The Autism Epidemic is Caused by EMFs, Acting via Calcium Channels and Chemicals Acting via NMDA-Rs: Downstream Effects Cause Autism/ASDs

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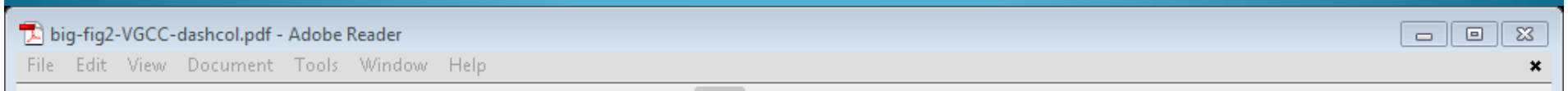
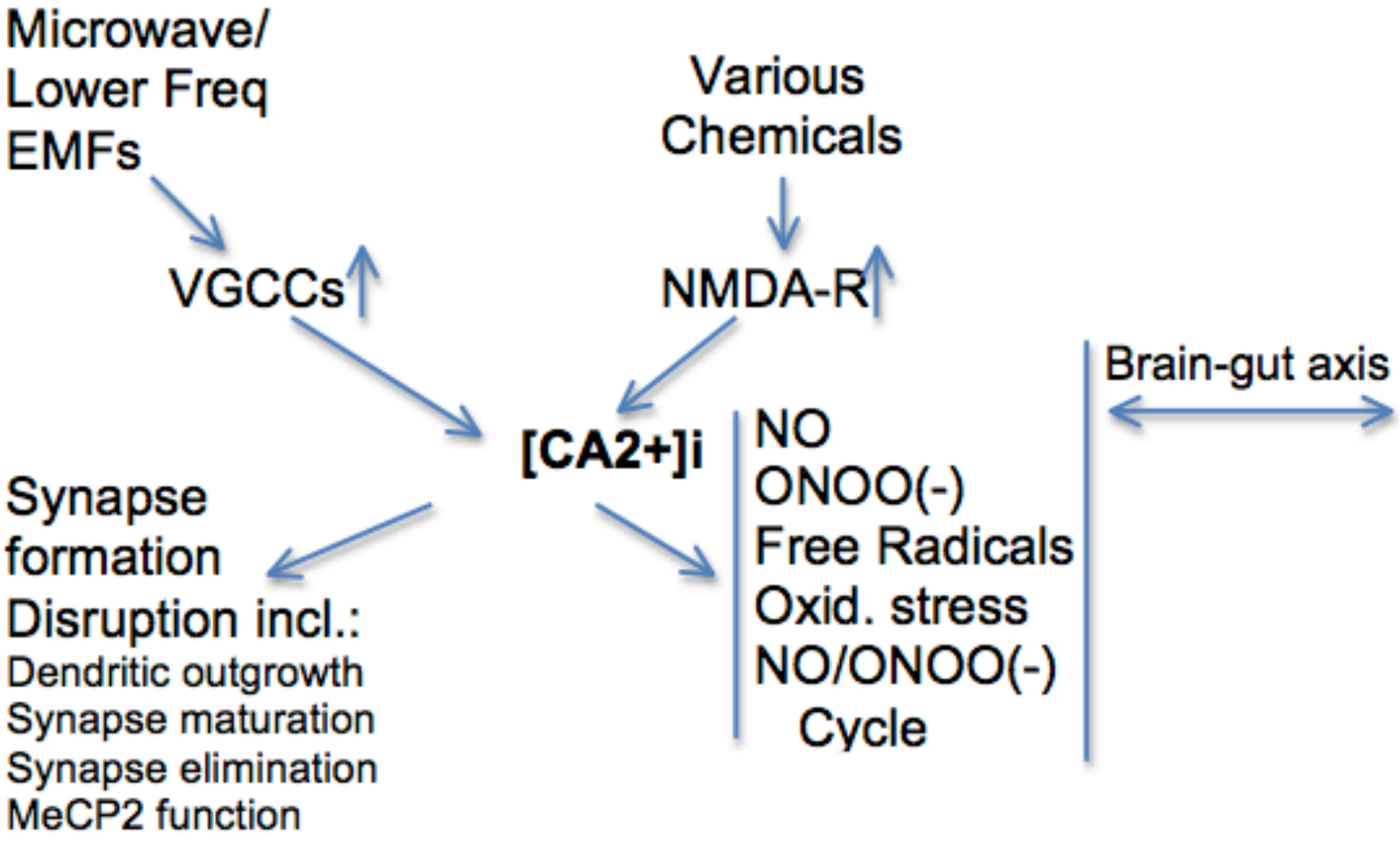


Autism

There are a number of researchers who have argued for autism being caused by microwave frequency EMFs, in part because of the difficulty in explaining the huge increase in incidence based on any other causal factor, or even set of factors.

1. Mariea TJ, Carlo GL. 2007 Wireless radiation in the etiology and treatment of autism: clinical observations and mechanisms. J Aust Coll Nutr Env Med 26: 3-7.
2. Thornton I. 2006 Out of time: a possible link between mirror neurons, autism and electromagnetic radiation. Med Hypotheses 67: 378-382.
3. Currenti SA. 2010 Understanding and determining the etiology of autism. Cell Mol Neurobiol 30: 161-171.
4. Pino-Lopez M, Romero-Ayuso DM. 2013 [Parental occupational exposures and autism spectrum disorder in children]. Rev Esp Salud Publica 87: 73-85.
5. Kane RC. 2004 A possible association between fetal/neonatal exposure to radiofrequency electromagnetic radiation and the increased frequency of autism spectrum disorders (ASD). Med Hypotheses 62: 195-197.
6. Lathe R. 2009 Electromagnetic Radiation and Autism. E J Appl Psychol 5: 11-30.
7. Goldworthy A. 2011 How electromagnetically-induced cell leakage may cause autism. http://mcs-america.org/June2011pg2345.pdf
8. Herbert MR, Sage C. 2013 Autism and EMF? Plausibility of a pathophysiological link - Part I. Pathophysiology 20:191-209.
9. Herbert MR, Sage C. 2013 Autism and EMF? Plausibility of a pathophysiological link part II. Pathophysiology. 2013 Jun;20(3):211-34.
10. Sullivan P. 2013 https://www.youtube.com/watch?v=muMVAK19GTM
11. Klinghart D. 2008 Autism may be linked to electromagnetic radiation in mother's bedroom during pregnancy. http://electromagnetichealth.org/media-stories/#Autism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Much of what I will be saying about the role of microwave EMFs acting via voltage-gated calcium channels (VGCCs) comes from two papers I have published, both of which are available, full-text, public access, from the PubMed database:

Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. Pall ML. J Cell Mol Med. 2013 Aug;17(8):958-65.
This paper was honored by being placed on the Global Medical Discovery web site as one of the most important medical papers of 2013.

Scientific evidence contradicts findings and assumptions of Canadian Safety Panel 6: microwaves act through voltage-gated calcium channel activation to induce biological impacts at non-thermal levels, supporting a paradigm shift for microwave/lower frequency electromagnetic field action. Pall ML. Rev Environ Health. 2015 Apr 16. pii: /j/reveh.ahead-of-print/reveh-2015-0001/reveh-2015-0001.xml. doi: 10.1515/reveh-2015-0001. [Epub ahead of print]

How can electromagnetic fields (EMFs) impact our biology and medicine?

There has been a great puzzle about how EMFs can influence our biology, for better or for worse. These EMFs are composed of low energy photons, with energy per photon too low to influence the chemistry of the body! How can they influence our biology through non-thermal effects? And yet there is a substantial literature reporting that they do.

I have recently solved this important puzzle. EMFs act to activate voltage-gated calcium channels (VGCCs). The key piece of evidence is that in 26 different studies, the effects of these microwave and lower frequency EMFs were blocked or greatly lowered by calcium channel blockers!

