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Review

The possible contributory role of the S allele of 5-HTTLPR in the emergence of suicidality

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Abstract

Suicide is a complex and challenging human phenomenon, and, although knowledge is expanding concerning its risk factors, its background is still not fully understood. There is currently an increasing interest in genetic factors associated with suicide, since these may lead to the emergence of personality traits and temperaments that may be long-term predictors of suicidal behaviour. One of the most likely genetic candidates in the background of suicide is the 5-HTTLPR polymorphism of the serotonin transporter gene. This review focused on papers published on the association of the 5-HTTLPR polymorphism of the serotonin transporter gene and suicidal behaviour as well as research on possible endophenotypes related to suicide. Although there are contradictory results, several studies and meta-analyses support the idea that the S allele plays a role in the background of violent suicide. However, in order to be able to delineate the genetic background of suicide, different types of suicidal behaviour should be distinguished, since studies indicate that these may have different genetic factors. Also, personality traits and temperaments should be identified that may play a modulating role between genetic factors and suicidal behaviour. So far, neuroticism, affective temperaments, and impulsive aggression have been found to be associated with both the S allele and suicidal behaviour. This study aimed to integrate findings concerning possible endophenotypes modulating between genetic factors and manifested suicidal behaviour.

Keywords

5-HTTLPR, endophenotype, polymorphism, serotonin transporter, suicide

Introduction

Suicide is a complex human phenomenon with multiple causes and underlying processes which is very hard to explain from both philosophical and psychological–psychiatric aspects, and poses an equally great challenge for contemporary science and our society in general. Several models have been proposed to explain suicide and several studies have been aimed at delineating the factors and processes playing a role in its background. The best-known and most widely accepted risk factors of suicidal behaviour deal mainly with psychiatric–psychological and socioeconomic factors; we know less, however, about the biological, neurochemical and genetic correlates and contributors of suicidality.

Suicide accounts for almost 2% of deaths worldwide, and attempted suicide is more frequent than completed suicide, with a prevalence of 3.5% (Suominen et al., 2004). Suicide varies with age and gender, and suicidal behaviour and suicide rates show significant geographic, regional and national variations (Rihmer, 2009), but suicide seems to have a strong genetic determination. Genetic effects on suicide are expected to be represented as small size effects of several gene variants which are involved in regulating processes playing a role in suicidal behaviour, as well as the interaction of these genetic variations and their interaction with environmental factors (Bondy et al., 2006; Marusic, 2005).

The presence of a psychiatric disorder is a major risk factor for suicide. However, while the majority of suicidal patients have a psychiatric disorder, mostly major depression and to a lesser frequency schizophrenia, when committing suicide (Coryell and Young, 2005; Rihmer, 2007), the majority of psychiatric patients do not commit or attempt suicide

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(Hendin, 1986), so the question remains as to what factors even within psychiatric disorders, or independently of them, predispose people to suicide. A positive family history is one important predictor of suicidality, which, especially in the light of results of twin and adoption studies, also points to the role of genetic factors (Roy et al., 1997). In order to investigate the genetic background of suicide, besides determining possible genotypes (the base sequence of a given gene of an individual) associated with suicidal behaviour, we must also clearly determine the phenotypes of suicidality, that is, observable characteristics related to this phenomenon, which is the joint product of both genetic factors and environmental influences (Gottesman and Gould, 2003). The most important step in research into the genetic factors contributing to the emergence of suicidal behaviour is to identify and describe endophenotypes. Endophenotypes, or intermediate phenotypes, are cognitive or behavioural markers that are associated with a psychiatric condition, but are also observable in healthy relatives of patients at a higher rate than in the healthy population, and are heritable. Endophenotypes are better defined and more quantifiable measures than a complex psychiatric condition, and are expected to be more closely related to the functional effect of genes; therefore, we try to decompose a given complex psychiatric condition to such behavioural or cognitive characteristics in order to investigate their association with a given polymorphism (Flint and Munafo, 2007; Gottesman and Gould, 2003).

Our aim was to review papers published on the association of the 5-HTTLPR polymorphism of the serotonin transporter gene and suicidal behaviour as well as research on possible endophenotypes related to suicide. We also aimed to integrate our findings concerning possible endophenotypes modulating between genetic factors and manifested suicidal behaviour.

