Electronic properties of memantine (Alzheimer's disease) and amantadine (anti-flu) drugs

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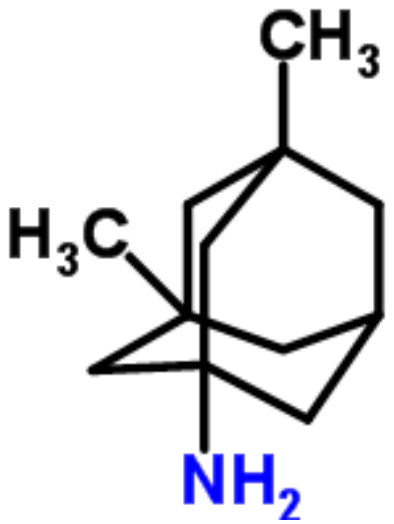


http://www.chemspider.com/Chemical-Structure.3914.html

Motivation

- Alzheimer's Disease is the 5th leading cause of death for Americans 65 and older

- Treatment
  - The U.S. Food and Drug Administration

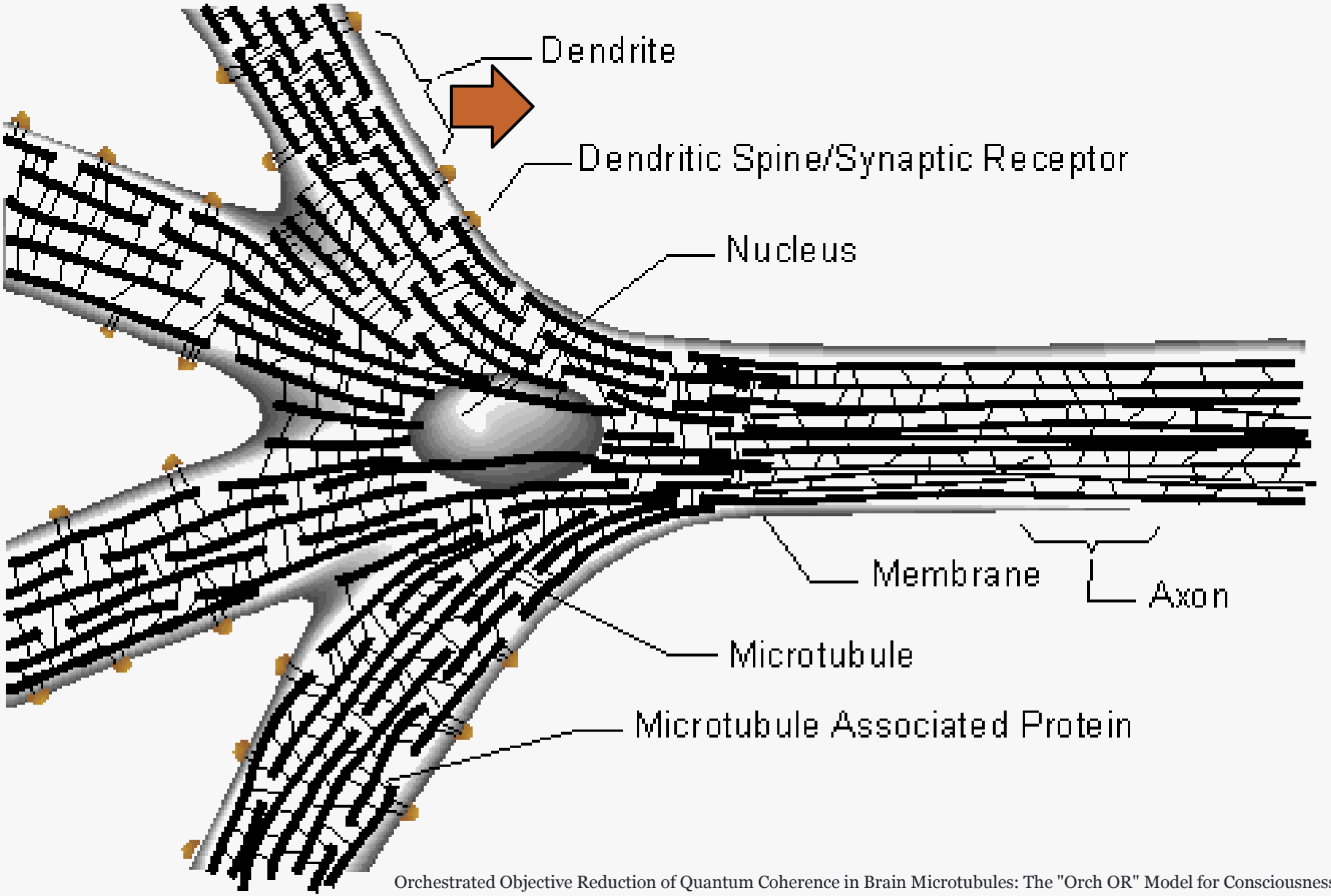
  - **Only five drugs approved that "temporarily slow worsening of symptoms for about six to 12 months."**

