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## **Orally Active Vasopressin V1a Receptor Antagonist, SRX251, Selectively Blocks Aggressive Behavior1**

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Arginine vasopressin functions as a neurochemical signal in the brain to affect social behavior. There is an expanding literature from animal and human studies showing that vasopressin, through the vasopressin 1A receptor (V1A), can stimulate aggressive behavior. Using a novel monocyclic beta lactam platform, a series of orally active vasopressin V1a antagonists was developed with high affinity for the human receptor. SRX251 was chosen from this series of V1a antagonists to screen for effects on serenic activity in a resident-intruder model of offensive aggression. Resident, male Syrian golden hamsters were given oral doses of SRX251 or intraperitoneal Manning compound, a selective V1a receptor antagonist with reduced brain penetrance, at doses of 0.2 µg, 20 µg, 2 mg/kg or vehicle. When tested 90-120 min later, SRX251, but not Manning compound, caused a significant dose-dependent reduction in offensive aggression toward intruders as measured by latency to bite and number of bites. The reduction in aggression persisted for over 6 hrs and was no longer present 12 hrs post treatment. SRX251 did not alter the amount of time the resident investigated the intruder, olfactory communication, general motor activity, or sexual motivation. These data corroborate previous studies showing a role for vasopressin neurotransmission in aggression and suggest that V1a receptor antagonists may be used to treat interpersonal violence co-occurring with such illness as ADHD, autism, bipolar disorder, and substance abuse.