression (Sher et al., 2012). Postmortem studies have shown that the HC of suicide subjects has a stronger binding potential of AR-α2, as evidenced by increased receptor density and binding affinity relative to non-suicidal depressed patients and non-psychiatric controls (González et al., 1994; Meana et al., 1992). In contrast, AR-β expression in the HC did not exhibit alterations between suicide and control (Gurguis et al., 1999), yet the asymmetric expression of AR-β2 between hemispheres in the control group was absent in suicidal cases (Joyce et al., 1992). So far, the mechanisms of androgen involvement in suicidality remain elusive.

5. Anti-suicidal interventions associated with cognitive improvement

5.1. Cognitive-behavioural therapy

Cognitive-behavioural therapy (CBT) has been widely applied, and its efficacy towards suicide prevention has been proven across ages and following various adverse life triggers, including self-injury, post-traumatic stress disorder, sexual assault, and cognitive degeneration. Early intervention with CBT, via education and support to access community treatment, is crucial for decreasing suicide thoughts and self-injury, especially in young people at risk of suicide, who are, however, frequently not seeking treatment (Asarnow et al., 2017; Hetrick et al., 2017; Weinstein et al., 2018).

In adults, CBT is effective in preventing suicide attempts for patients with depression and/or a history of recent suicide attempts (Brown et al., 2005). Brief CBT and mindfulness-based cognitive therapy have been shown to reduce suicide risk by regulating cognitive reactivity, including measures of hopelessness and suicide beliefs (Chesin et al., 2016; Roberge et al., 2019). Given that mild cognitive impairment and dementia have been implicated in part of the aged suicide attempters, supportive services and cognitive reappraisal intervention may prevent the elderly from being hospitalized for suicidality (Günak et al., 2021; Lin et al., 2019). Of note, cognitive and working memory deficits may result directly from polysubstance use in the elderly and contribute to current serious suicidal ideation and attempts (Pompili et al., 2007). However, CBT was not beneficial in reducing suicidality when this occurred as a comorbidity of substance abuse (Morley et al., 2014), indicating that addiction-suicide interactions can have an independent impact on the pathogenesis and therapeutic barrier of suicide. Thus, cognitive improvement, possibly via CBT, plays an important role and marks the favourable prognosis of anti-suicidal therapies.

As we summarized in Fig. 1, a decrease of neurotrophic intracellular molecules has been associated with alterations in several signalling pathways. A correction of BDNF levels may therefore improve the deficiency of downstream cytoplasmic molecules and, eventually, reverse intranuclear transcriptional regulation. A clinical trial has shown that plasma levels of BDNF can serve as an indicator of treatment response associated with the recovery of suicide ideations (Grunebaum et al., 2017). In addition, therapeutic effects of CBT are dependent on the BDNF Val66Met polymorphism (Peters et al., 2020). Therefore, we hypothesize that the serum increase of BDNF could be a long-term effect of CBT therapies (Kobayashi et al., 2005), and the increase itself may be antisuicidal.

