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The case for basic research on the psychopharmacology of aggression

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Comai et al. (1;2) address a sorely understudied topic in psychopharmacology, namely the clinical management and treatment of aggressive behavior (3). The authors pursue a most promising and rational approach by proposing to translate basic preclinical findings to the clinical application. The history of this research – since the beginning of modern psychopharmacology – has been driven by serendipitous observations with little support from mechanistic studies. For example, the potential for treating highly agitated and aggressive individuals with lithium was discovered by Cade in 1949 (4) in the absence of insights into the neurobiological actions of this substance. Also, the calming effects of benzodiazepines became apparent in early preclinical screens of chlordiazepoxide in feral monkeys without understanding the sites and mechanisms of action of these compounds (5).

Work on the psychopharmacology of aggression has been impeded by insufficient recognition of these behavioral domains in consecutive versions of the Diagnostic and Statistical Manual, discouraging the development of serenics or compounds with anti-aggressive effects (6;7). One cardinal criterion for novel medications is their degree of specificity for reducing aggressive behavior in the absence of undesirable side-effect profiles. In order to achieve this goal it is necessary to study the features of aggressive behavior in the context of a wider behavioral repertoire. The reviews by Comai et al. (1;2) recognize this problem, but provide little information on the behavioral specificity by which antipsychotics, anticonvulsants or lithium reduce aggressive behavior. Future work should beneficially provide guidance as to assessing aggressive behavior in conjunction with other non-aggressive elements in the behavioral repertoire. In preclinical work with novel anti-aggressive compounds such as 5-HT_{1B} agonists, CRF R1 antagonists, or vasopressin V1 antagonist quantitative ethological methods enable the comparison of reductions in aggressive acts with effects on non-aggressive behavior in order to learn about the behavioral specificity of these compounds (8–11).

The reviews by Comai et al. point to the heterogeneous nature of aggressive behavior, recognizing that fundamentally different kinds of aggressive behavior have been characterized in laboratory studies with experimental animals and in clinical studies in human and veterinary medicine (12–18). The neurobiology of impulsive, hostile, violent

acts differs from that of premeditated instrumental aggressive acts (19). It needs to be appreciated that different kinds of interventions are effective in targeting these two types of aggressive behaviors. Similarly, studies in animals differentiate adaptive types of aggressive behavior such as in establishing and maintaining dominance hierarchies, defending territories and protecting the offspring in a maternal context, from those that study aggressive behavior in excess of the species-typical level (14;20). Comai et al. seek support from mechanistic studies in preclinical models of aggressive behavior for advocating medications that are promising in the clinic. It will be valuable to focus on evidence from preclinical models of escalated, maladaptive aggressive behavior as a source of information in order to enhance the translational significance of these data.

A fundamental question to be resolved pertains to the neurobiological mechanisms mediating escalated aggressive behavior relative to those for species-normative patterns of behavior. Based on minimal empirical data, in the first decades of this research, a relatively simple circuit in the limbic system was proposed as the critical site for the regulation of intensely emotional, raging aggressive acts in monkeys and cats. By now, the neurocircuits for different kinds of aggressive behavior encompass cells in the mesencephalon projecting to hypothalamic nuclei, amygdaloid, septal and hippocampal forebrain structures, striatal and thalamic loops with the frontal and pre-frontal cortex as well as important feedback loops to limbic and mesencephalic nuclei (14). It remains a challenging task to identify discrete neurocircuits that mediate specifically *escalated* types of aggressive behavior. The recent optogenetic studies of mouse aggression evoked this behavior from discrete hypothalamic neurons that may be distinct from other types of motivated behavior (21).

Consider our emerging understanding of the neurobiology of serotonin and its role in different kinds of aggressive behavior as summarized by (22). By now, the classic serotonin deficiency hypothesis that links defects in synthesis, release, receptor activation or metabolism to a heightened propensity to engage in aggressive behavior, has been largely replaced with a framework that accommodates a much more detailed set of modulatory and regulatory mechanisms.

For example, activation of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A/2C} receptors in mesocorticolimbic areas can reduce species-typical and other intense types of aggressive behaviors in several animal species. However, agonists at 5-HT_{1A} and 5-HT_{1B} receptors in the medial prefrontal cortex or septal area can increase aggressive behavior under specific conditions, pointing to regional specificity of receptor subpopulations. It will be important to learn where in the brain of aggressive individuals the gene expression for 5-HT_{1B} receptors is changed by polymorphisms.

Furthermore, a significant role of MAOA in aggressive behaviors is supported by genetic studies of a deleterious mutation of MAOA gene in humans and knockout mice. At variance with the serotonin deficiency hypothesis, these findings suggest that chronically increased 5-HT levels that result from reduced MAOA function – trait-like change – may promote or intensify escalated aggressive displays.

Consistent studies demonstrate the effectiveness of SSRIs in controlling aggressive outbursts, which was initially thought to result from the uptake blockade. Yet, the neuroplastic changes in transporter molecules that are required for the repeated administration of these compounds to become effective remain to be determined. Moreover, the genetic studies in human and nonhuman primates also suggest 5-HTT polymorphisms such as the short allele as a risk factor for violent traits, which seems to be particularly relevant in combination with environmental stress. Gene polymorphism studies of MAOA, 5-HTT and Tph2 revealed critical gene-environment interactions as risk factors for violent traits. Individuals with a certain allele are particularly prone to engage in violent behavior when they have a history of early life maltreatment, but the effect disappeared when they are reared in an environment with low stress.

Finally, from the viewpoint of targeting novel neural sites for intervention, a host of studies reports modulatory influences of serotonergic cellular activity in the dorsal raphe nucleus. Particularly, GABA, glutamate and neuropeptides such as CRF and opioid peptides acting on specific receptor subtypes appear relevant to modulating escalated aggressive behavior. Genetic analyses of aggressive individuals have identified several molecules that affect the 5-HT system directly (e.g., Tph2, 5-HT_{1B}, 5-HT transporter, Pet1, MAOA) or indirectly (e.g., Neuropeptide Y, α CaMKII, NOS, BDNF).

Hopefully, the current discussion of the reviews by Comai et al. will initiate renewed interest in the basic neurobiology of pathological aggressive behavior and reactivates this largely neglected area of research.

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