Neural Bases of Aggression in Alzheimer Patients

Allan Siegel

Abstract

The purpose of the present paper is to identify, on the basis of recent studies, the primary sites in cerebral cortex linked to aggressive behavior in Alzheimer Disease (AZ) and to describe the likely neural circuits that normally suppress aggressive behavior but whose inhibitory mechanisms are disrupted by neural loss in such patients.

Recent studies reveal that, although there are widespread degenerative changes in the cerebral cortex in AZ, two regions are associated with aggressive behavior: the prefrontal cortex and temporal lobe. Concerning the prefrontal cortex, the most likely circuit governing suppression of aggression includes a polysynaptic pathway projecting from the mediodorsal thalamic nucleus and then through a series of short interneurons that project rostrally to the anterior hypothalamus. It may be assumed that loss of such input in AZ potentiates aggressive behavior as seen in these patients. Other possible circuits arising from prefrontal cortex that might suppress aggression include direct pathways to hypothalamus and midbrain periaqueductal gray (PAG) as well as a pathway to the lateral amygdala, which ultimately supplies the PAG. Regarding the temporal lobe, damage to the region presumably releases aggressive behavior because of a major loss of the mechanism mediating suppression of aggression. This is due to loss of input to the lateral and central nuclei of amygdala, which project to the PAG in which the inhibitory mechanism is mediated through opioid µ receptors in the PAG. It is possible that pharmacological intervention targeting this receptor might be effective in treatment of aggression in AZ.

INTRODUCTION

The general objective of the present review is to provide an understanding of the neural bases of aggressive behavior present in Alzheimer disorder (AZ). This review considers both the regions of cerebral cortex implicated in AZ related aggression as well as the neural pathways associated with these regions that likely mediate suppression of aggressive behavior in the healthy, intact brain.

Nature of the aggressive response

Following analysis of the multitudes of studies conducted in both human and sub-human mammalian species, one can categorize aggressive forms of behavior as falling into one of two general forms – defensive or hostile aggression and predatory or instrumental aggression which are clearly different behaviors with different physiological properties distinguishable from each other [1-3]. It is of interest to point out that there are remarkable similarities between animals and humans with respect to these two forms of aggression. In brief, major features of defensive behavior include intense sympathetic arousal and an impulsive attack upon a real or perceived threat object. This response may be real or delusional, but occurs in order to reduce the level of threat, which the aggressor believes is present within his environment. Earlier reports of such ‘intermittent explosive’ behavior were described in the writings of Monroe [4] who characterized it as an ‘episodic dyscontrol’ syndrome. In contrast, in predatory or instrumental aggression, the response is not impulsive and there is typically only minor sympathetic arousal. It may be planned over hours, days, weeks, months or even years. It is specifically directed at a particular individual or individuals such as political assassinations or murder of a criminal opponent.

The primary regions of the brain from which defensive behavior is expressed include the medial hypothalamus and the midbrain periaqueductal gray (PAG). In contrast, expression of predatory attack is localized mainly in the lateral aspects of the hypothalamus.

Aggression in AZ patients

It is now reasonably well established that aggressive behavior constitutes one prominent characteristic associated with AZ [4-17]. Because of the differences in the neural substrates underlying each of these forms of aggression [3], it is further useful to initially indicate the form of aggression associated with individuals displaying AZ. The basic characteristics described...
from a variety of studies reveal that such individuals display response patterns, which include impulsivity in aggressive patterns in particular, agitation, verbal rage episodes, physical rage, and irritability. The complexity of these behavioral patterns clearly indicates that the mode of aggression expressed by AZ patients is defensive or hostile aggression rather than predatory aggression. Therefore, the section discussed below is directed at describing how defensive aggression is regulated by selective regions of the cortex and limbic system, which could thus account for the presence of AZ following brain damage in AZ patients.

While clinical reports have indicated that AZ results in degenerative processes associated with wide areas of the cerebral cortex, two regions appear to be commonly affected. These regions include the prefrontal cortex and the temporal lobe and involve the presence of neuro pathologival changes such as neuro fibrillary tangles, and neurodegenerative alterations of cell atrophy and cell loss [5,18]. Examples of clinical studies that provided evidence of the relationship linking AZ with damage to the prefrontal cortex have been reported [6]. Likewise, evidence of the association of AZ with damage to regions of the temporal lobe has been shown in several studies as well [16,19].

Cortical regions and associated pathways implicated in aggression in AZ

This section provides a summary of the key regions of cerebral cortex affected by AZ and further, specifically identifies the likely neural pathways associated with these regions over which suppression of aggression is normally mediated in healthy individuals.