5.2. Serotonin receptor 2A ligands

The observations discussed above indicate that increased postsynaptic 5-HT2AR level in the human HC may be involved in the pathogenesis of suicide. One may thus assume that either agonists or antagonists of the 5-HT2AR could provide an anti-suicidal effect. So far, however, most 5-HT2AR agonists or antagonists did not yield an improvement of the onset or progression of suicidality. However, some prescribed formulations have even been found to be associated with elevated suicide risk, possibly due to initial responses and adaptations in the 5-HT system. Among the agonists, for example, clinical application of 25I-NBOMe that maps the cerebral localization of 5-HT2AR was found to be associated with more suicide attempts (Nichols and Grob, 2018; Suzuki et al., 2014). In addition, partial agonists of 5-HT2AR caused more lethal and negative psychiatric effects. Among human immunodeficiency virus-infected adults treated with efavirenz, an antiretroviral compound that is also a 5-HT2AR agonist, an increased risk of suicidal ideation was related to its plasma level (Mollan et al., 2014, 2017; Ophinni et al., 2020). Furthermore, exposure to mefloquine, an antimalarial drug, has also been associated with violent acts and suicidal behaviours (Nevin, 2012; Ritchie et al., 2013). Moreover, selective 5-HT2AR antagonists that inhibit serotonin reuptake, such as trazodone and mirtazapine, were both related to higher rates of suicide ideation, attempts, and self-harm behaviours (Coupland et al., 2015; Lavigne et al., 2019; Tubbs et al., 2021). The atypical antipsychotic olanzapine, whether or not it was associated with higher suicide-related events or the prevention of suicide, was found to be dependent on the underlying psychiatric illnesses of patients (Delapaz et al., 2021; Reutfors et al., 2013). A 5-HT2AR antagonist is more likely to play a positive role in suicide intervention when it also blocks the dopaminergic system, as it is in the case of risperidone or olanzapine (Reutfors et al., 2013). Similarly, cyproheptadine is a preventive measure to reduce the adverse effects triggered by efavirenz-included antiretroviral therapy (Dabaghzadeh et al., 2013). It seems thus that simply activating or blocking the activity of the 5-HT2AR does not relieve suicidality, but synergism with other neurotransmitters and neuromodulators may be effective. Evidently, more studies are needed to illustrate the mechanistic involvement of 5-HT2AR in suicide.

5.3. Ketamine

In recent years, ketamine has become a novel drug in suicide interventions. Many studies have confirmed that ketamine can rapidly alleviate suicide thoughts regardless of the administered frequency (single/repeated) or mode (intravenous/intranasal/oral) (Beaudequin et al., 2020; Domany and McCullumsmith, 2021; Grunebaum et al., 2017, 2018). Ketamine has been broadly prescribed to patients with MD, SCZ, or non-psychiatric individuals with recent suicide ideations (Domany et al., 2020; Fan et al., 2017; Grunebaum et al., 2017, 2018). The benefit of the significant reduction in suicide ideations induced by ketamine is enhanced by its being safe and well-tolerated. Its anti-suicidal effect is partly independent of the underlying psychiatric disorders or mood dysregulation (Ballard et al., 2014; Kang et al., 2021).

Interestingly, improvements in BDNF levels and memory, especially working memory, emerge as promising markers for the anti-suicide efficacy of ketamine treatment (Chen et al., 2021; Grunebaum et al., 2017). In clinical practice, short-term ketamine administration has pro-cognitive effects, e.g. in improving executive function and emotional processing (Lee et al., 2016). To date, both animal and human studies profiling neurobiological phenotypes and mechanisms have demonstrated that short-term ketamine intake is associated with reduced neuroinflammation, normalized glutamatergic hyperexcitability and synaptic plasticity (including BDNF, GSK-3, and TrkB receptor), modified dopamine synthesis and parvalbumin expression, and

activation of the opioid system in the HC (Al Jurdi et al., 2015; Kokkinou et al., 2020; Luo et al., 2020; Nowak et al., 2019; Williams et al., 2019; Zanos and Gould, 2018). In addition, acute ketamine administration has been found to induce dopamine release in the rodent brain, further supporting its antidepressant potential (Kokkinou et al., 2018). This observation also suggests that reducing the intracellular dopamine content may be a putative anti-suicidal target. Moreover, MDD patients who bear a BDNF Val66Met polymorphism showed a weakened antidepressant response of ketamine as compared to non-Met carriers (Laje et al., 2012). Interestingly, this allele also impairs ketamine-stimulated synaptogenesis in mice (Liu et al., 2012).

