3.3.2 Case Study 2: SAR Studies on α-Aminoadipic Acid: Development of Competitive NMDAR Antagonists

A breakthrough in the development of competitive NMDAR antagonists came about when a chain extended form of glutamate, (*RS*)-α-aminoadipic acid (α-AA) (Figure 3.8), was shown to selectively antagonize NMDA-induced responses in an electrophysiological assay. In a similar fashion to the agonist SAR study, the effects of the stereochemistry, terminal acidic group, and chain length were investigated.

Testing of the individual enantiomers of α-AA revealed that the antagonist activity resided in the *R* form whereas the *S* form was a NMDAR agonist with moderate affinity. SAR studies on α-AA revealed that the linker chain length and the nature of the terminal acidic group played an important role in determining the affinity of the NMDAR antagonist.

With regard to the terminal acidic group the rank order of affinity of α-AA analogs was $PO_3H_2 > CO_2H \gg SO_3H$. The phosphonate analog (*R*)-AP5 (Figure 3.8) was the first NMDAR antagonist to be widely used as a tool to block NMDAR activity in functional studies. Schild analysis of the antagonism by (*R*)-AP5 of the NMDA-induced response in an electrophysiological assay on the neonatal rat spinal cord showed that it had a competitive mode of action. One explanation for the potent NMDAR antagonist activity observed upon phosphono substitution was the possibility of two interactions with the receptor via the two ionizable OH groups of the phosphonate group. The pK_a values for the ionization of the hydroxyl groups on the phosphonate group are <1 and 7.8. When the experimental pH was increased from 7.3 to 8.2, the potency of the antagonist activity of (*R*)-AP7 was increased approximately fourfold, suggesting that the doubly charged phosphonate group was optimal for antagonist activity. In support of this theory, when the phosphonate group of AP5 was replaced by a phosphinate group (with only one ionizable OH group), the NMDAR antagonist activity was reduced considerably.

Changing the inter-acidic group chain length of (*R*)-AP5, by adding or removing CH_2 groups, revealed an interesting relationship between chain length and NMDAR antagonist affinity. A chain of three CH_2 groups, as observed in (*R*)-AP5, or five CH_2 groups, as observed in (*R*)-AP7 (Figure 3.8)

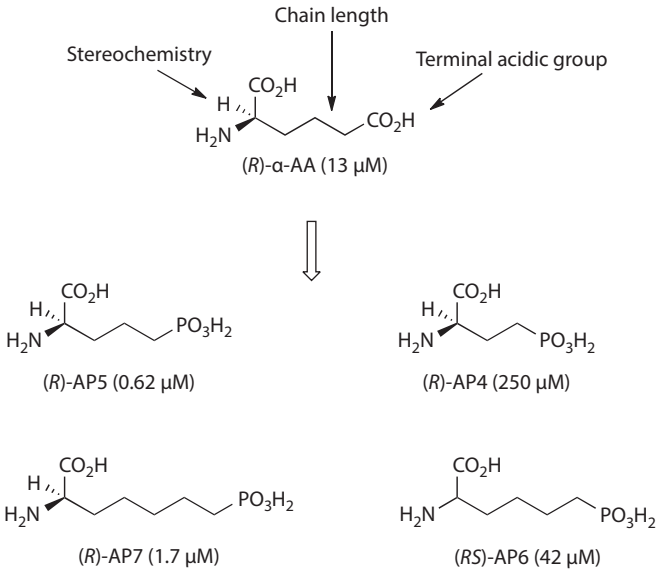

FIGURE 3.8 Structure–activity relationship studies on (*R*)-AA led to the development of (*R*)-AP5 and (*R*)-AP7, which had the optimal inter-acidic group chain length. (*R*)-AP4 and (*R*S)-AP6 had lower *N*-methyl-D-aspartate receptor affinity. IC_{50} values from competition binding assays on rat brain membranes using [^{3}H] AP5 are given in parenthesis.