  - Effective for **only** about **half** of all patients

Alzheimer's Association, 2011 Alzheimer's Disease Facts and Figures, http://www.alz.org/downloads/Facts_Figures_2011.pdf

Contents

- Introduction: brain function and Alzheimer's disease
- Memantine's role as a treatment
- Results
- Conclusions



Orchestrated Objective Reduction of Quantum Coherence in Brain Microtubules: The "Orch OR" Model for Consciousness, Stuart Hameroff and Roger Penrose, http://www.quantumconsciousness.org/penrose-hameroff/orchOR.html

Memantine, an Alzheimer's Drug

- $C_{12}H_{21}N$

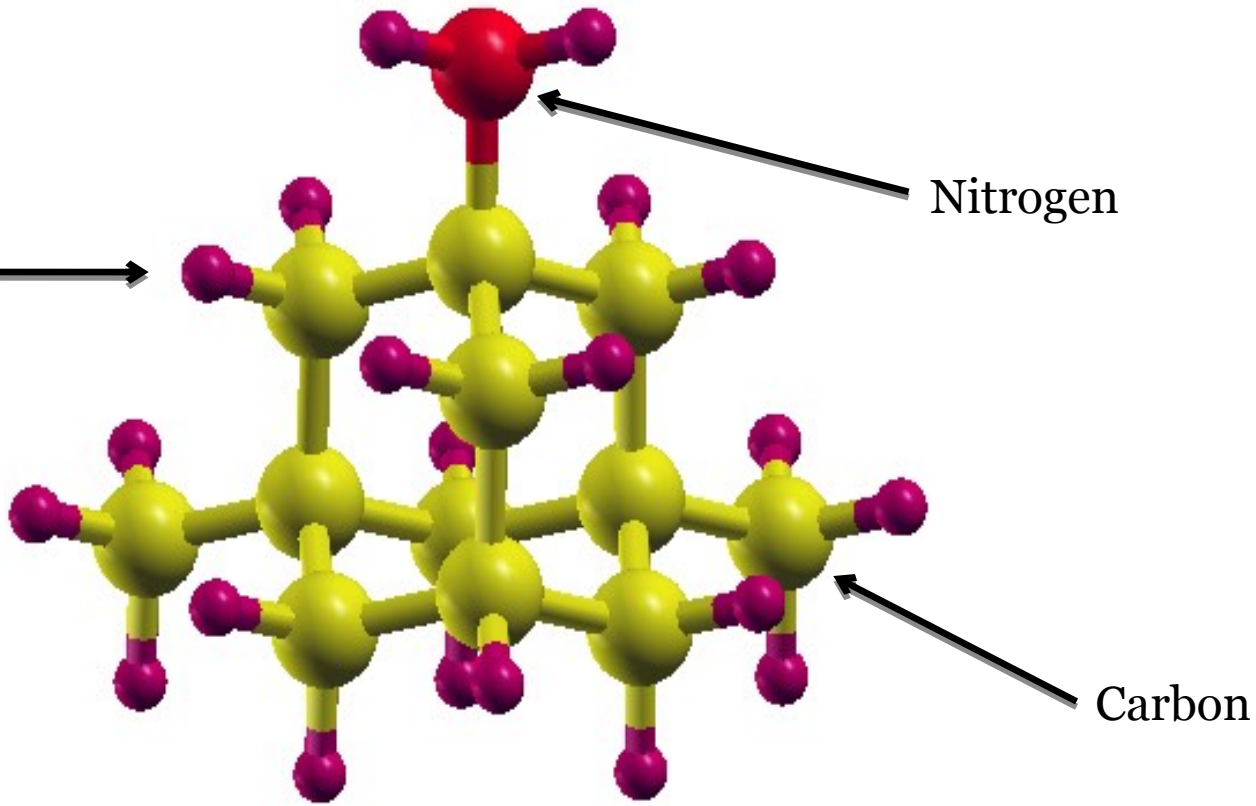


Image created with XCrySDen, http://www.xcrysden.org/

Physical Properties

- Electron affinity
  - Comparisons between:
    - Memantine and Mg^{2+}
    - Protonated memantine and Mg^{2+}
    - Memantine and amantadine

Create

- Create coordinates using Hyperchem
- Convert files to .g03 format

Optimize

- Density functional theory method
- Optimize the structure
  - Vary the basis set

