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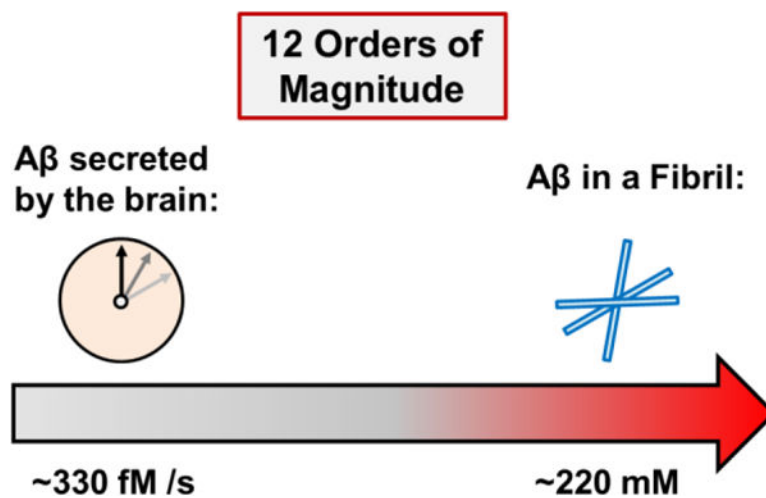
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Abstract

Alzheimer’s Amyloid beta can perform a wide variety of actions that are highly concentration-dependent. This note aims to provide a framework for basic considerations on what might be considered brain-relevant concentrations of the peptide. Some implications for the therapeutic implementation of the recently emerged oligomer-to-fibril strategy are discussed.

Graphical Abstract



A question of concentration: Alzheimer’s Amyloid β 42 has an unusually wide range of differential activity as a function of concentration. The present analysis suggests that, in order to better understand the system, it needs to be considered over twelve orders of magnitude – from femtomolar to millimolar.

Amyloid β (A β) is an intrinsically disordered peptide and, in its 42 amino acid long isoform is the believed culprit of Alzheimer’s Disease.^[1] Much attention has been focused on its biophysical, biological and electrophysiological properties and, depending on the context, the concentrations at which A β 42 was studied ranged from femtomolar to millimolar, covering a remarkable twelve orders of magnitude.^a

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^aFor comparison, a human hair has a thickness of ~ 0.1 mm and the distance from Los Angeles to Beijing is $\sim 10,000$ km. This corresponds to eleven orders of magnitude, one less than the concentration range of A β 42.

The highest concentration of A β 42 in the human brain is found in senile plaques,^[2] where the peptide is packed into a dense composite of A β fibrils, as well as other biomolecules.^[3] As the hypothetical upper boundary of physiologically relevant A β 42 concentration, the fibrillary state appears reasonable, although plaque heterogeneity will produce somewhat lower values (*vide infra*). A β 42 has a molar mass of 4514 g/mol. Assuming fibril density of ~1 g/mL (*i.e.*, similar to water, although likely slightly higher, since fibrils do sediment slowly in water), this yields a concentration of 221.5 millimolar (*i.e.*, 221.5 mmol / L) A β 42 “monomer-in-fibril”. Quantitative *post mortem* analyses of patient-derived senile plaques revealed A β (40 and 42) as their predominant components,^[2] but also showed a remarkable heterogeneity of the deposits, additional plaque constituents including diverse proteins and peptides,^[2b, 4] lipids,^[5] RNA, carbohydrates, as well as various metal ions.^[3] As a result, the A β 42 concentration in a senile plaque is expected to be somewhat lower than 221.5 mM, but certainly still in the high mM range. In consequence of a recent paradigm shift, A β fibrillary deposits are no longer considered to be the culprit of Alzheimer’s Disease, but instead benign, possibly even protective, which is likely a consequence of fibril-borne A β 42 being packaged into a relatively inert state with very low biological activity.^[1b, 6] Still, because A β 42 fibrils exist in the brain, the staggeringly high concentration of 221.5 mM of “monomer-in-fibril” is formally relevant, although clearly only so in the context of plaques. It should be considered the absolute upper boundary. Such fibrillary deposits are formed very slowly, over decades, and the more disease-relevant, soluble species of A β are unlikely to exist in the brain anywhere near those extreme concentrations.^[1b, 7]