Journal of Cellular and Molecular Medicine 2013:17:958-965.

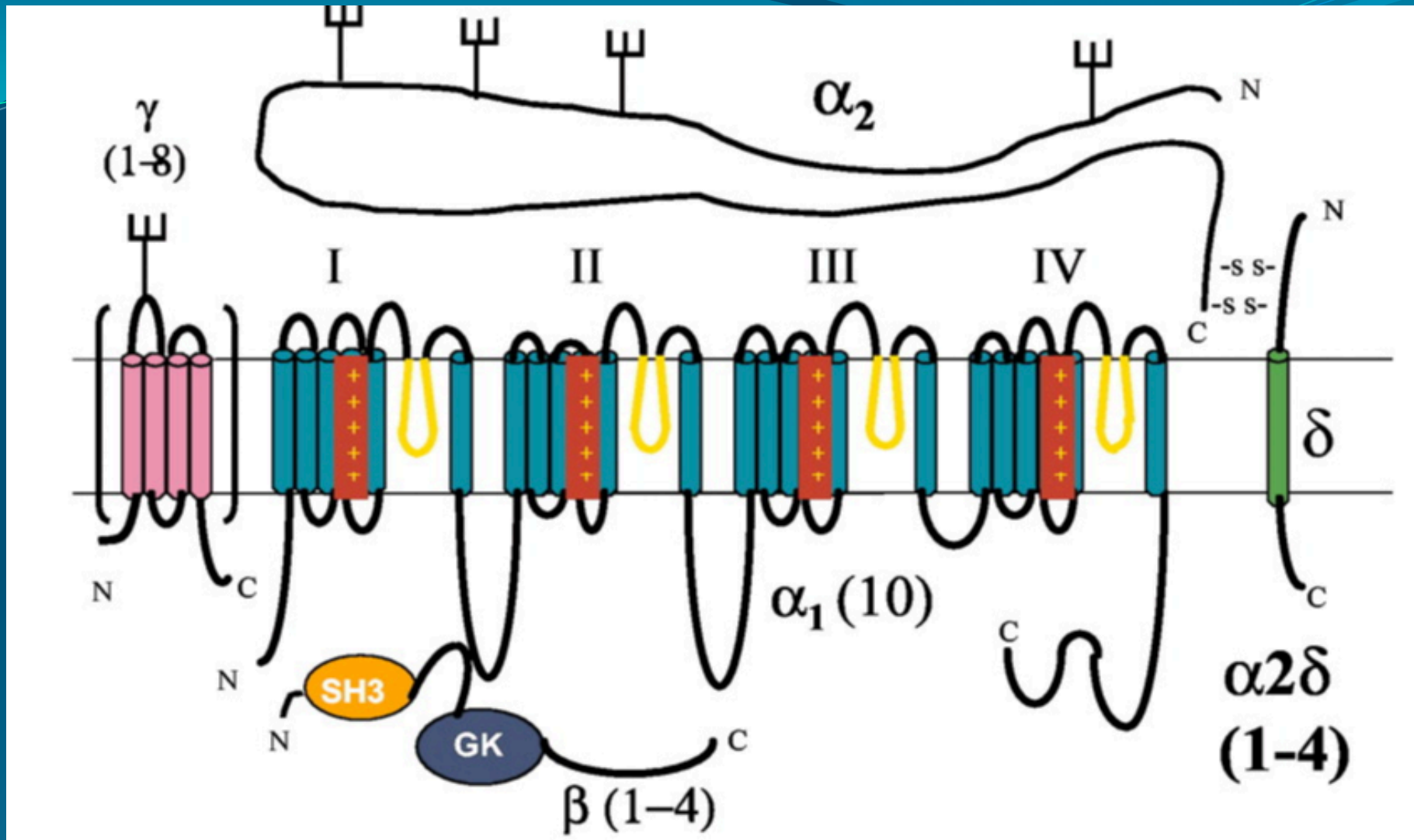
In these studies, when multiple responses to microwave EMF exposure were studied, each of these were blocked or greatly lowered by the calcium channel blockers.

There are close to 1000 studies showing effects of microwave EMFs on calcium fluxes and calcium signaling in cells, effects that can be explained by VGCC activation.

An important study (Pilla, 2012) showed that the increase in intracellular calcium [Ca2+]i seems to be almost instantaneous – argues for a direct effect.

The VGCCs each have a "voltage sensor" which detects electrical changes and opens the channel in response to those electrical changes. The physical properties of the voltage sensor predict that it is extremely sensitive to low intensity EMFs – probably 6 orders of magnitude of more sensitive than any other target outside the plasma membrane.

Pall ML. Rev Environ Health 2015 Apr 16. pii: /j/reveh.ahead-of-print/reveh-2015-0001/reveh-2015-0001.xml. doi: 10.1515/reveh-2015-0001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(1-4)

If autism is caused by EMF exposure to the brain, then one would predict that hyperactivity of the main L-type VGCC in the brain, $Ca_v1.2$ will cause autism. This has been shown to be true. A mutation in the main gene encoding this channel (CACNA1C) causes Timothy syndrome, which is characterized by autism and autism spectrum disorder (ASD) symptoms, as well as cardiac changes that are lethal a very low age. This mutation produces hyperactivity of the channel, because the mechanism that closes the channel in response to prolonged depolarization and calcium elevation, is dysfunctional, such that the channel stays open much longer, allowing much larger fluxes to flow into the cell. A derivative of this Timothy syndrome mutation also causes autism in transgenic mice with symptoms described as showing "markedly restricted, repetitive, and perseverative behavior, altered social behavior, altered ultrasonic vocalization, and enhanced tone-cued and contextual memory following fear conditioning."

The Timothy syndrome mutation is not the only rare mutation that causes autism by causing excessive activity of the VGCCs. There are also mutations in the beta subunit of the L-type VGCCs that make the channel slow in closing that cause autism. And in addition there are mutations similar to the Timothy syndrome in the main subunit of an L-type VGCC (CACNA1F) that is expressed only a low levels in the brain that cause symptoms of autism but not full-fledged autism. Finally mutations that produce a deficiency in the calcium-activated potassium channel (KCNMA1) – a channel that acts to help close the VGCCs, also cause autism.

In summary, we know that four types of mutations, each of which cause excessive VGCC activity, each cause autism or symptoms of autism. But this does not tell us whether elevated VGCC activity commonly causes autism in the broader population afflicted with autism.

Question: Is elevated VGCC activity involved in causing autism in the general population of autism individuals??