Collect

- Use the .log file to find the total surface energy

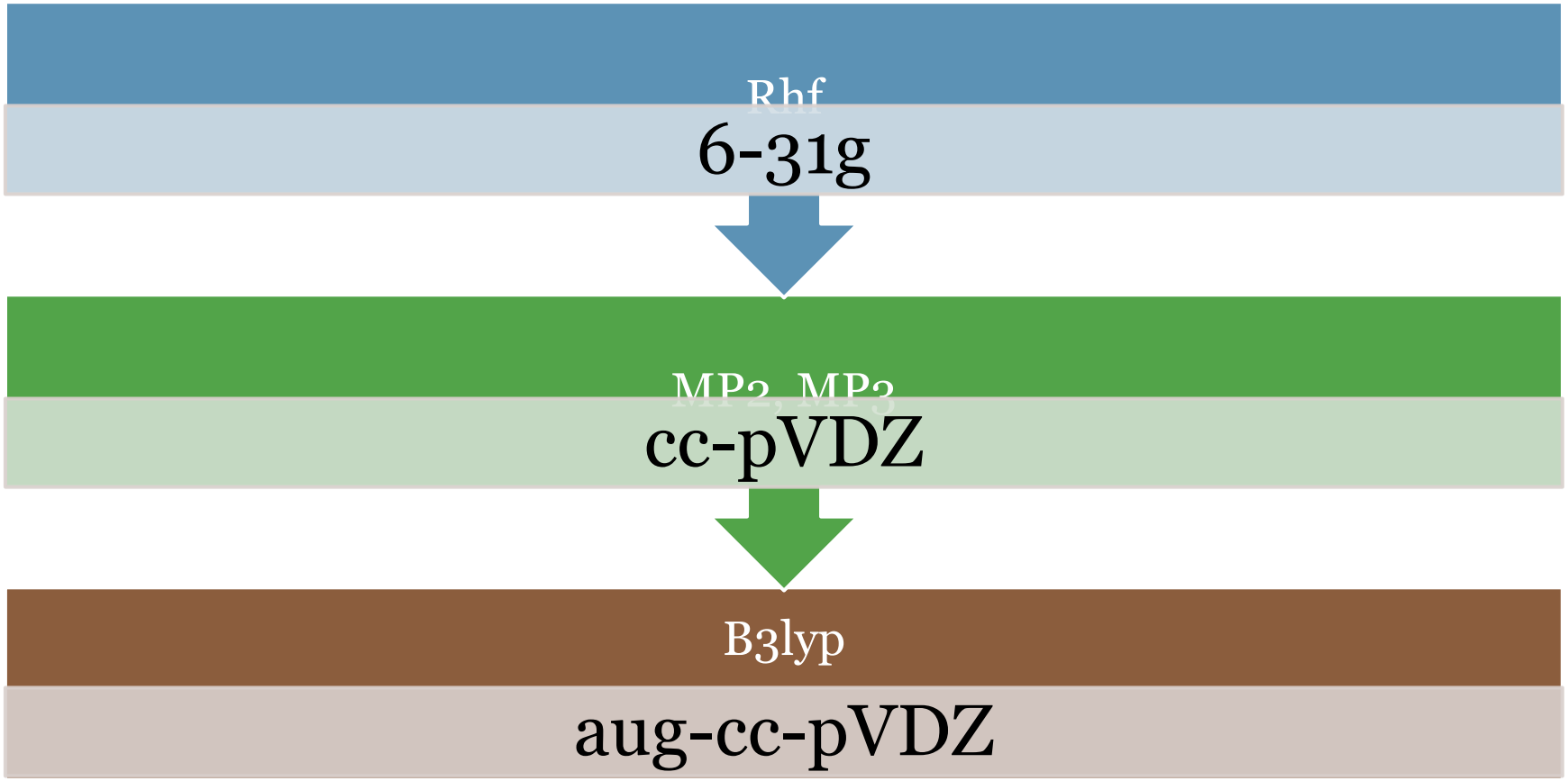
Optimize

- Optimize the structure with an additional electron
- Find the total surface energy

