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Review article

Functional imaging, serotonin and the suicidal brain

K. AUDENAERT[1,2], K. PEREMANS[2,3], I. GOETHALS[2] and C. VAN HEERINGEN[1]

[1]Department of Psychiatry and Medical Psychology, Gent University, Gent, Belgium ; [2]Division of Nuclear Medicine, Gent University Hospital, Gent, Belgium ; [3]Department of Medical Imaging, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

Abstract

The involvement of the serotonergic system in the pathophysiology of suicidal behaviour has been established through indirect and direct research on serotonin and its metabolites and on serotonin transporters and receptors. Indirect research results include a reduced 5-HIAA in cerebrospinal fluid in violent suicide attempters and a blunted increase in prolactin after a fenfluramine challenge. Direct post-mortem research demonstrated an increase in 5-HT_{2A} receptors.

Direct in vivo functional imaging with PET or SPECT demonstrated a reduction in 5-HT_{2A} binding index in suicide attempts in anxious and depressed suicide attempters and an increase in 5-HT_{2A} binding in impulsive suicide attempters. These results are in keeping with 5-HT_{2A} binding studies in depressed patients and impulsive animal research. Interestingly, both an increase and a decrease in 5-HT_{2A} binding index seem to normalize with SSRI treatment.

Key words : Suicidal behaviour ; PET ; SPECT ; serotonin ; 5-HT2A ; brain imaging.

Introduction

In this article a review will be given concerning the contribution of functional brain imaging studies in the understanding of serotonin in the pathogenesis of suicidal behaviour.

Of course, suicidal behaviour is not a psychiatric disorder. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR 2000) it is mentioned as a *symptom* of a depressive episode and as a *criterion* in the diagnosis of Borderline Personality Disorder (BPD). BPD is further characterized by a pervasive pattern of instability and marked impulsivity. Besides these disorders, suicidal behaviour can be present in a whole array of psychiatric conditions, such as psychotic and anxiety disorders, and can appear in periods of adjustment to serious life events. Suicidal behaviour poses a major challenge to clinicians and health policy makers due to its difficult prediction and prevention, and its substantial impact at individual and societal levels (Van Heeringen *et al*. 2004). Current psychobiological research points at hopelessness as a psychological factor, impaired sensory processing and reduced future fluency as neuropsychological components and impaired serotonergic neurotransmission and frontotemporal processing as major components in the pathogenesis of suicidal behaviour.

The involvement of serotonin (5-HT) in the pathophysiology of suicidal behaviour has been the target of considerable research in the last decades. There are two major research lines : (1) *indirect research* focuses at peripheral – and not central nervous – estimations of serotonergic neurotransmission, such as the dosage of serotonin or its metabolite in blood or in cerebrospinal fluid and (2) *direct research* focuses at the brain itself and comprises *postmortem* and *in vivo* estimations of the binding index serotonin transporters and receptors.

The first, and since then frequently replicated study on the involvement of serotonin in suicidal behavior dates from 1976. Asberg and collegues demonstrated lower 5-HIAA (5-hydroxy indole acetic acid ; the principal metabolite of serotonin) levels in the cerebrospinal fluid of attempted suicide patients (Asberg *et al.* 1976). Due to the invasive nature of cerebrospinal fluid sampling, much effort was spent on investigating serotonin and its metabolites on peripheral blood and blood platelets. These trials however turned out to be unreliable since peripheral and central serotonin or metabolite levels were not well correlated.

A further innovation in the demonstration of the role of serotonergic neurotransmission in suicidal behaviour was introduced by *pharmacological challenge tests.* In this technique, serotonin agonists, such as fenfluramine, were administered and prolactin levels were measured in peripheral blood. Fenfluramine increases the presynaptic release of serotonin, which then binds post-synaptically to serotonin receptors. Secondary and proportional to this postsynaptic receptor (> 5-HT_2) stimulation, the anterior pituitary releases prolactin in the circulation. If the serotonergic system is impaired, as is the fact in attempted suicide patients, a blunted increase in prolactin is found (Malone *et al.* 1996 ; Correa *et al.* 2000). Interestingly, it was

demonstrated that high lethality suicide attempters, as compared to low lethality suicide attempters, had a lower prolactin level in blood 3 h after fenfluramine administration (Oquendo *et al.* 2003). Hereby evidence was provided that the serotonergic system is the most impaired in the high lethality suicide attempters.

