Neurochemical basis of treatment in suicide – forensic implications

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Abstract: The understanding of neuroscientific substrates of suicidal behavior is essential for enhancing predictability and development of adequate therapeutical strategies. The goal of brain exploring by means of morphometrics, neurochemistry and recent methods of molecular biology and genetics is to create a map of cerebral neurochemical circuits correlated with self-aggression behavior. From the neurobiological viewpoint amygdala with its connections to the orbitoprefrontal and anterior cingulate cortices is the keystone of behavior. Serotonin is the most intensively studied neurotransmitter because it plays a key role in aggression and impulsivity and serotonergic functions have been demonstrated to bear similar relationships to aggression in animal models and clinical studies on suicide. Antagonists of 5-HT2A receptors and selective serotonin reuptake inhibitors have antiaggressive efficacy on both animal models and clinical trials. Lithium has antisuicidal effects acting directly on orbitoprefrontal and cingulate cortices. Advances in the understanding of the neurobiology of violence will contribute to a rational assessment and treatment of patients with suicidal behavior.

Key words: suicide, neurotransmitters, serotonin antagonists, selective serotonin reuptake inhibitors, lithium

Motto “...to violent crime, the amygdala is queen”

A recent one year study of World Health Organization reported worldwide 1.43 million people dying from self-violence, a suicide being attempted every 39 seconds, with an estimated 10 to 20 million non-fatal suicides victims [47]. The World Health Organization noted that self-destruction became one of the leading causes of death in the world [3]. Suicide, which is the most dangerous self-directed aggressive behavior, occurs for various reasons, including emotional pressure, desperation, anxiety, guilt, physical pain, and other undesirable situations.

It is deeply influenced by cultural views on existential themes such as religion, honor and the meaning of the life. In most individuals the acts of self-aggression are repetitive, driven by neurobiological mechanisms that are just beginning to be understood. The aim of this study was to review the literature concerning the neurochemical background of self-aggressive behavior and the efficacy of brain targeted drugs interventions in reducing the risk for attempting or committing suicide.

Brief review of neuroanatomical substrate of the suicidal behavior

The understanding of neuroscientific substrates of suicidal behavior is essential for enhancing predictability and development of adequate therapeutical strategies. The goal of brain exploring by means of morphometrics, neurochemistry and recent methods of molecular
biology and genetics is to create a map of cerebral neurochemical circuits correlated with self-aggression behavior. A brief remind of behavior neuroanatomy will reveal the central role of the limbic system, profusely interconnected rostrally with orbitoprefrontal and anterior cingulate cortices and distally with anterior and mediodorsal thalamus, lateral hypothalamus, ventral tegmental area, periaqueductal gray, locus coeruleus and raphe nuclei of the brainstem. The limbic system consists of two separate and interactive networks: a posterior one - the network of declarative memory, centered on hippocampus; and an anterior one - the network of emotional modulation and behavioral control, centered on amygdala.

From the neurobiological viewpoint amygdala is the keystone of behavior. Its connections with the orbitoprefrontal and anterior cingulate cortices are involved in stimulus reinforcements during association learning, correction of emotional stimuli for behavior drive, behavior modulation and decision making. Distal amygdalar connections are involved in autonomic responses integration and behavior modulation via various neurochemical pathways that act either directly on amygdala or indirectly on orbitoprefrontal and anterior cingulate cortices [3, 17, 25, 29, 31, 32]. This data are confirmed by the following clinical evidences:

a) the case of Phineas Gage, a young railroad worker who was injured by a tamping rod that penetrated his skull through orbital roof and destroyed the orbitoprefrontal and anterior cingulate cortices, interrupting anterior connections of the amygdala [2]. Following the injury, he became angry, irritable and impulsive in his behavior, lacking interest in his own life and without social judgment about the consequences of his actions.

b) the case of Charles Whitman, who, after he had killed his mother and his wife in 1966, climbed a tower of Texas University and for the next 90 minutes indiscriminately killed 14 and wounded 38 persons [19]. During the night before he wrote: I don’t really understand myself….I am victim of unusual and irrational thoughts that constantly recur...I felt overcome by overwhelming violent impulses....I decided to kill my wife....I love her and I cannot rationally pinpoint any reason for doing this. After my death I wish that an autopsy would be performed to see if it is any visible physical disorder. Autopsy revealed a walnut size multiforme glioblastoma that compressed his amygdaloid nucleus.