Calculate

- Calculate the electron affinity
- Compare molecules and ions

Calculation Methods and Basis Sets



http://www.gaussian.com/g_tech/g_ur/g09help.htm

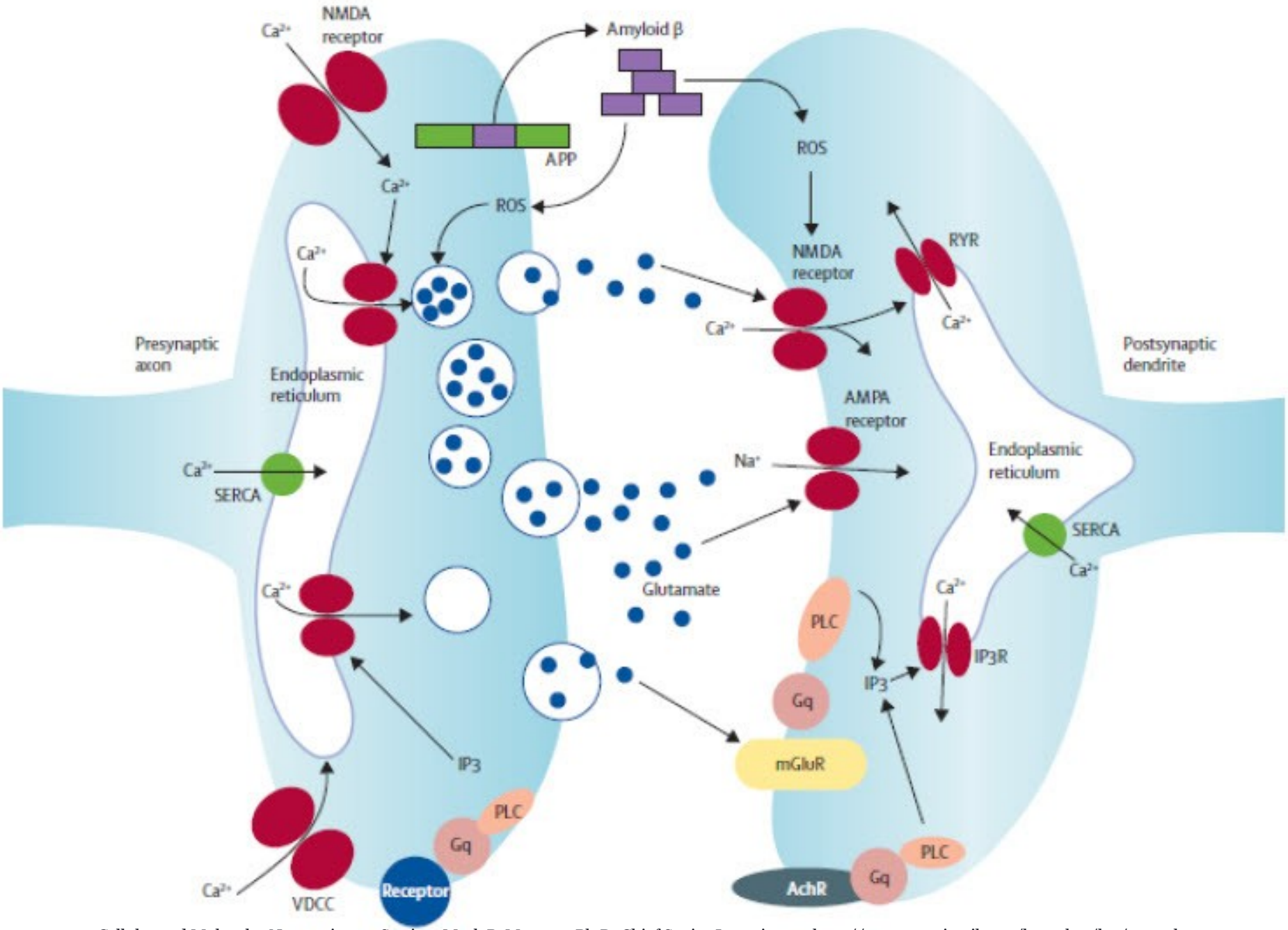
Calculation Methods and Basis Sets

- Hartree-Fock method – approximate