Next to the assessment of serotonergic functioning in general, also indirect estimations of binding index of serotonin transporters and receptors in particular, were carried out in attempted suicide patients. In these indirect paradigms, a correlation between central nervous system and peripheral blood platelet transporters (e.g. serotonin transporter ; SERT) and serotonin receptors (e.g. 5-HT_{2A}) is supposed. A reduction in platelet SERT (Marazziti *et al*. 2001) and an increase in platelet 5-HT_{2A} receptor binding index (Rao *et al.* 1998) in attempted suicide patients could be demonstrated. These indirect studies on peripheral fluids have the advantage they are non-invasive in nature, bear no radiation burden and can be repeated a substantial number of times. On the other hand these studies have questionable validity since a correlation between central and peripheral receptors and transporters in healthy volunteers and in pathological conditions has never been unequivocally proven (Muller-Oerlinghausen *et al*. 2004). Moreover these peripheral blood studies can give no clues on possible regional changes in transporter and receptor changes in brain.

In answer to the problem of questionable validity of these indirect estimations of transporter or receptor binding index, *postmortem* studies in suicide victims allowed for direct estimation of transporter and receptor status. Autoradiographic evaluation of brain tissue offers an excellent spatial resolution, even to a microscopic neuron layer level. However, since many years, methodological problems associated with post-mortem cerebral studies are described and include lack of sampling from multiple regions (Lowther *et al*. 1994) and rapid alterations in neurotransmitter concentration postmortem (Palmer *et al.* 1988). Further reasons that may have accounted for a variability in the study results are the heterogeneity with regard to the nature of the suicide act and the influence of treatment with antidepressant drugs or neuroleptics at the time of the suicide (Stockmeier *et al.* 1997).

Functional imaging techniques, such as Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) offer the advantage of a non-invasive *in vivo* direct estimation of regional brain functioning, with an acceptable spatial resolution, and the possibility of longitudinal research designs. With perfusion tracers such as ^{99m}Tc-ECD or ^{99m}Tc-HMPAO or metabolism tracers such as ^{18}F-FDG, functional brain imaging can offer insight in involved brain regions and circuitry in the pharmacological challenge studies with serotonergic agents (e.g. fenfluramine challenge test). Using radioligand tracers with specific affinity for the serotonin transporter (SERT), the serotonin-1A receptor (5-HT1A) or serotonin-2A receptor (5-HT_{2A}), functional brain imaging offers the possibility to investigate the binding index of these tracers to transporters or receptors. Importantly, and a major drawback, is the fact that these techniques cannot discern between receptor affinity (Kd) or number of receptors (Bmax). Recently PET alpha-11C-Methyl-Tryptophan trapping experiments were used as an estimation of serotonin synthesis (Leyton *et al.* 2006).

Surprisingly little use has been made of structural and functional neuroimaging studies. In the following we will focus on functional neuroimaging studies of suicidal behaviour and on studies of depression and impulsive behaviour, relevant for our understanding of suicidal behaviour.

Perfusion and metabolism in resting condition studies

Resting condition brain perfusion or metabolism studies are common practice in hospitals with nuclear medicine facilities. These brain scans are characterized by tracer injection that takes place in resting conditions, in a quiet room with closed eyes in order to minimize sensory or motor influences on brain tracer distribution. Despite the fact that these studies only offer indirect evidence in the study of serotonergic neurotransmitter in suicidal behaviour, they are necessary to facilitate the interpretation of pharmacological activation studies.

There are few studies on brain perfusion and metabolism in patients with suicidal behaviour that are not depressed. We performed a pilot study (^{99m}Tc-ECD SPECT) in attempted suicide patients without depression (N = 15) and found a bilateral prefrontal hypoperfusion and a left-sided thalamic increased perfusion (Audenaert *et al*. 2002a). Oquendo *et al*. carried out an ^{18}F-FDG PET study in high lethality (N = 16) versus low lethality (N = 9) suicide attempters of whom some were depressed. The study showed relative hypometabolism in high lethality attempters compared to low lethality attempters in the ventral, medial and lateral prefrontal cortex. This difference became more marked after fenfluramine administration, as will be discussed in the next paragraph (Oquendo *et al.* 2003). In an ^{18}F-FDG PET study in resting conditions of impulsive behaviour in non-depressed personality disorder patients (N = 13, all females), compared to healthy volunteers (N = 9), a significant bilateral hypometabolism in the medial frontal cortex was reported (Soloff *et al.* 2003b) In a comparable population, we used ^{99m}Tc-ECD SPECT in a study in impulsivity related personality disorders that demonstrated auto-aggressive and/or hetero-aggressive behaviour compared to age and gender

matched healthy volunteers and demonstrated a reduced perfusion in the right sided fronto-temporal cortex (Goethals *et al.*, 2005a) Interestingly these aforementioned study reports support a long-standing hypothesis of increased limbic drive in combination with reduced prefrontal executive functions, i.e. functions needed to execute appropriate behaviour in answer to sensory information, and reduced orbitofrontal abilities resulting in reduced recognition of internal and external emotions. This impaired frontal perfusion and metabolism has consequences on the cognitive functioning of suicidal patients as is discussed in the next paragraph.