Prefrontal cortex: In general, regions of the cerebral cortex that influence defensive aggressive behavior do so by directly or indirectly altering the excitability levels of neurons in the medial hypothalamus or midbrain periaqueductal gray [3]. It is now established that activation of an intact prefrontal cortex will powerfully suppress aggression [20,21]. There are three possible routes by which the prefrontal cortex can suppress hypothalamic functions. The first and most likely pathway (because of the massive numbers of fibers associated with this projection) involves a multi-synaptic projection from the prefrontal cortex, initially to the mediodorsal thalamic nucleus, and secondly through a short group of interneurons passing rostromedially into the region of the anterior hypothalamus [22,23]. The neurotransmitter from the prefrontal cortex, as with other regions of cortex, is likely glutamate, which is excitatory. The transmitters associated with the secondary interneurons are unknown. Nevertheless, it would seem that loss of this inhibitory input to the medial thalamus would thus release aggressive impulses. The other possible inhibitory pathways include: (1) direct projections to the hypothalamus and PAG from the prefrontal cortex [24,25] and (2) indirect projections through the lateral nucleus of amygdala [26]. (which ultimately supplies the midbrain PAG) to cause suppression of aggression [5]. However, it would seem that manifestation of aggression through the loss of function in these pathways following prefrontal damage would be somewhat less likely because of the fewer numbers of fibers associated with the latter two systems relative to those which supply the mediodorsal thalamic nucleus.

Temporal lobe: Destruction of neural tissue of the temporal lobe would likely affect major structures of the limbic system, namely, the amygdala and hippocampal formation. Both structures modulate aggressive behavior although the actions of the amygdala appear to be more powerful [5,27].

With respect to the amygdala, two regions modulate aggressive behavior in diametrically opposing ways Activation of the medial amygdala powerfully facilitates the expression of defensive behavior, while activation of the lateral and central nuclei of amygdala produce potent suppression of this form of aggression [5]. Because lesions of the temporal lobe in AZ cause increases in defensive aggression, it is reasonable to conclude that the pathway through the medial amygdala, which facilitates this form of aggression, is not involved, because if it were involved, then it would be expected that temporal lobe damage would lead to a suppression of defensive aggression which is not the case here. Therefore, the focus on the neural mechanism within the amygdala is its lateral and central nuclei. As noted above, each of the nuclei, when activated in the intact brain, causes powerful suppression of defensive aggression [5,28]. It does so through a direct pathway to the midbrain periaqueductal gray where it suppresses the rage mechanism at this site [5,29]. The suppressing effect is mediated through enkephalins acting upon opioid µ receptors in the midbrain PAG [28,29]. Therefore, it is likely that damage to the temporal lobe causes heightened aggression because it cannot activate the mechanism for suppression in the lateral and central amygdala. The data further suggest the possibility that pharmacological intervention which could activate opioid µ receptors in the midbrain PAG might cause suppression of impulsive defensive aggression.

Regarding the hippocampal formation, it is likely that damage to the temporal lobe would appear to affect more anterior regions of this structure. While the relationship between this aspect of the hippocampal formation and defensive aggression has not been extensively studied, the available data suggest the possibility that its actions upon defensive aggression may be to suppress this behavior [5]. The likely pathway involving such a mechanism would be indirect projections from the hippocampal formation to the medial hypothalamus via the septal nuclei [30,31]. Nevertheless, the data strongly indicates that the presence of aggressive behavior following lesions of the temporal lobe in AZ is mediated primarily by the loss of input into the lateral and central nuclei of amygdala, which normally suppress defensive aggression.

SUMMARY

On the basis of the data accumulated with respect to regions of the cerebral cortex sustaining damage following AZ coupled with our knowledge of the neural mechanisms governing aggression and rage behavior, the following suggested conclusions may be drawn.

i. The available data indicates that AZ patients display heightened defensive aggressive behavior

ii. The data further suggest that the likely areas of the cerebral cortex damaged in AZ patients who express defensive aggression include the prefrontal cortex and temporal lobe
Several major pathways affected by cortical loss results in heightened aggression in AZ patients. Two such systems mediating suppression of aggression in the healthy brain are underscored here: (a) with respect to the prefrontal cortex, the likely circuit includes an indirect pathway to the medial hypothalamus via the mediodorsal thalamic nucleus and short interneurons passing rostrally into the anterior hypothalamus; and (b) concerning the temporal lobe, the key circuit includes initial input from the temporal lobe to the lateral and central nuclei of amygdala which activate pathways from these nuclei that project to the region of the midbrain PAG (whose neurons normally suppress defensive aggression). It is presumed that in AZ patients, that the suppressive mechanisms against aggression are blocked by the lack of inputs from the respective cortical regions.

The presence of powerful suppression of defensive aggression manifest through the descending pathway to the midbrain PAG from the central and lateral nuclei of amygdala raise the possibility that pharmacological intervention involving activation of opioidergic receptors in the region of the PAG might serve to suppress aggressive behavior.

The possibility of pharmacological compensation for the loss of descending prefrontal cortical inputs directly or indirectly to the hypothalamus by activation of glutamatergic receptors in the mediodorsal thalamic nucleus is quite problematic. Namely, the massive numbers of neural systems that would be affected by such treatment could likely produce many side effects that could deem such an approach untenable.

REFERENCES

28. Sshaikh MB, Lu CL, Siegel A. An enkephalinereric mechanism involved