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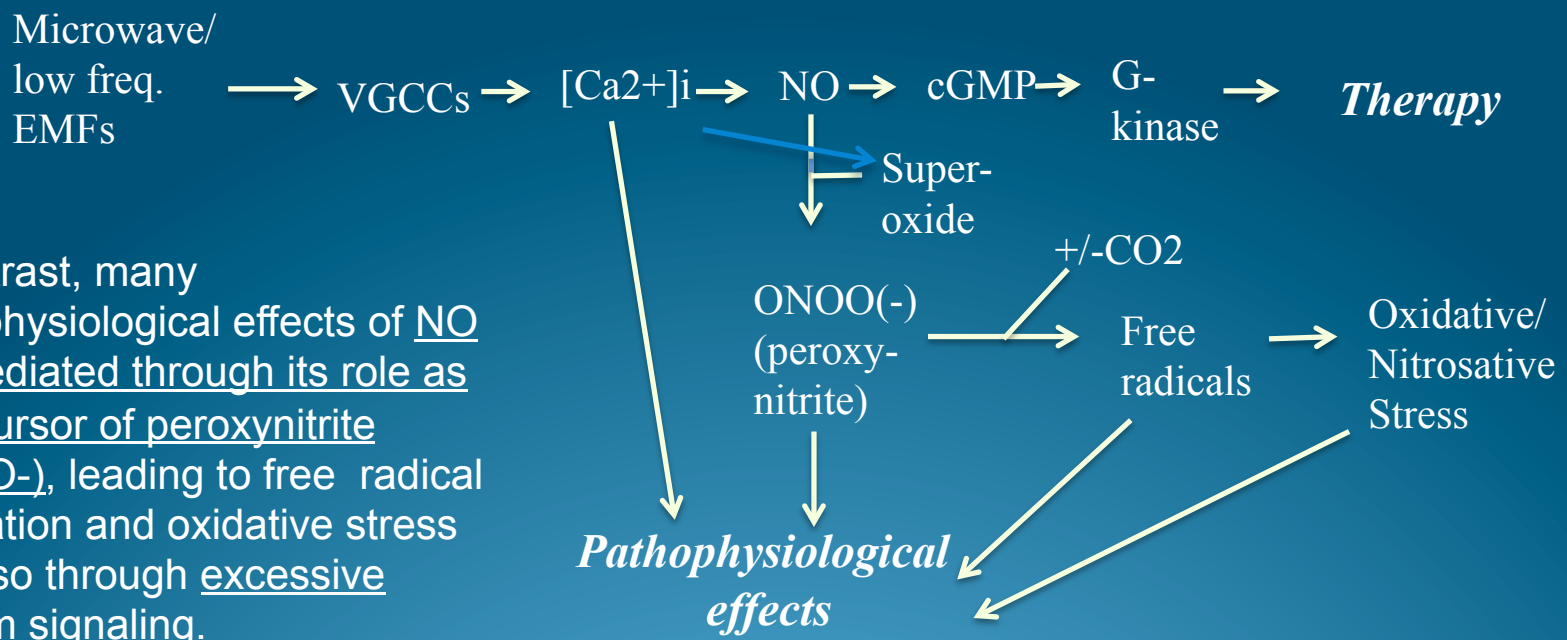
Answer is yes, based on genetic polymorphism studies. Genetic polymorphism studies done with the same gene that mutates to produce Timothy syndrome (CACNA1C) show that an allele of that gene which produces increased activity of the gene is associated with increased autism susceptibility – also has other widespread neuropsychiatric effects. In addition, genetic polymorphism studies of two T-type VGCCs alleles that produce increased activity also cause increased susceptibility to autism.

Argues strongly for broad role of the VGCCs in causing autism in the autism population – provides strong support, therefore, for microwave EMFs causing autism in the general population.

Most physiological responses to [Ca2+]i and NO, act as follows:

NO increases levels of cGMP, leading in turn to stimulation of the cGMP-dependent protein kinase (protein kinase G).



In contrast, many pathophysiological effects of NO are mediated through its role as a precursor of peroxynitrite (ONOO-), leading to free radical generation and oxidative stress and also through excessive calcium signaling.

There have been many researchers that have argued that the failure to develop proper synaptic connections is the central defect that occurs in autism/ASDs:

Bourgeron 2009. **A synaptic trek to autism**. Curr Opin Neurobiol 19:231.
Woolfrey et al 2009. Epac2 induces **synapse remodeling** and depression **and its disease-associated forms alter spines**. Nature Neurosci 12:1275
Zantomio et al, 2015. Convergent evidence for mGluR5 in **synaptic and neuroinflammatory pathways implicated in ASD**. Neurosci Biobehav Rev 52:172
McFadden & Minshew 2013 Evidence for **dysregulation of axonal growth and guidance in ASD**. Front Hum Neurosci Oct 22;7:671
Huda & Zoghbi 2003. **Postnatal neurodevelopmental disorders**: **Meeting at the synapse**? Science 302:826
Spooren et al, 2012 **Synapse dysfunction in autism**: a molecular medicine approach to drug discovery in neurodevelopmental disorders. Trends Phamaceut Sciences 33:669.
Gai et al, 2012 Rare structural variation of **synapse and neurotransmission genes to autism**. Mol Psychiatry 17:402.
Herbert 2011 SHANK3, the **synapse and autism**. New Engl J Med 365:173.

There have been many researchers that have argued that the failure to develop proper synaptic connections is the central defect that occurs in autism/ASDs:

The most convincing type of evidence for this is that mutations in genes encoding proteins with very specific roles in forming synapses, SHANK3 and NEUROLIGIN 3 & 4, cause autism. These studies clearly show that synaptic disruption is central to the production of the whole spectrum of symptoms causing autism.

Other important studies show that

1. Brains of autism patients (post-mortem) studies show many histological changes indicating synapse disruption.
2. Animal models of autism also show similar histological changes discussed in 1.
3. Brain dysfunction in autism patients also indicate synapse disruption.

Rodent studies showed many years ago, that the nervous system is THE most sensitive tissue in the body to low level microwave/lower frequency EMFs (Tolgskaya & Gordon, see below).

Synaptic connections in regions of the brain are disrupted (p.65-74, 97,113,121,136), with many of these studies showing deformation of spines near the ends of dendrites, spines known to have essential roles in forming synaptic connections.

With still more sessions of low-intensity irradiation, spines disappeared entirely (p. 70). At the extreme, some neurons are completely asynaptic (p.73). It can be seen from this, that non-thermal exposures well within current safety standards, can cause severe disruption of synapse formation in animals.

Tolgskaya MS, Gordon ZV. 1973 Pathological Effects of Radio Waves, Translated from Russian by B Haigh. Consultants Bureau, New York/London, 146 pages.

A very recent study showed a close linkage between synapse development and autism in the mouse

(Schuster et al, NOMA-GAP/ARHGAP33 regulates synapse development and autistic-like behavior in the mouse. Mol Psychiatry 2015 Apr 14).

This study showed that a mutation that produces autism-like social behavior in the mouse, showed aberrant synapse development and aberrant dendritic spine morphology.

A recent study has shown that synaptic pruning deficits can produce autism-like symptoms in the mouse.

Tang et al (2014 Neuron) showed that mutations in the mTOR gene causes changes in synaptic pruning and also causes autism-like social behavioral deficits in the mouse.

This study demonstrates the complexities of the connections between synapse formation and autism – failure to form proper synapses and in addition, failure to remove inappropriate synapses (pruning) can each have roles in the development of autism symptoms.

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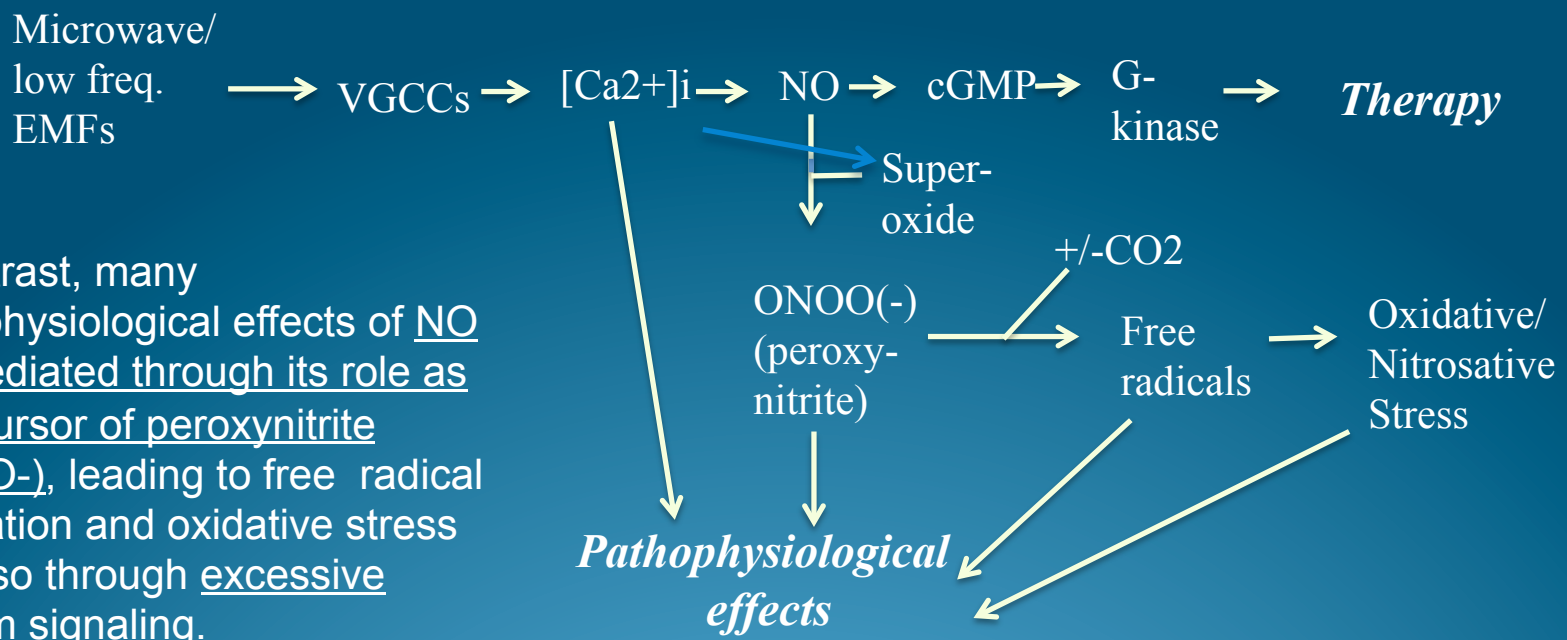