Neurotransmitters of suicidal behavior

The neurochemical studies of suicide neurochemistry have been targeted to main neuroendocrine axes and to neurotransmitters. Neuroendocrine systems were not as intensively investigated as neurotransmitters. Nevertheless, the earliest report of neurobiological abnormalities was recorded at a seriously suicidal patient with Cushing's syndrome that presented elevated ACTH levels [39]. This data suggest the hypothesis that suicidal behavior might be associated with dysregulation of hypothalamic-pituitary-adrenal axis.

Subsequent studies of American National Institute of Mental Health reported contradictory relationships between suicidal behavior and plasma cortisol levels before and after dexamethasone administration. More recently, reduced binding of corticotropine-releasing factor (CRF) in the frontal cortex that has been found at suicide victims supports the idea that the hypersecretion of corticotropine-releasing factor may be associated with depression [39]. However, presented data seem to be inconsistent for supporting the suicidal behavior.
The majority of neurobiological and neuroclinical studies of suicide have been targeted on monoaminergic neurotransmitters produced in the brainstem nuclei and distributed to the forebrain via various neurochemical circuits that form together the distal connections of amygdala [3, 17, 25, 29, 31, 32].

**Serotonin**, produced in brainstem raphe [29], is the most intensively studied neurotransmitter because it plays a key role in aggression and impulsivity and serotonergic functions have been demonstrated to bear similar relationships to aggression in animal models and clinical studies on suicide. Serotonin has facilitant action on orbitoprefrontal and anterior cingulate cortices, that are involved in modulation and suppression of aggressive behavior primarily by acting on local serotonin 5-HT$_2$ receptors.

Deficiencies in serotonergic innervation of forebrain result in disinhibition of aggression upon provocation and selective serotonin reuptake inhibitors (SSRIs) reduce impulsive aggression [7]. Other neurobiological studies demonstrated low concentrations of the 5-hydroxyindoleacetic acid (5-HIAA) – the primary metabolite of serotonin - in aggressive personality disorders or individuals who have had violent suicide attempts [28, 35].

Primate experimental models have shown the association between lower serotonergic activity and aggression in freely moving animals and also the decreasing of learning, cooperation and perception of microenvironment [18, 46].

Antagonists of 5-HT$_2$A receptors including atypical neuroleptics with prominent 5-HT$_2$A antagonism have antiaggressive efficacy on both animal models and clinical trials [22, 45]. On the other hand, the agonists acting on 5-HT$_2$C receptors reduce impulsivity and suggest a complementary role of the two serotonin receptor subtypes in the regulation of aggression in animal model systems [5]. Other study showed that direct activation of 5-HT$_2$C receptors by metachlorophenylpiperazine increases impulsivity and activity [8].

Recent PET imaging studies on patients with impulsive aggressive personality disorder and on depressed patients with a history of suicide attempts have demonstrated the reduction of orbitofrontal activation in response to D-1-fenfluramine [26, 38]. The cortical mapping showed the localization of the reduced prefrontal activation near the site of the lesion of Phineas Gage. Fenfluramine reduced activation in similar cortical regions at suicide attempting patients [38]. Positive correlation between the activity of amygdala and prefrontal cortex was also demonstrated on PET imaging studies [16]. Receptor binding of 5-HT$_2$A measured by $^{[11]C}$-altanserin is significantly increased in physically aggressive patients with personality disorders [36] suggesting that increased 5-HT$_2$A receptor binding may be associated with suicide. Other experimental studies have shown that 5HT$_2$A antagonists reduce impulsivity [45]. The SSRI fluoxetine also increases 5HT$_2$A receptors sensitivity and reduces aggressive behavior. In conclusion, the alteration of the serotonergic systems of the suicide victims brains support the hypothesis that lower serotonergic activity is associated with suicide [1].