- Density Functional Theory method
  - Treat electron correlation differently than RHF
- Basis sets – how accurately the true wave-function is represented

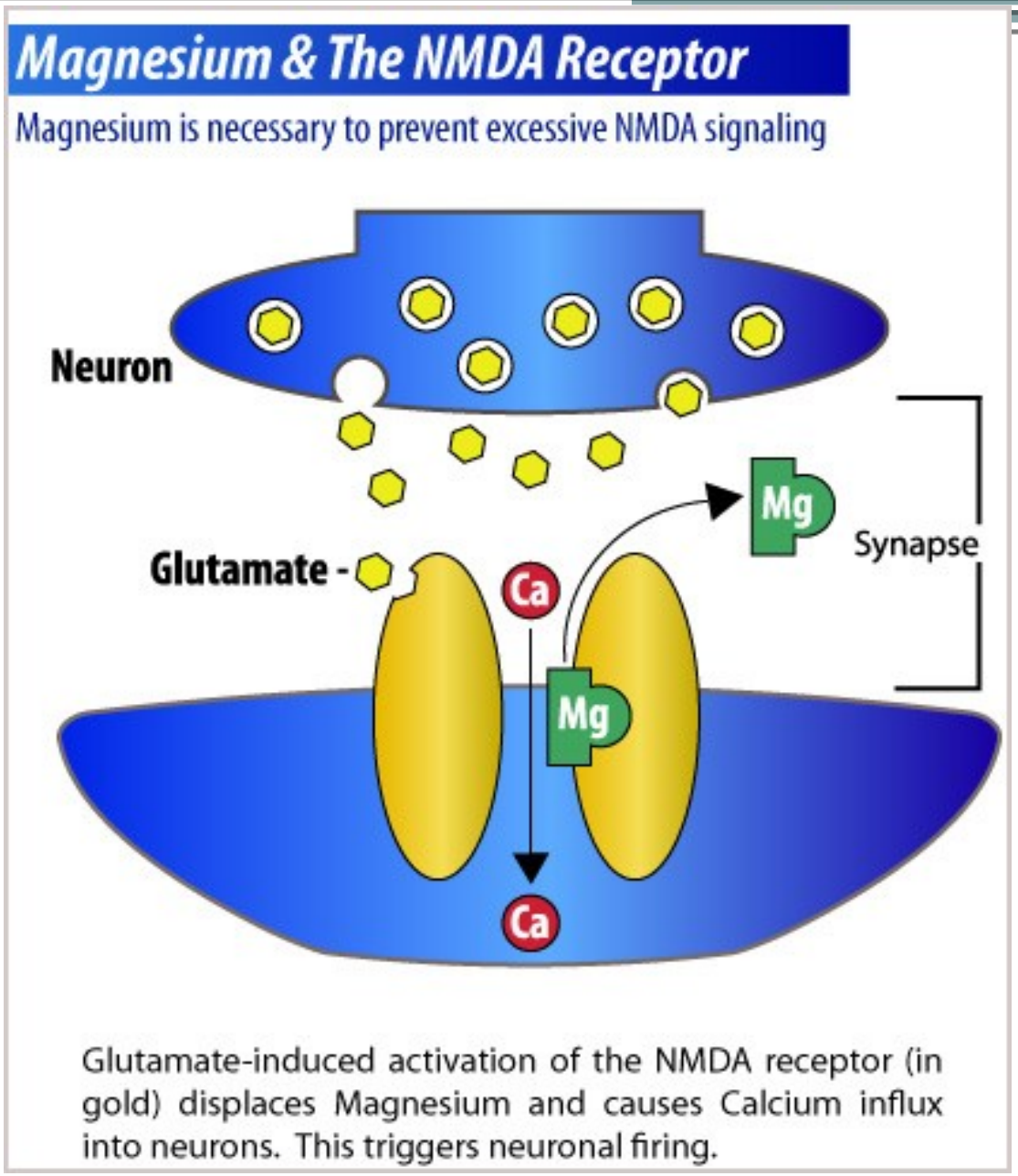
For more information:
http://www.gaussian.com/g_tech/g_ur/g09help.htm

