I28 A Model for Mapping the Neural Circuits Underlying Impulsive Aggression

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Learning Overview: After attending this presentation, attendees will understand some of the major neural circuits underlying impulsive aggression through the comparison of the mechanisms of actions of three different Anti-Impulsive Aggressive Agents (AIAAs) of different classes: fluoxetine, phenytoin, and valproate.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by serving as a review of the mechanisms of action of three of the most studied agents used to manage impulsive aggression, as well as an outline of the proposed neurobiology of impulsive aggression. Discussion of the underlying mechanisms of action in the diverse range of medications that mitigate impulsive aggression provides a useful paradigm for clinicians and forensic evaluators managing a population with anger control problems, as well as consideration for future research.

Currently, there are no Food and Drug Administration (FDA) -approved medications with indications for treatment of impulsive aggression or intermittent explosive disorder. However, symptoms related to this condition significantly impact quality of life for patients and their families. The paucity of approved treatment options establishes an urgency for the development of effective therapeutic modalities. Three of the most widely used AIAAs are classified based on heterogeneous applications: Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant (fluoxetine), anticonvulsant (phenytoin), and anticonvulsant and mood stabilizer (valproate/divalproex).[1]

An emerging model for impulsive aggression is the "top-down/bottom-up" hypothesis, where top down refers to the controlling neurotransmitters such as serotonin in the frontal lobes and Gamma-Aminobutyric Acid (GABA) and bottom up corresponds to excitatory neurotransmitters, specifically glutamate.[2] According to this hypothesis, an imbalance between control and excitation can lead to poorly controlled aggression. This can be the result of too little control from the prefrontal cortex or too much excitation from the amygdala. The role of fluoxetine in diminishing impulsive aggression is believed to be, in part, due to serotonin's effect in enhancing prefrontally mediated self-control.

Impulsive aggression also represents an imbalance of the glutamatergic and GABAergic activity in the amygdala-hypothalamus-periaqueductal gray circuits. In line with the top down/bottom up hypothesis, and particularly the GABA-glutamate balance, there is evidence that valproate enhances GABA functioning by several direct and indirect mechanisms.[3-5] Valproate has also been shown to decrease glutamate activity by mainly indirect mechanisms, although the effects are less clear and the evidence less consistent across species.[6,7]

Because both seizure disorders and impulsive aggression are disorders of dysregulated neuroexcitement, it is conceivable that explanations of phenytoin's anticonvulsant action may pertain to its therapeutic effect on impulsive aggression as well. In addition to limiting neuronal firing, phenytoin has been shown to increase GABAergic activity and decrease glutamatergic activity, which was found to be responsible for its anticonvulsant efficacy.[8-10] Given the evidence for GABA/glutamate imbalance as a neural mechanism for aggressive behavior, these findings could contribute toward understanding phenytoin's mechanisms for reducing impulsive aggression.

Through review of current off-label treatment modalities, this study overviews the potential biochemical pathways that may be involved in impulsive aggression and could be potential targets for further research and development.

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