Phenotypes of suicidal behaviour

Suicidal behaviour can be manifested in several different forms, and research indicates that different forms of suicidal behaviour differ not only in manifestation, but also in their background. As the contributory role of background factors, especially genetic factors, is small, studying heterogeneous samples of suicidal patients may mask important effects. Different suicidal phenotypes encompass several distinct types and phenomena, each of which may have a distinct biological background (Courtet et al., 2004). Therefore, to establish the possible role of individual genes in suicidal behaviour, different types of suicidal behaviours should be carefully described and distinguished.

Different manifestations of suicidal behaviour can be viewed along a spectrum. Different forms of suicidality range from suicidal ideations, to impulsive suicide attempts with low lethality, to highly lethal failed suicide attempts and to completed suicide (Bondy et al., 2000). From another aspect, suicidal behaviour can be categorized according to the intent to die, and according to lethality of method, whether violent or non-violent (Bondy et al., 2000). The impulsive or aggressive nature of the act is another possible classifying factor. The method of suicide is not randomly distributed, and violent methods are often associated with male gender and specific psychiatric morbidities such as severe major depression, substance abuse or psychotic disorders (Bondy et al., 2000; Dumais et al., 2005).

Attempted suicide is a self-damaging act aimed at ending one's life and it can lead to varying degrees of medical emergency. Within attempted suicide it is very important to distinguish between two subcategories, failed suicide and suicide gesture. Failed suicide, provoked by a strong intent to die, involves careful planning and a highly lethal method, usually leading to severe medical damage. Suicide gesture, on the other hand, with a low intent to die and usually provoked by an interpersonal conflict, is preceded by less preparation, involves a less lethal method and usually leads to less medical damage (Mann, 1998). Subjects with non-violent suicide gestures are very distinct from violent suicide attempters and are a more heterogeneous group, which also implies that in studies including non-violent suicide attempters important associations may be masked or obscured (Lin and Tsai, 2004). On the other hand, suicide attempts with high medical damage are probably associated with a strong intent to die, which suggests that they are probably more closely related to completed suicide than suicide attempts with low medical damage (Wasserman et al., 2007). It should be noted, however, that suicide attempts and completed suicide are overlapping categories: about two-thirds of suicide victims have made one or more prior suicide attempt(s), and non-violent suicide attempters frequently change their suicide method from non-violent to violent (Rihmer, 2007).

Genetic influences on the emergence of suicidality

The influence of genetic factors is obvious in the case of most psychiatric conditions, and the family aggregation of suicidal behaviour also points to an important role for genes in determining the emergence of suicidality. Suicide in the family increases the risk of suicide. It is not clear, however, whether this effect is mediated by biological variables, or by similar coping styles, roles, or other variables acquired by learning. Although first-degree relatives of suicide victims also commit suicide mainly during major depression, research suggests that the familial aggregation cannot be fully explained by either similar rearing conditions or inheritance of psychiatric disorders (Brent and Mann, 2005).

Studies emphasize the role of inherited components over the effect of a shared environment (Arango et al., 2003; Brent and Mann, 2005; Pompili et al., 2006; Roy, 1993; Roy and Segal, 2001; Roy et al., 1995; Statham et al., 1998). According to studies, an estimated 43% of the variability of suicidal behaviour can be explained by genetic factors (Roy, 1993; Roy et al., 2009), and the heritability of suicidality seems to be composed of the liability to manifest psychiatric disorders and the liability to impulsive aggression, the risk being highest if both factors are present (Bondy et al., 2006). This also suggests that the inheritance of a psychiatric disorder associated with suicide risk does not in itself account for the genetic risk for suicide, and genetic factors in the background of suicidal behaviour seem to be independent of the transmission of psychiatric disorders (Bellivier et al., 2000; Mann, 1998; Roy et al., 1997).