In contrast, many pathophysiological effects of NO are mediated through its role as a precursor of peroxynitrite (ONOO-), leading to free radical generation and oxidative stress and also through excessive calcium signaling.

So how can excessive VGCC activity acting through excessive [Ca2+]I perturb synapses during brain development? Excessive [Ca2+]i can impact impact three processes involved in synaptic connections in the developing nervous system:

- The growth of processes from neurons towards the proper sites.
- Subsequent formations of the first synapses.
- Further formation of synapses as well as breakages of some synaptic connections.

Each of these three processes requires appropriate calcium control and is disrupted by excessive intracellular calcium!! (Reviewed in Cohen & Greenberg, Annu Rev Cell Dev Biol 2008;24:183-209; Lohmann C, 2009, Prog Brain Res 175:443)

Lohmann argues that dysfunction of each of these 3 processes has an essential role causing autism, consistent with the earlier arguments supporting an essential role of disruption of synapse formation in causing autism.

There is a fourth process that impacts synapse formation in the developing brain, one that is partly overlapping the processes discussed in the previous slide and one that is partly independent of them. It involves the MeCP2 gene and the MeCP2 protein (which is a calcium regulated transcriptional regulator) produced by the gene.

Mutations that knock out function of MeCP2 gene are known to cause Rett syndrome, considered part of the autism spectrum. This produces **changes in regulation of genes that have roles in synapse development** and therefore disrupts synapse development.

Calcium-dependent phosphorylation of the MeCP2 protein, lowers its activity and causes the protein to behave as if it were a mutant protein.

So this is another way in which elevated [Ca2+]i can disrupt normal synapse development!

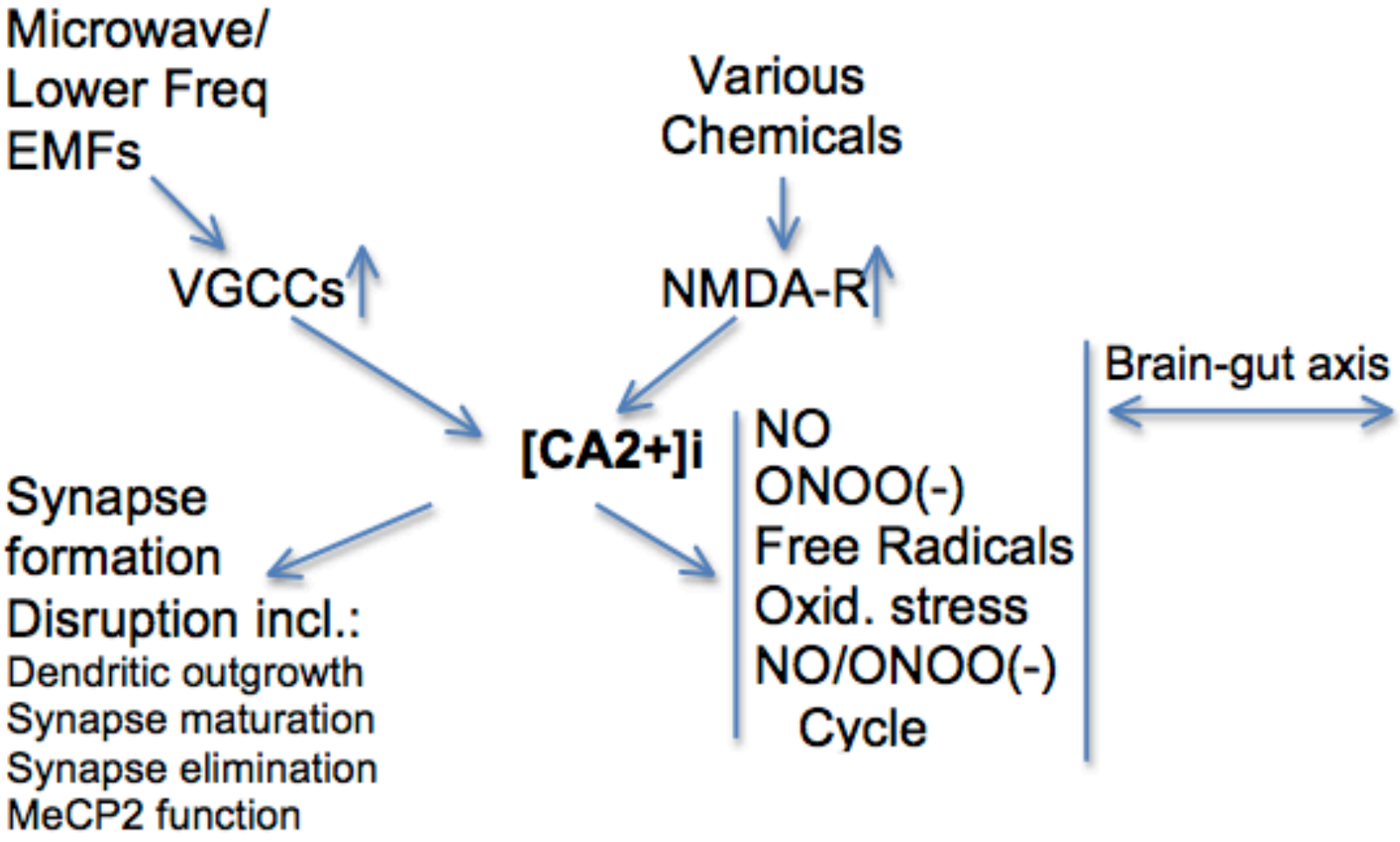
We started this discussion with the parallel increase between microwave EMF exposures and the incidence and autism. Are there other epidemiological &/or clinical observations that also suggest a linkage?

In Brick Township, New Jersey where a radar station leads to substantial levels of exposure over the town, the autism incidence was somewhat unusually high. Bertrand J, et al. Pediatrics 2001 108(5):1155.

Dr. Dietrich Klinghardt reported that the EMF intensity where pregnant mothers slept who produced autism children was over 20 times higher than for mothers who produced normal children – with totally non-overlapping values. Small study but with high statistical significance!

Two physicians each reported that their autism patients showed very substantial improvements in symptoms, when moved into an environment with much lower field exposures.