Further, a possible explanation of hypofrontality could lie in a deficient serotonergic neurotransmission, as is discussed in the paragraphs on pharmacological activation paradigms and on serotonergic transporter and receptor ligand studies.

Cognitive activation studies in suicidal patients

Neuropsychological assessment studies

The consequences of hypofrontality were demonstrated by *neuropsychological assessment studies*. As an example, Keilp investigated neuropsychological function in different domains (general intellectual functioning, motor function, attention, memory and executive function) in healthy volunteers (N = 22), depressed non-suicide attempters (N = 21), depressed low-lethality attempters (N = 14) and depressed high-lethality attempters (N = 15). This group demonstrated that the scores of general intellectual functioning, attention, memory and executive function, were substantially lower in the high lethality attempters. It was concluded that at least reduction in attention and executive functions could be attributed to the frontal cortex functioning (Keilp *et al*. 2001). Indeed, the prefrontal cortex is largely involved in frontal-subcortical circuitry that involves higher cortical functions, such as planning, problem-solving, strategic thinking etc., besides it's role in attentional system circuitry.

Cognitive characteristics of suicidal individuals and functional imaging

Knowledge about the state of mind of suicidal individuals remains limited. While thoughts and attitudes around the time of a suicidal act may predict future suicidal behaviour (Beck *et al*. 1999), relatively little is known about the most basic aspects of cognitive processing in suicidal individuals. However, impaired cognitive functioning in psychiatric disorders where suicide risk is elevated is now well documented (Mann *et al*. 1999), and insight in the cognitive characteristics of suicidal individuals is increasing (Williams *et al*. 2001). It has thus become clear that three characteristics differentiate between depressed suicidal individuals and depressed non-suicidal individuals. These characteristics include (1) *a sensitivity to particular life events reflecting signals of defeat*, based on attentional biases ('perceptual pop-out') leading to involuntary hypersensitivity to stimuli signalling 'loser' status ; (2) *the sense of being trapped*, which is related to an insufficient capacity to solve problems, which are commonly of an interpersonal or social nature and (3) *the absence of rescue factors*, mediated by a subjective and objective inability to prospectively anticipate problems, and leading to feelings of hopelessness.

While the involvement of these cognitive characteristics in the development of suicidal behaviour has been shown consistently, little is known about the neural basis of these characteristics of suicidal individuals.

With regard to the *sensitivity to particular life events*, early studies focused on the hypothesis that a generalised cognitive rigidity mediates the relationship between stressful life events and suicidal behaviour. Using a modified Stroop task, it was demonstrated that that the level of suicidal ideation in depressed individuals correlates particularly with biases in selective attention (Becker *et al*. 1999). Although clearly much more research is needed, these findings suggest a role of attentional biases in the development of suicidal ideation but not suicidal behaviour in depressed individuals.

Williams and Pollock (2001) have convincingly argued with regard to the second characteristic that the *sense of being entrapped* is associated with trait-dependent deficiencies in problem-solving skills, which in turn appear to depend upon deficits in autobiographical memory. Several studies have showed an association between attempted suicide and over-general autobiographical memory (Evans *et al*. 1992 ; Sidley *et al*. 1997). These studies indicate that over-general autobiographical recall (probably mediated by the frontal lobes) affects suicidal behaviour by its effect on the ability to recall specific memories among attempted suicide patients, which correlates positively with the effectiveness of the solutions suggested for solving hypothetical social problems. A reduction in problem solving abilities, related to a deficient prefrontal perfusion, was demonstrated with ^{99m}Tc-ECD SPECT and a Tower of London neuroactivation paradigm in depressed subjects compared to healthy volunteers (Goethals *et al*. 2005b).

With regard to the third cognitive characteristic, *the absence of rescue factors*, associated with a reduction in future fluency, the relatively new research approach which addresses prospective cognition may well be useful. Impaired future fluency can be defined as the inability to generate positive outcomes or strategies in future life. We found a blunted prefrontal perfusion with ^{99m}Tc-ECD

SPECT in a neutral verbal fluency paradigm between suicide attempters and non-depressed controls (Audenaert *et al*. 2002b). By using a modified fluency test it was recently demonstrated that attempted suicides were less fluent in addressing positive events that might happen in the future. Moreover, hopelessness, which is a core psychopathological characteristic in association with suicidal behaviour, was found to correlate significantly with the lack of generating future positive events and not with an excessive anticipation of negative things in the future (Williams *et al.* 2001).