Electron Affinity

- Standard:
  - Positive: electron acceptors
  - Negative: electron donors
- Goal: understand how different molecules interact



Cellular and Molecular Neurosciences Section, Mark P. Mattson, Ph.D, Chief Senior Investigator, http://www.grc.nia.nih.gov/branches/lns/mcnu.htm



Stress, Anxiety, Depression, and Magnesium, Glutamate in Mood Disorders, http://www.integratedsupplements.com/intsup/intsup0008.newsletter201005

Memantine and Mg^{2+}

Basis Set	Memantine(eV)	Mg^{2+}(eV)
6-31g	-3.2187	14.7040
cc-pVDZ	-2.4803	14.7100
aug-cc-pVDZ	-0.3189	14.7103

- Memantine does compete with Mg^{2+}
  - Data does **not** agree with experimental results

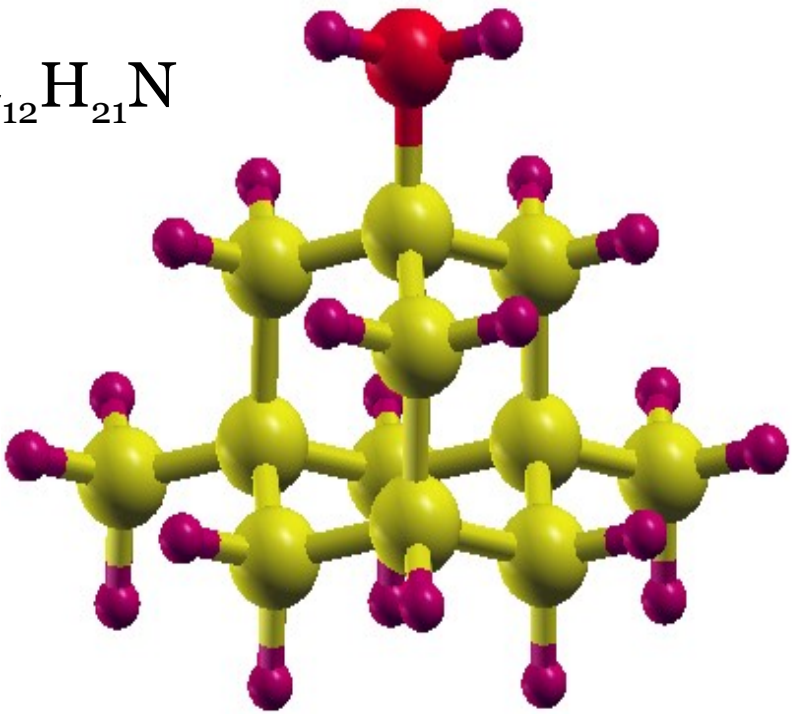
Protonated Memantine and Mg^{2+}

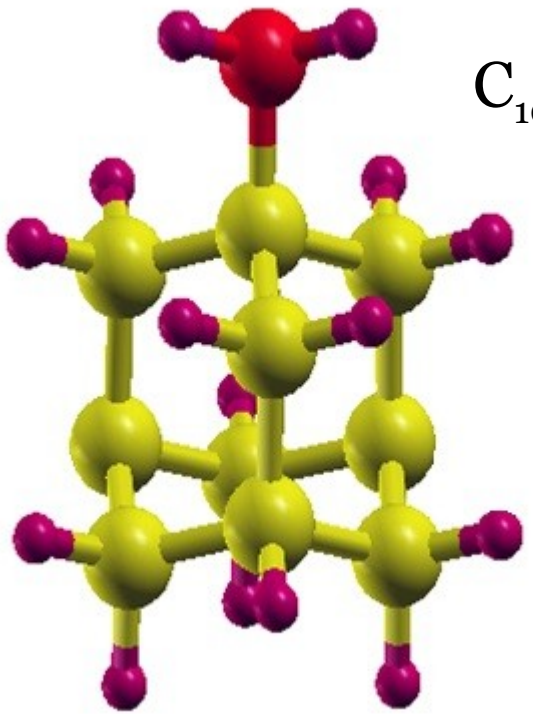
- Protonated memantine is not a competitive antagonist with Mg^{2+}
  - Consistent with experimental results

Basis Set	Protonated Memantine(eV)	Mg^{2+}(eV)
6-31g	2.2571	14.7040
cc-pVDZ	2.0626	14.7100
aug-cc-pVDZ	3.5742	14.7103

Memantine versus Amantadine

$C_{12}H_{21}N$





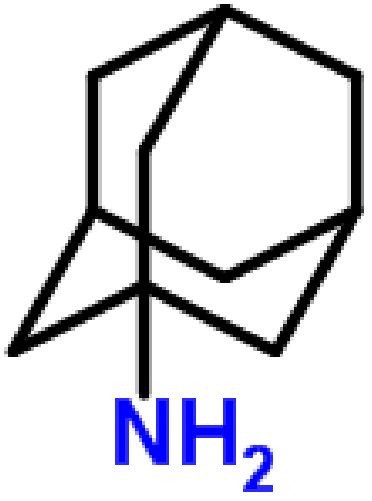