No doubt we need many more similar studies.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Summary of evidence EMFs → VGCCs → [CA2+]i → Synapsis ↓

4 types of evidence that microwave EMFs act via activation of VGCCs

Rare mutations in 4 genes that produce excessive VGCC activity each cause autism (4)

Genetic polymorphism in CACNA1C gene producing elevated activity produces increased susceptibility to autism and genetic polymorphisms in 2 T-type genes also act similarly (3)

Central cause of autism thought to be disruption of normal synaptic development process (3)

- Supported by neurophys changes in autism patients
- Supported by changes in brain structures (post-mortem) in autism
- Supported by changes in brain structures in rodent autism models

Rodent brains very sensitive to microwave EMFs, with changes including many changes in synaptic connections (2)

Summary of evidence EMFs → VGCCs → [CA2+]i → Synapsis ↓ (continued)

Mutations in Shank3 and two neuroligin genes (specific roles in forming synapses) each cause autism in humans (3)

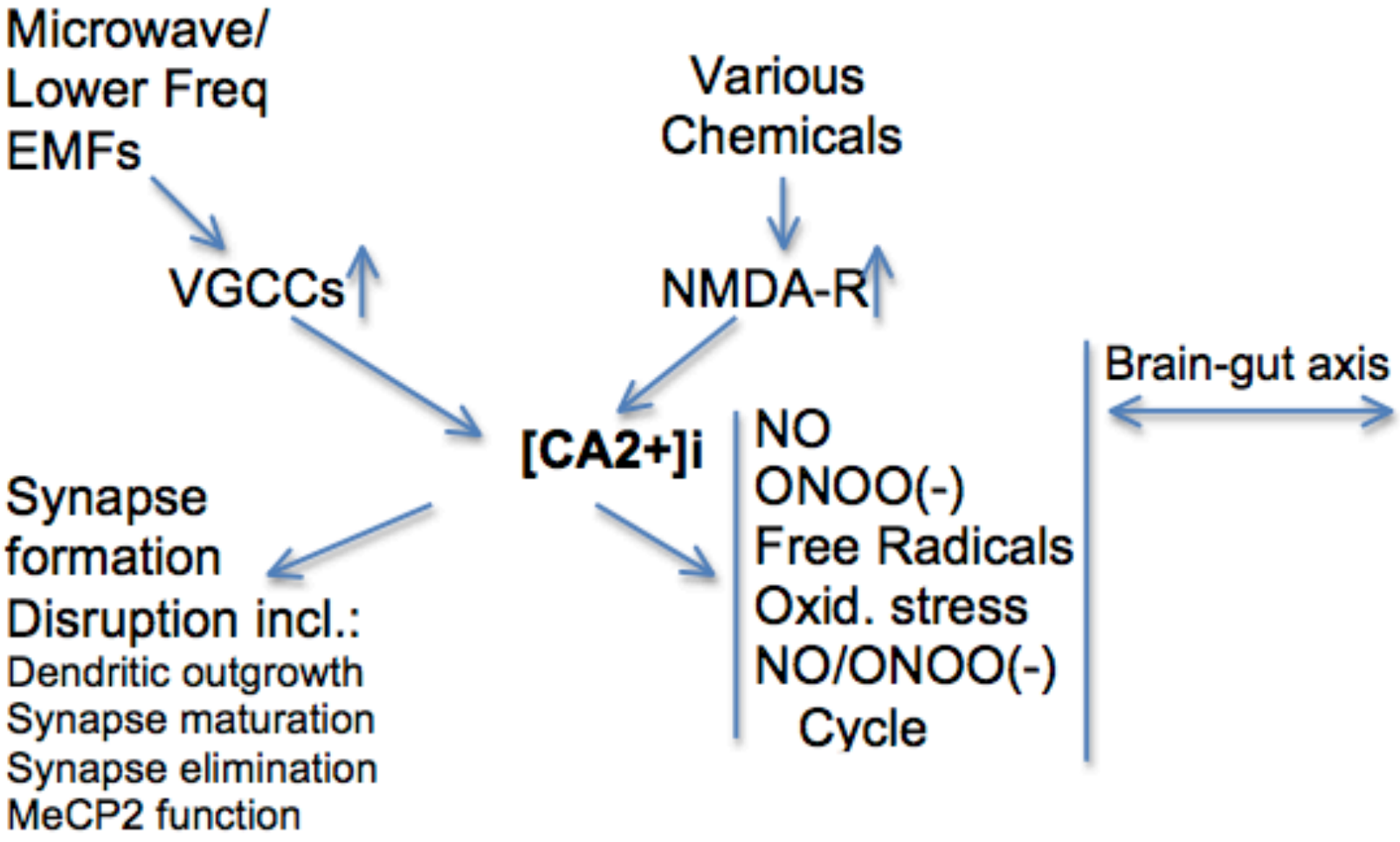
Autism mouse models produced by mutations that cause synaptic disruption (1)

Excessive [Ca2+]i causes dysfunction of 4 different mechanisms each of which have important roles in forming proper synapses (4)

Dysfunction of each of the 4 (immediately above) have roles in autism (4)

4 types of epidemiological or clinical observation studies (4).

Total of 32 types of evidence supporting the sequence shown at the top of slide, 16 on previous slide and 16 shown on this slide.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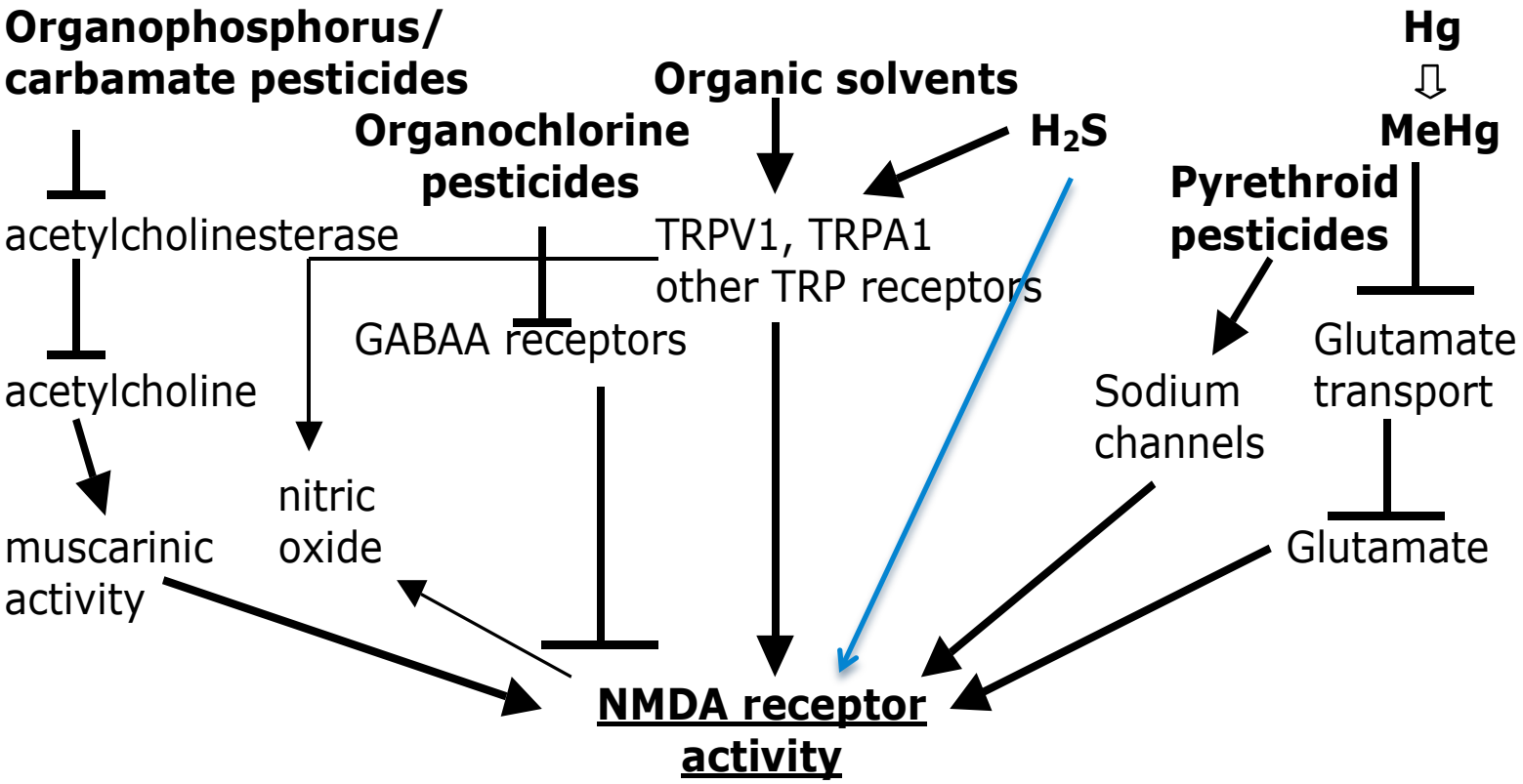
Chemical Action in MCS