It thus appears that the three core cognitive psychological characteristics, which differentiate between depressed suicidal and depressed non-suicidal patients, are associated with biases in neuropsychological functioning in terms of attention, memory and fluency, respectively.

Pharmacological challenge studies with serotonergic drugs

The link between brain perfusion or metabolism and serotonin was elegantly demonstrated through pharmacological activation studies with serotonin agonists, such as fenfluramine. As was mentioned in the introduction, fenfluramine is a serotonergic agonist. Besides an increase in prolactin, fenfluramine also increases frontal cortex metabolism (Soloff *et al*. 2003a).

In a first study, six patients with major depression and six healthy volunteers were studied using ^{18}F-FDG PET and a challenge with the oral serotonin agonist d,l fenfluramine . The depressed subjects, two of whom were suicide attempters, showed a blunted metabolic response to fenfluramine compared to the normal controls (Mann *et al*. 1996). In a second study, ^{15}0-H20 PET was used to assess changes in cerebral blood flow (CBF) after intravenous d-fenfluramine in 13 depressed women and 18 healthy women (Meyer *et al*. 1998). No differences in response between the two groups could be demonstrated. The authors of the second study suggested that the presence of suicidal behaviour among patients in the first study may have accounted for the decreased responsivity to fenfluramine. However, the findings can also be explained by the inclusion of only females in the second study's samples, and the fact that cerebral blood flow and not metabolism was measured (Oquendo *et al*. 2001). More recently, 16 high-lethality suicide attempters were compared to nine low-lethality attempters with ^{18}F-FDG PET and fenfluramine challenge. After controlling for age, lethality of the attempt appeared to be inversely correlated with metabolism in the ventromedial prefrontal cortex after fenfluramine challenge. Indeed, after this challenge a lower mean regional cerebral metabolic rate of glucose uptake (rCMRglu) correlated with higher lethality suicidal behaviour. It should be noted that the authors also demonstrated that higher verbal fluency correlated positively with rCMRglu in the same regions of the prefrontal cortex. As discussed before, these authors demonstrated that lethality of the suicide attempt inversely correlated with prolactin after challenge (Oquendo *et al.* 2003) Since it is demonstrated that 5-HT_{2A} receptors are involved in the serotonin-prolactin link, one could expect a general reduction in serotonin neurotransmission after fenfluramine and/or a specific dysregulation in 5-HT_{2A} receptors. This shall be discussed in further paragraphs.

Oquendo *et al.* (2003) found a lower CMRgluc in high versus low lethality suicide attempters. Interestingly this hypometabolism in frontal cortex structures was related to the degree of suicide intent and impulsivity and not to depression.

Serotonergic transporter and receptor ligand studies

Besides these indirect strategies to estimate serotonergic function research with serotonergic radioligands can directly assess serotonergic transporter (SERT) and receptor function.

Serotonin transporter

In their landmark study in 1997, Tiihonen, using ^{123}I-ßCIT SPECT demonstrated a reduced frontal and midbrain SERT binding index in impulsive violent subjects (assault, homicide, arson, ... ; N = 21) (Tiihonen *et al*. 1997).

In contrast to this reduced SERT binding, it was demonstrated in a population of drug naive or drug free depressed patients (N = 13 ; 7 Major Depressive Disorder and 6 Bipolar disorder) and 21 healthy controls that SERT binding was increased in the thalamus and unchanged in midbrain. These authors used ^{11}C- McN5652 PET (Ichimiya *et al*. 2002). At present, no studies are available that assess SERT binding in attempted suicide patients.

Serotonin-1A receptor (5-HT_{1A})

Concerning the 5-HT_{1A} receptor, Parsey demonstrated an inverse correlation between PET ^{11}C-WAY-100635 binding in the orbital frontal cortex and the Brown-Goodwin life-time aggression score (Parsey *et al*. 2002).

In a PET experiment, using the same tracer, Sargent *et al* compared 25 depressed patients of whom 15 were initially drug naive en 10 were medicated with an SSRI. The initially drug naïve patients were scanned twice : one scan before and one during SSRI treatment and the medicated patients were scanned once during SSRI treatment. These patients were compared to 18 healthy

controls. The authors found a reduced 5-HT_{1A} binding index in the depressed patients in the frontal and temporal regions. Interestingly, there were no differences between SSRI treated and non-treated depressed patients (Sargent *et al*. 2000). There are no studies that assess 5-HT_{1A} binding in attempted suicide patients available.