The role of the serotonergic system and 5-HTTLPR in the background of suicidal behaviour

The specific genes associated with suicide have not yet been delineated (Arango et al., 2003; Brezo et al., 2008; Ernst et al., 2009). However, since suicide has most strongly been associated with reduced serotonergic neurotransmission, most studies focus on genes encoding elements of serotonergic neurotransmission. It has been extensively reported that there is low serotonergic activity in violent behaviour and impulsive aggression (Arango et al., 1997; Asberg et al., 1976; Mann, 1998; Roy, 1993, 1999) and in violent suicide as well (Lester, 1995; Linnoila and Virkkunen, 1992; Mann et al., 1992). On the molecular level, lower affinity of the serotonin transporter for serotonin has been described in suicidal depressives compared with non-suicidal depressives and controls (Roy, 1999). At the same time it has been observed that postsynaptic $5HT_{1A}$ and $5HT_{2A}$ receptors are upregulated in the prefrontal cortex of suicide victims, probably as a compensatory mechanism in response to low serotonergic activity (Mann, 2003). $5HT_{1A}$ upregulation is localized to the ventral prefrontal cortex, which plays a role in behavioural and cognitive inhibition, and low serotonergic input in this area may lead to impaired inhibition of aggressive, impulsive and suicidal acts (Bondy et al., 2006; Mann, 2003), which may be an important underlying factor in the emergence of suicidality.

There is extensive research supporting a role for the serotonergic system in the background of suicidal behaviour; therefore, genetic studies have primarily concentrated on genes encoding the elements of this system. The most studied candidate genes in relation to suicide include the tryptophan hydroxylase, the serotonin transporter and the $5\text{-}HT_{1B}$ and $5\text{-}HT_{2A}$ genes. The serotonin transporter is an especially likely candidate, since it regulates the magnitude and duration of serotonergic activity by removing serotonin from the synaptic cleft, and thus it regulates serotonin turnover and serotonin level in the synapse (Lesch et al., 1996). Support for the association between 5-HTTLPR and suicidality comes from studies in which SSRIs have been proven to reduce suicidality (Ludwig et al., 2009; Zisook et al., 2009) and this effect was found to be independent of their antidepressive action (Verkes et al., 1998). One major limiting factor that must be considered when interpreting the results of 5-HTTLPR studies is that in 2006 the 5-HTTLPR was found to be functionally triallelic (LA, LG, and S). The L allele, with a common G substitution (24% in African–Americans and 14% in US Caucasians), showed a lower expression, nearly equivalent to expression for the S allele. This is a potential limiting factor in case studies that did not perform a triallelic analysis (Hu et al., 2006; Risch et al., 2009).

There is expanding research targeted at delineating the possible role of the 5-HTTLPR polymorphism in the background of suicide. Although the results reported by some individual studies are contradictory, several studies and meta-analyses have reported a significant positive association between the S allele and certain, well-characterized subtypes of suicidal behaviour. Therefore, if we consider the results of previous studies differentiating among the different types of suicidality within the samples, the picture is much clearer. This also in part explains the contradictory results of some studies, because many studies investigating the characteristics of suicidal behaviour use small and heterogeneous samples. Considering each type of suicidal behaviour individually, and based on the meta-analyses, it seems that the serotonin transporter gene S allele is significantly associated with violent completed suicide (Bondy et al., 2000), violent suicide attempts (Bayle et al., 2003; Bellivier et al., 2000; Courtet et al., 2001) and repeated suicide attempts (Courtet et al., 2004), and also with violent suicidal behaviour in bipolar patients (Neves et al., 2010). It has also been shown that the frequency of the S allele is not increased in a sample of non-violent suicide attempters (Courtet et al., 2003) and the S allele is not associated with suicidal ideation, although the L allele may have an interaction effect on suicidal ideation in combination with the G allele of the rs11568817 polymorphism of the HTR1B gene (Wang et al., 2009).

Several meta-analyses strongly support the role of the S allele in suicidality. Anguelova et al. in a meta-analysis reviewed 12 studies with a total of 2539 suicide attempters or completers and healthy controls (Anguelova et al., 2003) and found a significant association in the case of the S allele of the 5-HTTLPR and suicidality, and stratification according to the different types of suicidality suggested that this association was valid especially for attempted suicide, although of the 12 studies only three investigated suicide completers. In another meta-analysis, a strong positive association has been described between the S allele of the 5-HTTLPR and suicidal behaviour, both overall and when subgrouping the investigated studies according to the samples studied (Li and He, 2007). In another meta-analysis it was found that the presence of the S allele was significantly more frequent in suicide attempters than in non-attempters with the same psychiatric diagnoses, and that the S allele was significantly associated with violent suicide but not with non-violent suicide compared with normal controls (Lin and Tsai, 2004). In this meta-analysis, however, no association was found between 5-HTTLPR and suicidal behaviour in general, which may be due to the differences in statistical methodology within the studies included in the meta-analysis. When violent suicidals were compared with normal controls and also with non-violent suicidals in this meta-analysis, an association was found for the 5-HTTLPR, and the authors concluded that the S allele is associated with planned and more medically damaging impulsive violent suicide attempts, which parallels earlier results on the association of the S allele with violent aggression (Lin and Tsai, 2004; Moffitt et al., 1998). Another study concludes that the presence of the S allele leads to the emergence of violent aggression or a high determination to commit suicide, which is manifested in the application of more damaging and lethal methods when attempting suicide (Wasserman et al., 2007).