$C_{10}H_{15}N$

Images created with XCrySDen, http://www.xcrysden.org/


What • Why • How

Comparison to Amantadine

- Anti-viral drug
- Anti-Parkinson drug



- Similar to memantine:
  - Shape of structure
  - Purpose of treatment
  - Advanced Parkinson's patients suffer from dementia
    - Amyloid plaques and neurofibrillary tangles

Image from: http://www.chemspider.com/Chemical-Structure.2045.html?rid=976f177d-1d99-4871-91b0-7b0398d216d2

Memantine and Amantadine

- Additional methyl groups have little effect on E_{EA}
- Both compounds are electron donors

Basis Set	Memantine(eV)	Amantadine(eV)
cc-pVDZ	-2.4803	-2.729
aug-cc-pVDZ	-0.3189	-0.3892

Conclusions

- Protonated memantine does not compete with Mg^{2+} within the Ca^{2+} ion channel
  - Theory: memantine could replace Mg^{2+} as a gate to the Ca^{2+} ion channel

Compound	Electron Affinity(eV) B3lyp/aug-cc-pVDZ	Electron donor versus acceptor
Memantine	-0.3189	Donor
Protonated Memantine	3.5742	Acceptor
Mg^{2+}	14.7103	Acceptor
Amantadine	-0.3892	Donor

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