Serotonin-2A receptor (5-HT_{2A})

Concerning the serotonin-2A receptor we demonstrated a reduced ^{123}I-R91150 binding in the frontal cortex in patients with a recent suicide attempt. Interestingly, 5-HT_{2A} binding index was significantly lower in the deliberate self injury patients compared to the deliberate self poisoning patients (Audenaert *et al*. 2001). These findings are in keeping with studies in unmedicated depressed patients that demonstrated no alteration or a decrease in 5-HT_2 receptor binding index (Biver *et al*. 1997 ; Massou *et al*. 1997 ; Attar-Levy *et al*. 1999 ; Meyer *et al*. 1999).

The 5-HT_{2A} binding index correlated significantly and negatively with levels of hopelessness, as measured with the Beck's Hopelessness Scale, and with the temperamental personality dimension harm avoidance (Van Heeringen *et al*. 2003). This finding indicates that anxiety was involved in our patient population.

Based on the evidence that a reduced serotonergic function is implicated in depressive disorders and impulsive behaviour, drugs that enhance the serotonergic system, such as selective serotonin reuptake inhibitors (SSRIs) are widely prescribed in the treatment of these disorders. Although there is evidence for a beneficial effect of SSRIs in patients with suicidal behaviour (Verkes *et al*. 1998 ; Verkes *et al*. 2000) there are no available imaging studies evaluating the effect of SSRIs in patients with suicidal and impulsive behaviour. In depressed patients Massou *et al* reported a lowered 5-HT_{2A} binding index (Massou *et al*. 1997) that normalized after treatment with antidepressants.

Peremans (2003) reported a significant increase in 5-HT_{2A} binding (^{123}I-R91150 SPECT) in highly impulsive-aggressive dogs (N = 19) (several severe biting incidents without warning) that were refractory to behavioural therapy (Peremans *et al*. 2003). This finding – an increase in 5-HT_{2A} binding index – is in accordance with preliminary results in 5-HT_{2A} receptor imaging in highly impulsive patients with borderline and/or antisocial personality disorder (K Bernagie, personal communication). In this animal study, a subgroup of these dogs were not euthanized for security reasons as their owners requested to keep them alive. These dogs were included in an open-label trial with the SSRI citalopram (1 mg/kg) for 8 weeks. The authors described a reduction in 5-HT_{2A} binding index to normal values in eight of the nine dogs and this reduction correlated significantly with a reduction in impulsive behaviour (Peremans *et al*. 2004).

In addition, Leyton *et al.* used alpha-(C-11) methyl-L-tryptophan as a PET tracer and demonstrated reduced radioligand trapping in orbital and ventromedial prefrontal cortex in high-lethality suicide attempters. Moreover tracer trapping in these regions correlated negatively with suicide intent (Leyton *et al.* 2006)

These findings demonstrate that the serotonergic impairment, related to suicidal behaviour may become manifest as a reduced 5-HT_{2A} receptor binding in depressed and anxious patients or as an increased binding in impulsive aggressive patients and dogs Interestingly, both the anxious or depressed patients with a reduced 5-HT_{2A} binding index (Massou *et al.* 1997 ; Audenaert *et al.* 2001) and the impulsive patients, dogs (Peremans *et al.* 2003) and humans with an increased 5-HT_{2A} binding index demonstrated a normalization in 5-HT_{2A} binding after treatment with serotonergic agents.

Conclusion

This overview demonstrates how functional brain imaging studies can contribute to a better understanding of the suicidal brain. Resting condition studies could demonstrate the involvement of the prefrontal cortex in suicidal behaviour. Functional imaging studies with neuroactivation paradigms further demonstrate a blunted increase in perfusion after challenging the prefrontal cortex. The link between the serotonergic system and the prefrontal cortex was demonstrated with pharmacological challenge studies.

Further, direct imaging of the serotonergic system showed a disturbance in 5-HT_{2A} receptor binding index in patients with suicidal behaviour. A relation with anxiety or with impulsivity seems to influence the direction – pathological increase or reduction – in 5-HT_{2A} binding index. There is growing evidence that SSRI treatment can normalize the 5-HT_{2A} binding index, associated with an improvement in the behavioural disturbances.

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Kurt AUDENAERT,
Department of Psychiatry and Medical Psychology,
Gent University Hospital – 1K12F,
De Pintelaan 185,
B-9000 Gent (Belgium).
E-mail : kurt.audenaert@ugent.be.