There are a whole series of similarities between the NMDA receptors and the L-type VGCCs:

1. Both open up an ion channel when activated.
2. Both channels stay open are relatively long time period compared with other channels.
3. Both allow substantial amounts of calcium to flow into the cell.
4. The effects of both are thought to be mediated by excessive cytoplasmic calcium.
5. Both lead to the production of large amounts of nitric oxide, due to the action of two calcium-dependent nitric oxide synthases, with the nitric oxide often leading in both to production of peroxynitrite.
6. Both have been shown to be able to stimulate long-term potentiation, the process in the central nervous system involved in learning and memory by producing neural sensitization.

Genetic polymorphism studies on NMDA receptors and autism:

There are genetic polymorphisms in both the GRIN2A gene, which produce elevated NMDA activity, apparently cause increased susceptibility to autism.

Similarly there is a common allele of the GRIK2 gene, that produces increased activity of the kainate (glutamate) receptor that works along with the NMDA receptor, and also apparently produces increased susceptibility to autism.

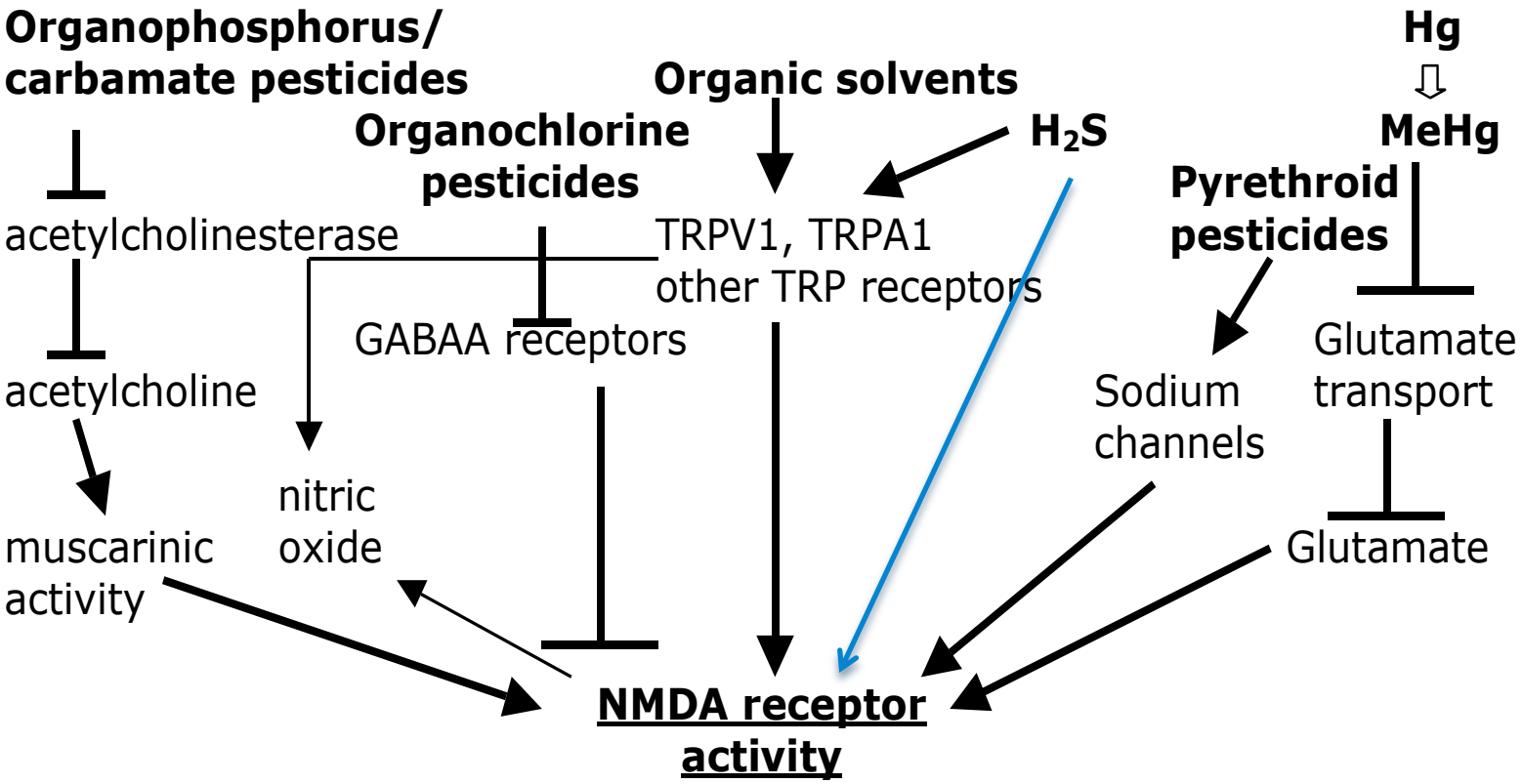
The problem with explaining the autism epidemic via these chemicals is that three classes of these chemicals:

- Organic Solvents and other Sensory Irritants
- The organophosphorus and carbamate pesticides
- The organochlorine pesticides

Each of these had their largest increases in synthesis in the 30 years following World War II, before there were substantial increases in the incidence of autism. So these alone are unlikely to have major roles here, although they may act synergistically along with EMF exposures.

What about other chemicals where we may have had substantial increases since that time?