In general, although results are sometimes contradictory and inconclusive, mainly due to small and heterogeneous samples and poorly defined suicide phenotypes, meta-analyses clearly show that the 5-HTTLPR may be one component of the genetic susceptibility to suicide, and from the above it seems that the S allele of the serotonin transporter

is associated not with suicidality in general, but with violent suicidal behaviour (Courtet et al., 2001). Considering these results together, it seems that subjects with the S allele are prone to poor impulse control and aggression directed either inward or outward, and consequently subjects carrying the S allele may use highly lethal methods when acting on the impulse for suicide or violence (Lin and Tsai, 2004). Since in several studies it was consistently found that there is no association between non-violent suicide and 5-HTTLPR, it seems that the presence of the S allele does not carry a genetic risk for non-violent suicide, and also that it is possible that non-violent suicide is biologically and genetically more heterogeneous than violent suicide (Lin and Tsai, 2004). Suicide completion seems likely to be associated with a different biological, genetic and neurochemical background than other suicidal phenotypes.

Besides the serotonin transporter, other genes, such as the brain-derived neurotrophic factor (*BDNF*) gene, have been implicated in the background of certain types of suicidal behaviour, and what makes the *BDNF* gene an especially promising candidate is that *BDNF* plays a role in the regulation of the development of serotonergic neurons. In earlier studies the Val66Met (rs6265) functional polymorphism of the *BDNF* gene has been found to be associated with suicidal behaviour (Roy et al., 2009; Vincze et al., 2008), and it seems to play a role in antidepressant-induced suicidal ideation as well (Perroud et al., 2009). However, an interaction between the *BDNF* and serotonin transporter gene polymorphism influencing suicidal behaviour has not been described so far (Vincze et al., 2008). It would be very important to investigate other genetic candidates for suicidal behaviour and also their possible interaction effects with the serotonin transporter gene.

5-HTTLPR, psychiatric disorders and suicide

Serotonergic function is altered in both depressives and suicide victims (Purselle and Nemeroff, 2003). Although a recent meta-analysis reported no association between 5-HTTLPR and depression (Risch et al., 2009), in many studies and meta-analyses the 5-HTTLPR has been found to be associated not only with suicide but with affective disorders as well (Clarke et al., 2010; Kiyohara and Yoshimasu, 2009), which leads to questions as to whether the biological background of suicide is the same as the biological background of depression. Although results point to some overlap, increasing evidence suggests a distinct biology for suicidality (Purselle and Nemeroff, 2003).

Although the 5-HTTLPR has been found to be associated with psychiatric disorders associated with suicide, such as affective disorders, alcoholism and schizophrenia (Cho et al., 2005; Fan and Sklar, 2005; Underwood et al., 2004), results suggest that the possibility that the association of 5-HTTLPR and suicide is due only to the association of 5-HTTLPR and psychiatric disorders can be excluded, since a higher significance was found for the association when comparing suicide attempters with non-suicide attempter controls than when comparing them with healthy controls (Li and He, 2007).