However, our knowledge of safety data on long-term ketamine use, such as irresponsive cases, tolerance, possible adverse effects associated with discontinuation, and potential abuse is worth mentioning. For example, compared to individuals with acute and moderate suicidality, those who had a chronic and strong suicide ideation responded with less anti-suicidal effects to ketamine (Ballard et al., 2018; Zhan et al., 2019). In addition, suicide attempts during maintenance ketamine treatment were also reported (Cusin et al., 2020). Strikingly, it has been shown that long-term ketamine use could produce cognitive deficits partly because it restrains synaptic signalling (Luo et al., 2020). Therefore, understanding the specific mechanistic alterations in subjects who have suicide ideations or attempted suicide, but did not die by suicide, can help in the future to avoid or modify risk factors and adverse actions that occur in suicide interference. The study of hippocampal brain samples of such individuals may be particularly useful in that regard and in further developing novel pertinent therapeutic strategies.

6. The future of suicide research: a promise and a focus on novel technologies

6.1. Opportunities using the hippocampus of legal euthanasia donors

Suicide is a progressive disorder and we presume that suicide thoughts, suicide attempts and their severity, and suicide completion correlate with increasing neuropathological alterations in the human brain. Aberrant signal pathways summarized above have indicated the presence of a molecular diversity implicated in the HC in relation to suicidality. However, the neurobiological changes exhibited by subjects who completed suicide are generally considered as strong molecular features of the underlying mental illnesses. Our previous studies were devoted to unravelling the neuropathology of psychiatric diseases and suicide as separate entities that have revealed different molecular changes in relation to MD and suicide (Zhang et al., 2020a, b; Zhang et al., 2021a; Zhao et al., 2019).

In addition to completed suicide, we recently introduced, for the first time, brain samples from individuals who died of legal euthanasia (people who had strong death ideation or even attempted suicide but were eventually euthanized) to explore the stages of suicidality in different ways (unpublished results). First, with euthanasia samples, we could classify the pathogenesis of suicide thoughts and suicidal behaviours as single or repeated attempts, which may ultimately be essential for personalized medication applications according to severity and complications. Second, individuals who died of legal euthanasia may have comorbid psychiatric illnesses or be non-psychiatric 'controls', e.g. cancer patients. This way, we could distinguish biomarkers between subjects with psychiatric disorders, who died of natural causes, versus subjects who died of legal euthanasia. The same holds for the control cases, which will enable us to analyze whether differential gene expression may be due to suicide tendency per se, or to the underlying psychiatric disorders. Third, by comparing subjects who died of legal euthanasia but did not attempt suicide throughout their lifespan, and subjects who died of natural causes but had suicidal ideations during their lifetime, we can profile vulnerability or resilience gene signatures that explain the potential conversion from suicide thoughts to actual suicides. Fourth, by comparing the differential gene expression patterns derived from subjects with psychiatric illnesses, versus controls in the euthanasia group, and differential patterns derived from the same subset analysis within natural deaths, we hope to identify the target genes of high suicidality among patients with psychiatric disorders.

6.2. Application of single-nucleus RNA sequencing

Evidently, mapping the cellular and molecular complexity of the events that underlie the conversion from suicide ideation to suicide completion will be key to identifying novel and putatively druggable regulators and pathways. Only a handful of studies assaying the human 'suicide' brain in an unbiased, genome-wide manner, and in relation to MDs, or rather independently of them, have been published to date (Glavan et al., 2021; Jabbi et al., 2020; Pantazatos et al., 2017; Punzi et al., 2019; Zhou et al., 2018). Strikingly, a common theme emerging from all these reports is the involvement of immune and inflammatory responses in the transcriptomic signatures related to suicide. These responses were associated not only with neuronal cells and pathways but also with astrocytes and microglia, highlighting the significance of multi-cellular crosstalk in shaping behaviours linked to suicide. Moreover, these findings suggest that decoding hub regulators driving suicide-associated behaviours cannot be achieved by bulk approaches and necessitates single-cell resolution. Even though no such evidence currently exists with respect to suicide subjects, single-nucleus RNA sequencing has been successfully applied to a wide range of human brain disorders, ranging from neurodegenerative to neuropsychiatric illnesses (Al-Dalahmah et al., 2020; Davila-Velderrain et al., 2021; Del-Aguila et al., 2019; Mathys et al., 2019; Nagy et al., 2020). While some concerns have been reported with respect to how representative the nuclear transcriptome is for the cellular transcriptomic in the human postmortem brain (Thrupp et al., 2020), studies directly comparing gene expression data from single nuclei versus single whole cells have demonstrated a high degree of concordance (Bakken et al., 2018; Lake et al., 2017; Olah et al., 2020), while disease-specific cellular states in the human brain also have been reported (Davila-Velderrain et al., 2021; Leng et al., 2021; Olah et al., 2020). Taken together, these observations may pave the way for the application of single-nucleus omics technologies to profile the cellular and molecular signatures of suicidal behaviours, and thereby identify novel targets for therapeutic intervention.