Chemical Action in MCS

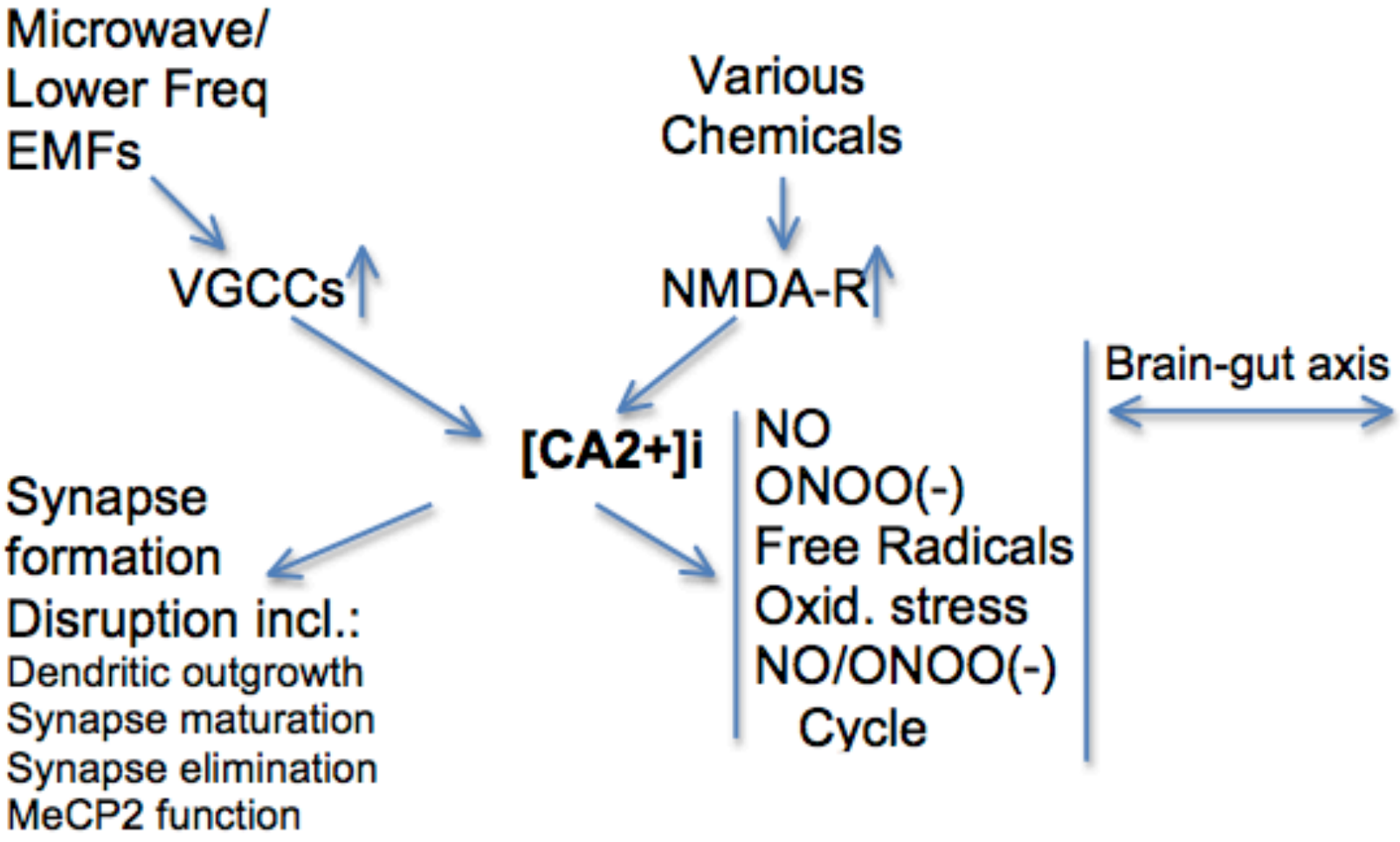


Chemical	Action	Comments
Acetaminophen acting via NAPQI	Reacts with thiol groups, may activate TRP receptors, inactivate glutamate transport, impact mitochondria leading to mitochondrial calcium release	Proposed by Dr. William Shaw to be important in autism.
Type 2 pyrethroids	May lead to increases in both NMDA and VGCC activity	Started production in late 1970s; Not previously proposed for autism role, to my knowledge
Glyphosate	Increases both NMDA and VGCC activities, according to Brazilian group. Acts in part via elevated glutamate.	Autism role proposed by Dr. Stephanie Seneff due to completely different proposed mechanisms; parallel increase between glyphosate and autism
Mercury; mercurials	Act via methyl/ethyl mercury through thiol reactions to lower glutamate transport and raise TRPC4/5 activities	
Fluoroquinolones	Produce increased NMDA activity	New for autism role

Both the NMDA receptors and the VGCCs act to partially depolarize the plasma membrane and they also are both activated, to some extent, by such depolarization. They both produce rises in [Ca2+]i. Consequently, stressors that activate one of these may act synergistically with stressors that raise the other, to raise [Ca2+]i and in this way cause autism.

It is likely, therefore, that both microwave EMFs and chemical exposures have substantial roles in causing the autism epidemic. It is my view that the EMFs are probably more important than are the chemicals, but I could be wrong about this; furthermore possible synergism means that simple additive roles cannot be assumed.

Prevention should focus on avoiding both types of exposures.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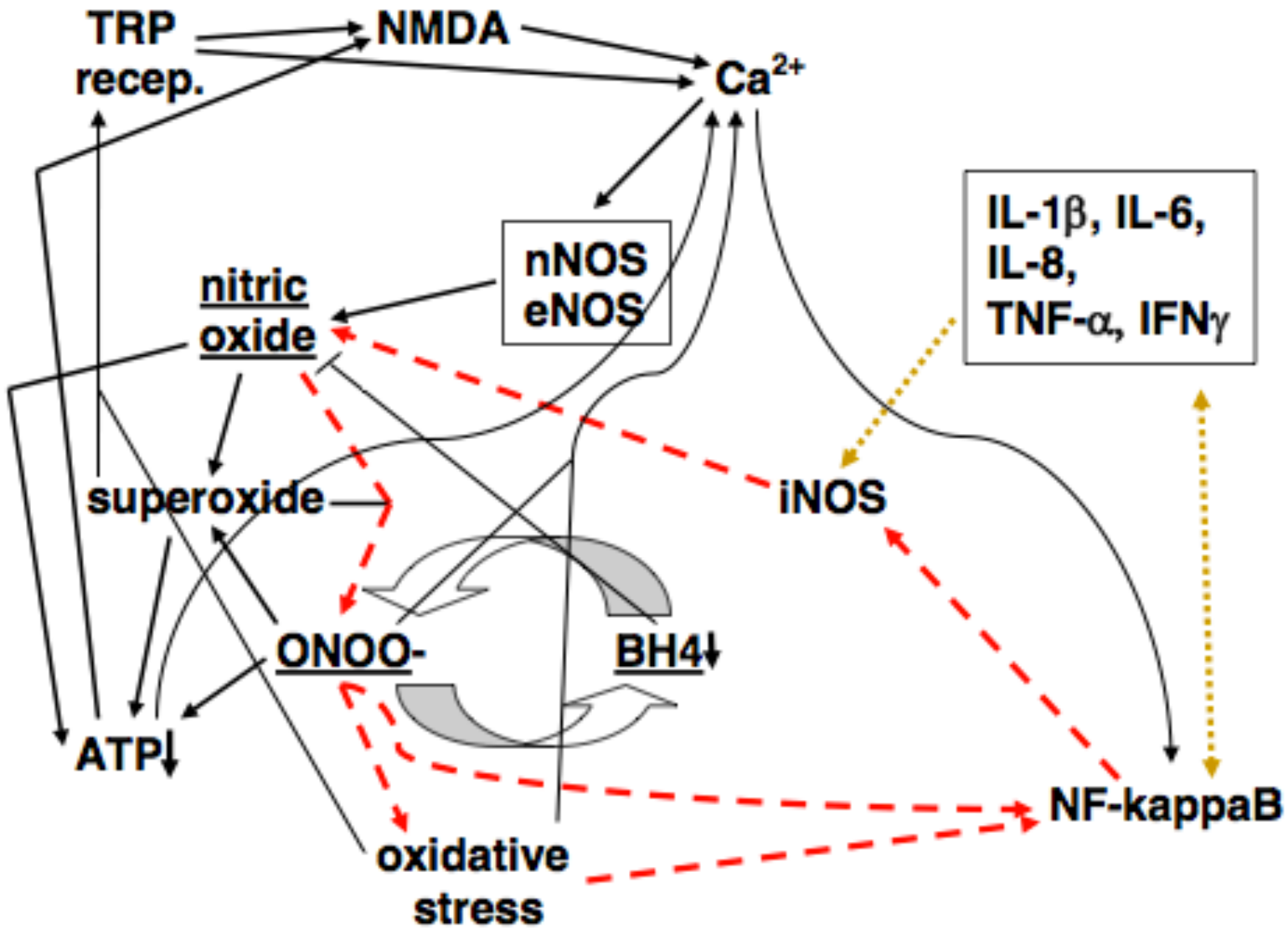
The last issue to be discussed here is the NO/ONOO(-) cycle, which was proposed, in my book, to be elevated in autism. Pall ML 2007, Explaining “Unexplained Illnesses”: … .

The NO/ONOO(-) is best explained in my heart failure paper: Pall ML 2013. The NO/ONOO- cycle as the central cause of heart failure. Int J Mol Sci. 2013 Nov 13;14(11):22274-330.