At the molecular level, lower affinity of the serotonin transporter for serotonin has been described in suicidal depressives compared with non-suicidal depressives and controls (Roy, 1999). This points to a difference between suicidal and non-suicidal depressives which further suggests that suicidality has a genetic and neurochemical background independent of major depression. It has been reported that suicidal behaviour and major depression are independently associated with serotonergic abnormalities detectable in the brain, cerebrospinal fluid and platelets (Mann et al., 2000), which raises the question of whether different brain regions are involved in depression and suicide. Several studies have supported the fact that, in suicide, serotonin transporter density changes are localized to the prefrontal (Du et al., 1999; Hrdina et al., 1993) or ventral prefrontal cortex (Arango et al., 1995; Mann et al., 2000), which plays a role in behavioural inhibition, and might therefore be the location of the diathesis for suicidality (Mann et al., 2000). It seems that alterations of serotonin transporter binding specific to suicide as opposed to major depression are concentrated in the ventral prefrontal cortex (Arango et al., 1995), while serotonin transporter density reduction is more widespread in major depression (Arango et al., 1995, 2003; Mann et al., 2000), and some studies even report increased serotonin transporter density in major depression (Bennett et al., 2002; Wrase et al., 2006). These results, therefore, indicate that low serotonin function is independently associated with suicide and major depression (Mann, 1998), which is supported by the observation from several studies that there is an association between attempted suicide and low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA) across several psychiatric diagnoses (Arango et al., 2003). Epidemiological studies also suggest that there is a genetic susceptibility to suicidal behaviour independently of psychiatric disorders (Courtet et al., 2001; Roy et al., 1997). Studies investigating the role of the 5-HTTLPR in the background of suicidality also yielded the same conclusion, since several studies found no significant difference between non-suicidal subjects with and without major depression with respect to the presence of the S allele, at least as far as the effect of environment was not considered (Caspi et al., 2003), indicating that major depression cannot in itself account for the differences between suicide attempters and controls (Courtet et al., 2001). The authors concluded that the S allele is associated with a trait that is more common in those subjects who have both major depression and a history of violent suicide attempt (Courtet et al., 2001). Research also shows that suicide in families can be transmitted independently of psychiatric disorders (Brent and Mann, 2005; Brent et al., 1996), indicating that genetically based alteration of the serotonergic system may predispose people to both psychiatric disorders and suicidality (Wasserman et al., 2007).

Interaction models of the effect of 5-HTTLPR and environmental influences

Most studies so far have investigated the role of environmental factors in the background of suicide, and the majority of identified risk factors are also sociodemographic and environmental in nature even among depressed suicides. Since the heritability of suicidality was recently estimated at 43% (McGuffin et al., 2001), focus has turned to the genetic

determinants of suicide, and more recently also to the interaction of genetic and environmental determinants of suicidality (Gibb et al., 2006). However, not everyone exposed to an adverse environment commits suicide, which raises the question of what moderates the effect of these factors and what determines whether or not suicide will eventually occur. There is widespread research supporting the interaction between life events and 5-HTTLPR genotype (Roy et al., 2009), first reported by Caspi et al. (2003) and later replicated by others, and Caspi et al. also reported that this significant interaction predicts the emergence of suicidal ideation or attempts in subjects carrying the S allele. In line with the stress–diathesis model, several studies investigate the role of the 5-HTTLPR in the development and emergence of suicidality in interaction with the environment, which is supported by genetic–epidemiologic studies estimating that up to half of the variance in suicide attempts can be attributed to genetic factors (Fu et al., 2002; Preuss et al., 2003; Roy et al., 2007; Statham et al., 1998). In one study it was found that 5-HTTLPR genotype interacts with childhood trauma in increasing the likelihood of the emergence of a suicide attempt, and among subjects with the SS genotype life events showed an association with suicide attempt, meaning that the SS genotype amplifies the suicide risk associated with childhood trauma (Roy et al., 2007). In another study it was found that 5-HTTLPR genotype moderates the effect of childhood physical and sexual abuse, but not emotional abuse, on the emergence of suicide attempt; therefore 5-HTTLPR seems to primarily mediate the effect of certain forms of negative life events only, which suggests differential pathways to the development of suicidality in the case of different negative life events (Gibb et al., 2006). 5-HTTLPR is therefore suggested to moderate the impact of life events on the development of depression and possibly also on the emergence of suicide (Caspi et al., 2003; Eley et al., 2004; Gillespie et al., 2005; Kaufman et al., 2004; Kendler et al., 2005). These findings are in line with the stress–diathesis model of suicide (Mann, 1998), which postulates that psychiatric illness and life stress precipitate suicide only in patients carrying a diathesis, such as some genetic factors.

