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Agitation in Alzheimer's Dementia: Exploring the Potential Role of Monoamines

ReachMD Announcer:
Welcome to ReachMD.
This medical industry feature, titled "Agitation in Alzheimer's Dementia: Exploring the Potential Role of Monoamines" is the second episode in a three-part series sponsored by Otsuka and Lundbeck.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host Dr. Jennifer Caudle, and joining me to explore the potential role of monoamines in agitation of Alzheimer's dementia, or AAD for short, is Dr. Stephen Stahl. Dr. Stahl is a Professor of Psychiatry at the University of California, San Diego. Dr. Stahl, welcome to the program.

Dr. Stahl:
Thank you for having me.

Dr. Caudle:
Let's dig a little further into agitation behavior. What brain processes are thought to be at play here?

Dr. Stahl:
So when we talk about agitation, we're describing a behavior that's rooted in an underlying emotion and is under the control of executive functioning. In this model of emotional regulation, there's a delicate balance between the reaction from emotional drive and the regulation from executive control. And based off that, we find that overactivity in brain regions affecting emotional drive, or a failure in areas involved in executive control, can lead to agitation.

We know that the prefrontal cortex of the brain controls emotions and behaviors. Think of this executive control as top-down, which can inhibit inappropriate impulses and mediate goal-directed behavior.

The amygdala is the emotional driver of the brain and plays a vital role in emotional processes. Think of this emotional drive as the bottom-up reactive, emotional, behavioral, and physiological response to stressors.

Dr. Caudle:
Now that we have an idea of what may be driving agitation, let's focus on what's happening in AAD. Dr. Stahl, could you walk us through some of the pathology seen in patients with AAD?

Dr. Stahl:
Research has shown that in patients with Alzheimer's dementia, agitation is associated with tau pathology, and neurodegeneration in the prefrontal cortex and amygdala.

Further studies revealed that AAD is associated with hypoactivity in prefrontal brain regions, as well as hyperactivity of the amygdala, potentially creating imbalance between emotional drive and executive function.

Hypothetically, the key to this disruption in balance between executive function and emotional drive lies in the dysfunction of underlying neurotransmitter systems among these brain regions, the monoamines, including norepinephrine, serotonin, and dopamine.

Dr. Caudle:
Now we discussed the brain regions involved in AAD, but how do their signal pathways affect executive and emotive balance? Dr. Stahl,

let's first take a look at norepinephrine; can you tell us about the role this neurotransmitter is sought to play in these symptoms?

Dr. Stahl:
Hypothetically noradrenergic hyperactivity is associated with impaired prefrontal cortex function and elevated amygdala function, which leads to an imbalance in the emotional regulation process. Specific to Alzheimer's dementia, tau protein damage and neuronal loss in the locus coeruleus theoretically trigger a compensatory noradrenergic hyperactivity response to maintain homeostasis.

Dr. Caudle:
And if we take a moment to dive into another monoamine neurotransmitter, serotonin, what can you tell us about the role it's thought to play in the pathophysiology of AAD?

Dr. Stahl:
Serotonin behaves similarly to norepinephrine in that it hypothetically causes impaired prefrontal cortex function, and elevated amygdala function. However, AAD is theoretically associated with decreased levels of serotonin in frontal cortex and amygdala, and loss of serotonergic neurons in the raphe nuclei, leading to an overall serotonergic system deficit.

Dr. Caudle:
And if we take a look at the third monoamine, dopamine, does it interact with the brain similarly to how the other monoamines do?

Dr. Stahl:
Dopamine is a bit different. Hypothetically, it's relatively spared in Alzheimer's dementia, but increased striatal dopaminergic activity has been seen in agitated behaviors. Since serotonin regulates dopamine activity, serotonin deficits in Alzheimer's dementia could lead to dysregulation in dopamine, resulting in agitated and aggressive behaviors.

Dr. Caudle:
Well unfortunately, we're almost out of time for today. But before we close, Dr. Stahl, what key takeaways would you like to leave our audience?

Dr. Stahl:
Well, I want to stress that agitation is a common neuropsychiatric symptom in Alzheimer's dementia, that is defined by criteria in four domains by the IPA. So, the primary issue leading to agitation is a theoretical imbalance between the prefrontal cortex or the center of executive control, and the amygdala, the emotional driver. And hypothetically, in patients with Alzheimer's dementia, dysfunction in the major monoamine systems of norepinephrine, serotonin, and dopamine play a significant role in AAD.

Dr. Caudle:
With those final thoughts in mind, I'd like to thank my guest, Dr. Stephen Stahl, for helping us better understand the pathophysiology behind agitation in Alzheimer's dementia. Dr. Stahl, it was great speaking with you today.

Dr. Stahl:
It was a pleasure to be here.

ReachMD Announcer:
This program was sponsored by Otsuka and Lundbeck. If you missed any part of this discussion, visit ReachMD.com/industry feature. This is ReachMD. Be Part of the Knowledge.

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