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Differences in degree of trapping between AR-R15896 and other uncompetitive NMDA receptor antagonists

Short Comment

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Summary. NMDA antagonists like AR-R15896 have been selected on the basis of their good therapeutic indices. As Dr. Rogawski has pointed out, there may be a number of molecular factors which can improve the therapeutic index of NMDA antagonists. In this paper we will consider three factors; use-dependence, low affinity/fast kinetics, and partial trapping.

Keywords: Amino acids – NMDA – Use-dependence – Partial trapping

In order to treat diseases such as neurodegeneration and epilepsy, we believe it is primarily important to block NMDA receptor hyperactivity, for example, ischemic depolarizations and seizure activity. On the other hand, NMDA receptor-mediated side-effects (PCP-like behaviors) probably result from tonic blockade of normal NMDA-mediated synaptic responses. One way, then, to improve the therapeutic index is to preferentially block receptor hyperactivity. This goal can be achieved by using a use-dependent (uncompetitive) antagonist, whereas competitive and noncompetitive compounds preferentially block normal activity or do not differentiate between normal activity and hyperactivity. Compounds such as AR-R15896, memantine, NPS-1506, ketamine, PCP, and dizocilpine are examples of use-dependent antagonists.

However, the expectation that use-dependent NMDA receptor antagonists would be safer has not been generally realized. Two factors, high affinity (potency) and receptor trapping, are likely to be responsible for this difficulty because they functionally eliminate use-dependence. In regard to affinity, Rogawski has noted that safer NMDA receptor antagonists, e.g. AR-R15896, exhibit low to moderate affinity. He pointed out that in order for use-dependent antagonists to block seizure- and ischemia-induced depo-

larizations, their time to produce block (once the receptor is activated) must be relatively short – seconds. For any specific compound, the onset of block (macroscopic on-rate) is shortened by using mass action, that is by increasing the concentration. Concentrations in the μM range are generally necessary to achieve blockade within seconds. The problem with high affinity compounds is that there is a mismatch between the magnitude of block produced and the speed of block required. That is, at μM concentrations, these nM affinity compounds will supramaximally block the receptor. This results in a complete shut-down of NMDA receptor activity and also prolongs the already slow off-rate of high affinity compounds. This is exactly opposite the way use-dependent compounds are supposed to act. The end result is a prolonged inhibition of all NMDA receptor activity and this probably produces the PCP-like side-effects. On the other hand, compounds whose affinity is in the μM range can modulate receptor activity because their affinity is in the same range as concentrations required for speed of onset.

This match between affinity and speed of onset is certainly an important component of the safety of low to moderate affinity antagonists. However, some low to moderate affinity antagonists, e.g. ketamine, still produce significant side-effects. Therefore, at least one other factor must play a role in determining therapeutic index. One likely candidate is the trapping of antagonist. Trapping means that after agonist leaves the antagonist-blocked receptor and the channel closes, antagonist is retained (is trapped) at its blocking site. Upon reactivation, the blocker is already in place and use-dependence is lost. The result is tonic blockade, resulting in side-effects.

We have noted that although AR-R15896 exhibits the property of trapping, the magnitude of this trapping appears to be much less than the nearly 100% that has been reported for dizocilpine and PCP. This suggests that different degrees of trapping may exist. We have compared the magnitude of trapping for three low-affinity use-dependent NMDA receptor antagonists. Two of these, AR-R15896 and memantine, appear to be safer in clinical use, while the third compound, ketamine, is known to produce a significant level of side-effects.

AR-R15896 and memantine are not completely trapped by the receptor when agonist is removed. The maximal degree of trapping seen with AR-R15896 is 54 ± 3%, with memantine it is 71 ± 4%, and for ketamine it is 86 ± 1%. AR-R15896 and memantine are trapped significantly less than ketamine. This correlates with their therapeutic indices and is consistent with the idea that trapping contributes to a lower therapeutic index.

Partial trapping could be a result of sequential blockade. However, we demonstrated that while the sequential NMDA receptor blocker, 9-aminoacridine, produced clear tail currents (a characteristic of sequential blockade) neither AR-R15896, memantine, nor ketamine produced tail currents. Therefore these three compounds do not appear to be mixed sequential/trapping blockers. The lack of tail currents suggests that the channel is closed before blocker is released. We therefore refer to the process of partial trapping as closed-channel egress.

One explanation for closed-channel egress is the creation of an open door through which antagonist can both leave and enter. We examined this hypothesis by leaving antagonist present during the interval between two applications of agonist. Open access would allow antagonist to block prior to the second application of agonist and closed-channel egress would not be present. However, closed-channel egress was evident and therefore a static open door has not been created.

Another explanation is that lipophilic antagonists can diffuse through the receptor or membrane and thereby escape. However, the magnitude of trapping of these three compounds does not correlate with their lipophilic character. This lack of correlation has now been extended to 21 analogs of AR-R15896 (slope = 0.022; r = 0.056).

We have noted that off-rate is correlated with degree of trapping. We envision that trapping results from compounds being retained in a "vestibule" comprised of the channel, i.e. the selectivity filter, which acts as a "bottom", through which these compounds do not pass, and a "top", located more extracellularly. We hypothesize that the closing rate of this top is much slower than channel closure (current shut-off). The difference in the rate of closure of this top and the off-rate of the antagonist determines the percent trapping for each compound. A compound with a faster off-rate is more likely to slip through before the top closes and thereby exhibit closed-channel egress.

Closed-channel egress provides a solution to the problem of side-effects brought on by trapping. The relationship between closed-channel egress and reduced PCP-like side-effects needs to be further examined.

References

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