We must also keep in mind that suicidal behaviour is modulated by several systems besides the serotonergic system, and even within the serotonergic system the impact of the 5-HTTLPR polymorphism is only modest. 5-HTTLPR interacts not only with environmental influences and life events in the background of suicidal behaviour, but also with the effects of other genes (Roy et al., 2009). The susceptibility model of suicide postulates the role of several genes each having a small effect in the manifestation of violent and suicidal behaviour. Besides the serotonin transporter, several other genes encoding elements of the serotonergic system are implicated, such as the tryptophan hydroxylase gene (Abbar et al., 2001; Mann et al., 1997) and the monoaminooxidase A gene (Preisig et al., 2000). If specific variants of these genes are present their combined effect can lead to the overall low activity of the serotonergic system (Courtet et al., 2001). Nevertheless, the role so far described for the 5-HTTLPR S allele in the background of suicidal behaviour, affective disorders and cyclothymic temperament draws a consistent pattern delineating the role of this polymorphism in the background of suicidal behaviour.

Behavioural and personality mediators between the 5-HTTLPR S allele and suicidal behaviour: Possible endophenotypes?

The focus of studies dealing with psychological suicide risk factors increasingly shifts from risk factors that predict the emergence of suicidality in the short term to such biologically determined risk factors as personality traits and temperaments. Temperaments simultaneously carry a disposition towards certain types of psychiatric illness, and are adaptive in other situations, and underlying mood disorders tend to manifest first in the form of affective temperaments (Akiskal, 1996). Temperaments have a strong genetic basis and are the environmentally influenced manifestation of biologically determined characteristics (Bouchard, 1994; Kochman et al., 2005). Personality traits and temperaments may be the strongest and most important long-term predictors of suicide, particularly among patients with major mood disorders (Akiskal et al., 2003; Maser et al., 2002; Oquendo et al., 2004; Pompili et al., 2008).

So far mainly impulsive and aggressive traits, anger-related traits and neuroticism- and anxiety-related traits have been proposed as endophenotypes for suicidal behaviour independent of axis I psychiatric disorders; however, they may be part of a developmental cascade that may lead to the emergence of suicidality in a subgroup of psychiatric patients (Baud, 2005; Bondy et al., 2000; Maser et al., 2002; Oquendo et al., 2004; Rihmer, 2007; Turecki, 2005; Zouk et al., 2006). Impulsive aggression has been described as being associated with low CSF 5-HIAA levels and is conceived as an endophenotype for suicidal behaviour (Roy and Linnoila, 1988; Zhou et al., 2005). Hostility has been described as predicting suicidality (Weisman et al., 1973). Impulsive and aggressive personality traits probably have a strong genetic background (Coccaro et al., 1994, 1997; Courtet et al., 2004) and they are also probably involved in the transmission of suicidal behaviour in families (Brent et al., 1996), suggesting that impulsive aggressiveness may be an endophenotype associated with the serotonergic genes and also with the emergence of suicidality (Courtet et al., 2004). Hopelessness, the most prominent clinical/cognitive aspect of severe major depression, has been found to be a predictor of suicide in several studies (Beck et al., 1985, 1989; Fawcett et al., 1987; Minkoff et al., 1973; Sokero et al., 2006), and it has also been reported that both hopelessness and suicidal tendencies vanish and disappear after clinical recovery from depression (Sokero et al., 2006). What is more remarkable, our group has previously reported that the S allele of the 5-HTTLPR shows a significant association with hostility and aggression and hopelessness in a psychiatrically healthy sample as well (Gonda et al., 2009). However, when considering the behavioural and personality consequences of 5-HTTLPR, it must be mentioned that men and women show different and opposite behavioural manifestations of the presence of the S allele; while in women it leads to an increased risk of the development of depression, in the case of men it acts in the opposite direction and seems to be protective, an effect that may be masked due to the majority of studies investigating mainly women (Brummett et al., 2008; Sjoberg et al., 2006).

Neuroticism is a psychological construct that has recently increasingly often been selected to characterize affective instability or negative emotionality, and it is among the traits most consistently associated with suicide ideation and attempts as well as with completions (Brezo et al., 2006). So the question emerges as to whether the effect of 5-HTTLPR on suicidal behaviour could be mediated by increased neuroticism. Neuroticism has been found to be higher with the S allele, but in meta-analyses the effect appears small (Munafo et al., 2005; Schinka et al., 2004; Sen et al., 2004), which is surprising given the associations between 5-HTTLPR genotype, vulnerability to adverse life events, neuroticism, and major depression. One possible explanation for this contradiction is that, because neuroticism is an undesirable and maladaptive trait, people develop cognitive and behavioural strategies to moderate their innate negative affectivity. This suggests that the effect of 5-HTTLPR is larger before adulthood. Indeed, a longitudinal study of children and adolescents using self and proxy reports has found that, while the effect of 5-HTTLPR on neuroticism was substantial at age 9 and still measurable at age 15, it had disappeared by the time the subjects became adults (Harro et al., 2009). Thus it is possible that the S allele contributes towards higher suicidality by increasing neuroticism, as, despite the mental defences built up during adolescence, inclination towards negative affect remains floating under the surface and can be revealed by adverse life events – not, however, leading to suicide, unless additionally associated with other factors.