6.3. Application of mass spectrometry histochemistry

The above indicates that genes and proteins involved in specific neuronal signalling are strongly linked to suicidal tendencies. In addition, localization of molecular alterations in the brain is crucial for the interpretation of their functional consequences.

Besides the conventional '-omics' technologies, we, therefore, envision a promising role in future HC studies for analytical methods, which allow the imaging of signalling biomolecules directly on histological sections. In this context, a reactive matrix-assisted laser desorption and ionization mass spectrometry imaging (MSI) method for visualizing neurotransmitters has been shown to work on cryosections (Shariatgorji et al., 2019). Moreover, recently technology has been developed based on high-resolution MSI for the localization of neuropeptides in historic collections of well-documented formaldehyde-fixed and paraffin-embedded (FFPE) tissue samples (Paine et al., 2018). Such FFPE tissues are abundantly stored in biobanks all over the globe, including the Netherlands Brain Bank (NBB). This FFPE method for localizing neuropeptides was designated MSHC. Unlike immunohistochemistry which requires specific antibodies for biomolecule detection/localization, MSHC allows the study of multiple molecules simultaneously, combining detained localization with a very high molecular specificity. Indeed, methodological aspects like the capacity to detect low expressed proteins and genes deserve attention. Techniques like MSHC together with new developments in spatial transcriptomics, RNAscope and

high-plex RNA imaging (Longo et al., 2021; Strack, 2021) allow for complete molecular structure characterization of tissue, combining high accuracy mass measurements with tandem mass spectrometry primary structure confirmation, and as such includes all the features necessary to evolve into a powerful non-targeted biomolecular discovery tool.

7. Conclusions

We have here synthesized the existing knowledge regarding the functional association of the hippocampal formation with suicide. Two major concerns merge from this review. First, the psychopathological basis of psychiatric disorders and suicide should be distinguished and studied separately. Neglecting this may very well be the reason for the so far less satisfactory effects of antidepressant or antipsychotic treatment for suicide prevention. Second, unravelling the neurobiological alterations in carefully stratified subject cohorts that fall under different categories of suicide classifications is key to ultimately enable the development of novel individual suicide treatment and prevention strategies. Considering the heterogeneity of the suicide alterations and their regional specificity in the human brain, we presented an overview of the current state of knowledge regarding pathological alterations, focusing on the HC since hippocampal atrophy and specific cognitive dysfunction are two major parameters implicated in suicidality. We have, therefore, initiated a comparative study of donors from the NBB (a scientific infrastructure that is capable to support a comprehensive analysis of the different stages of suicidality and selecting the right samples) who died of legal euthanasia, and those who completed suicide, in an attempt to detect in the human HC the neuropathological grading from the onset of suicide ideations, over single suicide attempts, to recurrent suicidal behaviours. These and other similar future studies employing multi-omics techniques on tissue samples from donors with different stages of suicidality will hopefully provide novel mechanistic insights into the pathogenesis of suicide across different stages.

Data availability

No data was used for the research described in the article.
Data will be made available on request.
The data that has been used is confidential.

Declaration of Competing Interest

The authors report no declarations of interest.

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