Toxicity of soluble A β 42 aggregation intermediates, *i.e.*, diffusible oligomers, can be robustly observed through exposure of cells to the peptide at low to intermediate μ M concentration.^[8] Assuming an IC₅₀ concentration of A β 42 on the order of ~10–100 μ M (IC₅₀ can vary to degree between preparation), this means that A β 42 oligomers are highly neurotoxic at a concentration that is ~3–4 orders of magnitude lower than that calculated for A β 42 “monomer-in-fibril”. If one hypothetically considers a human brain (~1.5 L volume) that is homogeneously filled with cerebrospinal fluid at 50 μ M A β 42 (a hypothetical neurotoxic concentration), oligomer-to-fibril conversion would condense it by a factor of 221.5 mM / 50 μ M = 221500 μ M / 50 μ M = 4430, *i.e.*, 0.34 mL A β 42 fibril. Because of identical arguments applied in reverse direction, 0.34 mL reservoir of A β 42 fibrils could, in principle, produce 1.5 L of a homogeneous, highly neurotoxic A β 42 solution at 50 μ M. This prompts a note of caution with regard to therapeutic approaches that act by solubilizing A β fibrils and plaques, since those approaches may result in the undesirable release of toxic entities. It is worth noting that A β 42 is also bactericidal, and is capable of killing 80 % of various microorganisms within 6 h of application at 50 μ g/mL (11 μ M).^[9] Whether A β 42 has truly evolved to be part of the host immune system remains subject of active research.^[10]

The A β 42 peptide has also received considerable attention for its synaptomodulatory activity in hippocampal neuronal networks.^[11] Exposure of (typically rat or mouse) hippocampal slices to oligomeric A β 42 preparations produces robust inhibition of long-term potentiation (LTP, a well-established model for synaptic plasticity and learning).^[11a] The effect is readily observed at ~50–500 nM concentration,^[11b] *i.e.*, ~2–3 orders of magnitude lower than the concentration required in order to produce neurotoxic effects. The mechanism of LTP-

inhibition by A β 42 remains subject of active research.^[1b, 11d, 12] It is intriguing to note that at ~100–300 pM concentration, A β 42 was shown to be LTP-enhancing,^[11b] which was later suggested to be a consequence of positive regulation of neurotransmitter release probability at hippocampal synapses.^[11c] A recent quantitative mass spectrometric study reported A β 42 concentrations of ~0.5 ng/mL (~110 pM) in the CSF of non-diseased humans. Intriguingly, this falls into the concentration regimen of A β 42, in which the peptide was found to positively regulate LTP.^[11b, c]

A β 42 was recently shown to be generated at a frequency of 2–4 molecules per neuron per second.^[13] With the human brain containing on the order of 100×10^9 neurons, this yields $\sim 3 \times 10^{11}$ A β 42 molecules per second for the brain. Using Avogadro's constant of 6×10^{23} , this can be converted to 330 femtomoles of A β 42 generated by the human brain every second, or 28.5 nanomoles of it per day. This number is likely to be somewhat of an underestimation, since the human brain has a comparable number of glial cells,^[14] including astrocytes, which have been found capable of producing A β under certain conditions, such as stress.^[15] The number listed above should therefore be considered a conservative estimate, a lower boundary. Under healthy conditions, accumulation and clearance are balanced, and sleep appears to play a vital role.^[16] Disruption of A β 42 brain clearance can result in accumulation of synaptotoxic peptide concentrations (~50–500 nM) within days or weeks, if clearance is impaired. Intriguingly, if all A β 42 produced by the human brain over the course of a year - a total of ~10.4 micromoles - were converted into pure fibrils, the resultant deposit would have a volume of 0.05 mL or 50 mm³. This is noteworthy, because, showing that large volumes of soluble A β 42 oligomers can be compacted into very small solid deposits, it highlights the potential of the recently established oligomer-to-fibril conversion mechanism, which was proposed as an alternative approach to eliminate neurotoxic, soluble A β 42 oligomers.^[8b, c, 17]

A remarkable property of the A β 42 system that emerges from this analysis is that, in order to better understand its action in the context of the human brain, an unusually wide range of concentrations must be considered. The purpose of this short note was to provide a set of ballpark concentration guidelines and to stimulate cross-disciplinary dialogue, which is vitally needed, so that advances can be made with regard to A β 42 actions in Alzheimer's Disease and beyond.

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Table 1.

Ballpark concentrations of A β 42 in a variety of physiologically relevant contexts.

Context	Ballpark Concentration
A β 42 “monomer-in-fibril”	221.5 mM
Neurotoxicity	~10–100 μ M
Negative LTP modulation	~50–500 nM
Positive LTP modulation	~50–500 pM
A β 42 generation by the brain	330 fM s ⁻¹

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