One important additional factor in suicidal behaviour is impulsivity, which is related to lower serotonergic function also in suicide completers (Brown et al., 1982). A higher prevalence of the S allele has been reported in impulsive suicide attempters (Baca-Garcia et al., 2005). In some tasks measuring disinhibition-related aspects of impulsivity the S allele has not been found to increase it (Fallgatter et al., 1999). Nor did the 5-HTTLPR genotype have any independent effect on impulsivity as measured using the Barratt Scale of Impulsivity (Preuss et al., 2003). While we have reproduced the latter finding in a large population-representative sample, we also found that S allele carriers had higher impulsivity in a visual discrimination task, performing at a similar speed to the LL subjects, but committing more errors (Paaver et al., 2007). Furthermore, carrying the S allele increased both self-reported and behavioural impulsivity dependent upon another marker of the serotonin system, platelet monoamine oxidase (MAO) activity. Together these findings suggest that 5-HTTLPR has specific effects on impulsivity dependent on other genotypes and situational demands on cognition, and this may be relevant to suicidal behaviour.

Specific situational demands that are strongly associated with suicidal behaviour are presented to the CNS by alcohol intake. Alcohol is a major risk factor for suicide (Varnik et al., 2007). While the data on the effect of the 5-HTTLPR genotype on alcohol intake appear contradictory, a meta-analysis has revealed an effect of the S allele on alcohol dependence (Feinn et al., 2005). Alcohol dependence, obviously, is the end result of many behavioural choices made over the life course, and it should be specified how the 5-HTTLPR genotype can exert its influence. Impulsivity could be one mediating factor, but also higher vulnerability to stress, as subjects who develop substance abuse more frequently come from unstable families. In female rhesus monkeys early life stress alters secretion of stress hormones in response to alcohol in S allele carriers of the rh-5-HTTLPR, and it also increases alcohol use in the S allele carriers (Barr et al., 2004).

Specific affective temperament types are the subaffective manifestations and often the precursors of major unipolar and bipolar affective disorders, and thus have a strong association with suicidal behaviours (Akiskal and Pinto, 1999; Pompili et al., 2008). Cyclothymic temperament is characterized by increased mood lability, impulsive and aggressive behaviours and emotional overreactivity (Akiskal, 1995; Kochman et al., 2005). In one study of children and adolescents, cyclothymic–hypersensitive temperament was shown to be associated with suicidal ideation and suicide attempts, increasing the odds ratio of suicidal ideation by 7.4 and of suicide attempt by 10.5; therefore the authors concluded that the presence of cyclothymic–sensitive temperament predicts suicidality (Kochman et al., 2005). Cyclothymic temperament has been shown to be a sensitive marker of soft bipolarity in adults, indicating its strong association with bipolarity (Hantouche et al., 1998), and evidence suggest that unipolar depressive patients with cyclothymic temperaments should be considered in the bipolar group (Akiskal, 1996; Oedegard et al., 2008). Especially those bipolar II patients who exhibit cyclothymic temperament and harm-avoidant traits are viewed as possessing the most threatening type of bipolarity and thus being prone to major affective episodes and impulsive suicide attempts (Pompili et al., 2008). Cyclothymic bipolar II patients report significantly more lifetime suicide attempts and are significantly more often hospitalized for suicide risk than non-cyclothymic bipolar II patients (Akiskal et al., 2003). Suicide attempts in bipolar patients have an increased lethal potential (Helbecque et al., 2006). Suicide rate in bipolar disorder is more than 25 times as high than in the general population (Tondo et al., 2003), and in a recent study taking the unipolar–bipolar conversion and distinction carefully into consideration a much higher suicide rate was found in bipolar than in unipolar depression (Rihmer, 2009; Tondo et al., 2007). This shows that, in general, bipolar disorders carry the highest risk for suicide, but bipolar II patients have an even higher risk than bipolar I (Akiskal, 2007; Tondo et al., 2003, 2007). Bipolar patients also use more violent and lethal suicidal methods than unipolars (Rihmer, 2007; Vieta et al., 1997; Zalsman et al., 2006). Cyclothymia and cyclothymic temperament, which can be considered an attenuated form of bipolar disorder (Rihmer, 2009), has been shown to predispose to suicidal behaviour and is associated with lifetime and current suicidality (Akiskal et al., 2003).