**Norepinephrine** is produced in the pontine nucleus locus coeruleus and profusely innervates both amygdalar and fronto-orbito-cingulate regions. Since it has an excitatory effect on amygdala, it might enhance the probability of direct aggression. The action of the alpha adrenergic receptor agonist clonidine has been correlated with irritability, although not with true aggressive behavior [37]. Other experimental data suggest that increased noradrenergic receptor sensitivity may be rather related to hyper-reactivity to the environment and only indirectly contributes to the aggression enhancement [10].

**Dopamine** innervates the crucial brain regions of aggressive behavior and is exclusively produced in the ventral tegmental area of mesencephalon. Dopamine was credited
by some authors with initiation and performance of aggressive behavior [13], and decreased D$_1$ receptors activity has been evidenced in depressed patients with anger attacks [14].

**Glutamate** is the ubiquitous excitatory neurotransmitter of the central nervous system. It is produced in the terminal boutons of the long axons of relay neurons that transport to amygdala neurosensorial information from visual, auditory and gustatory systems [3, 17, 25, 29, 31, 32]. It is demonstrated that glutamatergic enhancement increases aggression raising the possibility of excitation/inhibition imbalance [24].

**GABA (gamma-aminobutiric acide)** is the universal inhibitory neurotransmitter of the central nervous system. It is produced in the soma and terminal boutons of short axons of local inhibitory interneurons associated in local microcircuits that moderate the glutamatergic activity [3, 17, 25, 29, 31, 32]. The perturbation of glutamatergic/GABAergic activity equilibrium may contribute to hyperactivity of amygdalar and fronto-orbito-cingulate regions. It is reported that modulators of GABA$_A$ receptors might enhance aggression [15]. The GABA uptake inhibitor tiagabine decreases aggression possibly by suppressing reactions to aversive stimuli [23] and general reduced GABAergic activity may contribute to aggression.

**Acetylcholine.** According to Siever [34] the disfunction of brain cholinergic systems may contribute to hyperactivity of subcortical limbic regions and produce dysphoria and irritability, which can trigger aggression. Physostigmine, a well known acetylcholinesterase inhibitor, has been demonstrated to increase depression on patients with major mood disorder compared with placebo [40].

**Vasopressin** is a neuropeptide of neuroendocrine origin acting both as neurotransmitter and comediator. On patients with history of aggression and personality disorder, a positive correlation between cerebrospinal fluid (CSF) vasopressin concentrations and hyperserotonergic activity has been reported [9]. In animal models higher density of anterior hypothalamic neurons containing vasopressin was associated with selective aggression towards unfamiliar conspecifics.

**Oxytocin** is a neurohormone implicated in affiliative behavior [44]. In humans it reduces amygdala activity [20], and the deficits of oxytocin might realise the preconditions (hostility, fear and mistrust) contributing to aggression triggering.

**Endogenous opioid neurohormons.** Endogenous morphine-like hormones have been related to self-directed aggression, especially increased metenkephalin activity being associated with self-injurious behavior [12]. Antagonists of opioid hormones are credited with inhibition of suicid behavior [42]. The decreasing of presynaptic opioidergic contacts may upregulate postsynaptic µ-opioid receptors, with analgesia in the context of self-directed behavior.

### Treatment strategies

The treatment strategies must be targeted to the correction of disturbed neurochemical mechanisms at the patients with self-directed aggressive behavior. Since the central mechanism of self-aggression seems to be the amygdalar disinhibition due to insufficient serotonin inervation of orbitoprefrontal and cingulate cortices, the first therapeutic strategy is to increase serotonin availability in these regions. The irritability and impulsivity will be reduced with mood stabilizers and anticonvulsants (valproate and gabapentin) [11, 21] that re-establish the glutamatergic/GABAergic equilibrium.

Recent studies have revealed that lithium has antisuicidal effects acting directly on orbitoprefrontal and cingulate cortices [43]. PET studies demonstrated that lithium administration to patients with repeated suicide attempts increases the volume and function of critical prefrontal area [6, 43, 48]. Future recommended strategies must include the use of...
neuromodulators as treatment after specific laboratory experiments and clinical data concerning aggressive behavior regulation. Thus, advances in the understanding of the neurobiology of violence will contribute to a rational assessment and treatment of patients with suicidal behavior.

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