The relationship between affective temperaments and suicide is complex, since not only cyclothymic temperament has been found to be associated with an increased suicide risk. In another study suicide attempters have also been found to score significantly higher than controls on all affective temperaments within the depressive superfactor, that is, depressive, irritable, anxious and cyclothymic temperament, but not on hyperthymic temperament (Rihmer et al., 2009). In another study it was found that, in addition to higher depression, hopelessness and anxiety, suicidal patients also show

higher levels of irritable temperament, and, as in the study mentioned before (Rihmer et al., 2009), hyperthymic temperament was also negatively associated with suicidality in this study (Pompili et al., 2008). The authors concluded that affective temperaments can be considered predisposing traits for emotional instability, and suicidal patients are thus predisposed to react to environmental stimuli with emotional lability of varying nature and degree from anger to dysthymia or even unstable elevated mood (Pompili et al., 2008). These people find it difficult to adapt to changing environments, and thus life's adversities are more dangerous and life-threatening. It seems that affective temperaments within the depressive superfactor may all lead to suicidal behaviour in different ways linked to the nature of the given temperament, and the common pathway is increased emotional lability and consequently worse adaptation in the face of environmental stimuli and life events. According to our previous studies, affective temperaments within the depressive superfactor also show an association with the S allele of 5-HTTLPR. We hypothesize that the S allele carries an increased liability towards emotional instability and worse adaptation to life events, and the exact nature of the resulting affective temperament will be determined by other genes (Gonda et al., 2006). The serotonin transporter gene seems to carry susceptibility to suicidality, and this could also, at least in part, explain the efficacy of lithium in suicide risk prevention (Cipriani et al., 2005; Helbecque et al., 2006), since lithium is known to enhance serotonin turnover.

Conclusion

Studies indicate that serotonergic dysfunction has a profound role in determining behaviour, and part of this effect is due to the effect of altered serotonergic function on the prenatal developing brain, influencing neurogenesis, apoptosis, axon branching and dendritogenesis, which in turn determine adult behaviour as well. In the prenatal development of the serotonergic system, the 5-HTTLPR plays a key role (Gaspar et al., 2003; Nordquist and Oreland, 2010). Based on our current understanding of the genetic background of suicide, it seems that the S allele of the 5-HTTLPR is an important element giving rise to certain phenotypes of suicidal behaviour. Violent completed suicide seems to be associated with the S allele of the 5-HTTLPR, while other types of suicidal behaviour are likely to have a different biological background. Furthermore, the presence of the 5-HTTLPR S allele may lead to the emergence of different possible endophenotypes associated with suicidality. The 5-HTTLPR polymorphism has so far been described to be related to several manifestations of altered serotonergic function, from susceptibility to affective disorders to pharmacological response to antidepressants, susceptibility to rapid cycling and antidepressant-induced mania, suggesting that the common underlying trait associated with these phenomena may be affective and behavioural instability (Bellivier et al., 2002; Courtet et al., 2004). This is in line with earlier findings concerning the association of the S allele with neuroticism-related traits, since it is quite possible that the serotonin transporter polymorphism has various differential effects related to the expression level in specific brain areas, as well as depending on the contributory role of other genes and environmental factors, which would manifest in different patterns of behavioural and mood instability (Courtet et al., 2004).

These intermediate phenotypes encompass different aspects and manifestations of mood lability and liability to impulsiveness and aggressivity. We propose that temperament is the mediating variable between the genetic makeup and manifested suicidal behaviour. The presence of the 5-HTTLPR S allele may lead to the emergence of different endophenotypes, which can be related to the manifestation of suicidal behaviour.

Expanding our knowledge and understanding of the role of the serotonergic system in suicidal behaviour may lead to better recognition of suicidal behaviour and of the prodromal symptoms of suicidal behaviour, and may also play an important role in developing drugs with a potential to reduce suicidality (Li and He, 2007).

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