The cycle is a primarily local biochemical vicious cycle with a series of elements elevated through their mutual interactions.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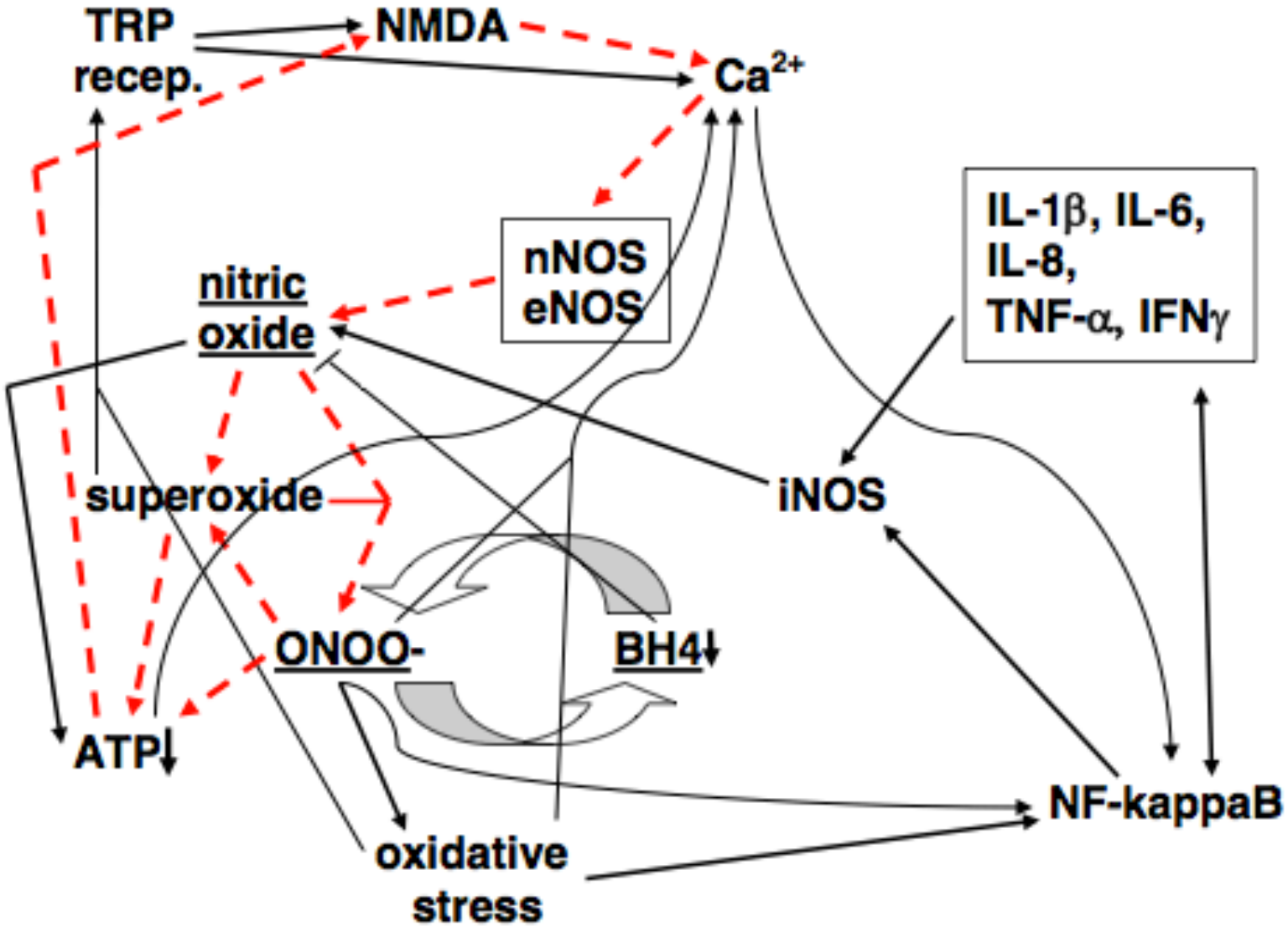
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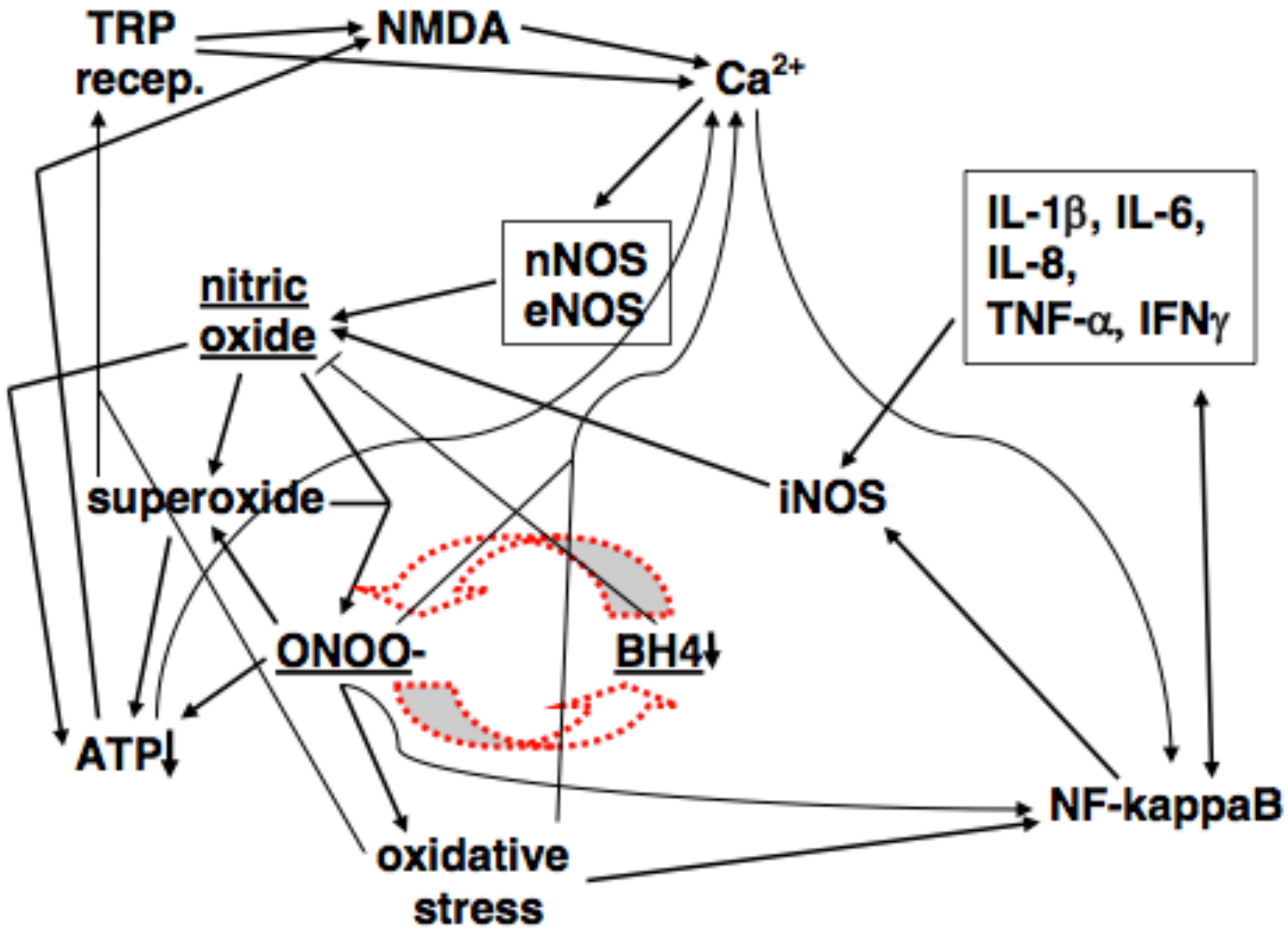
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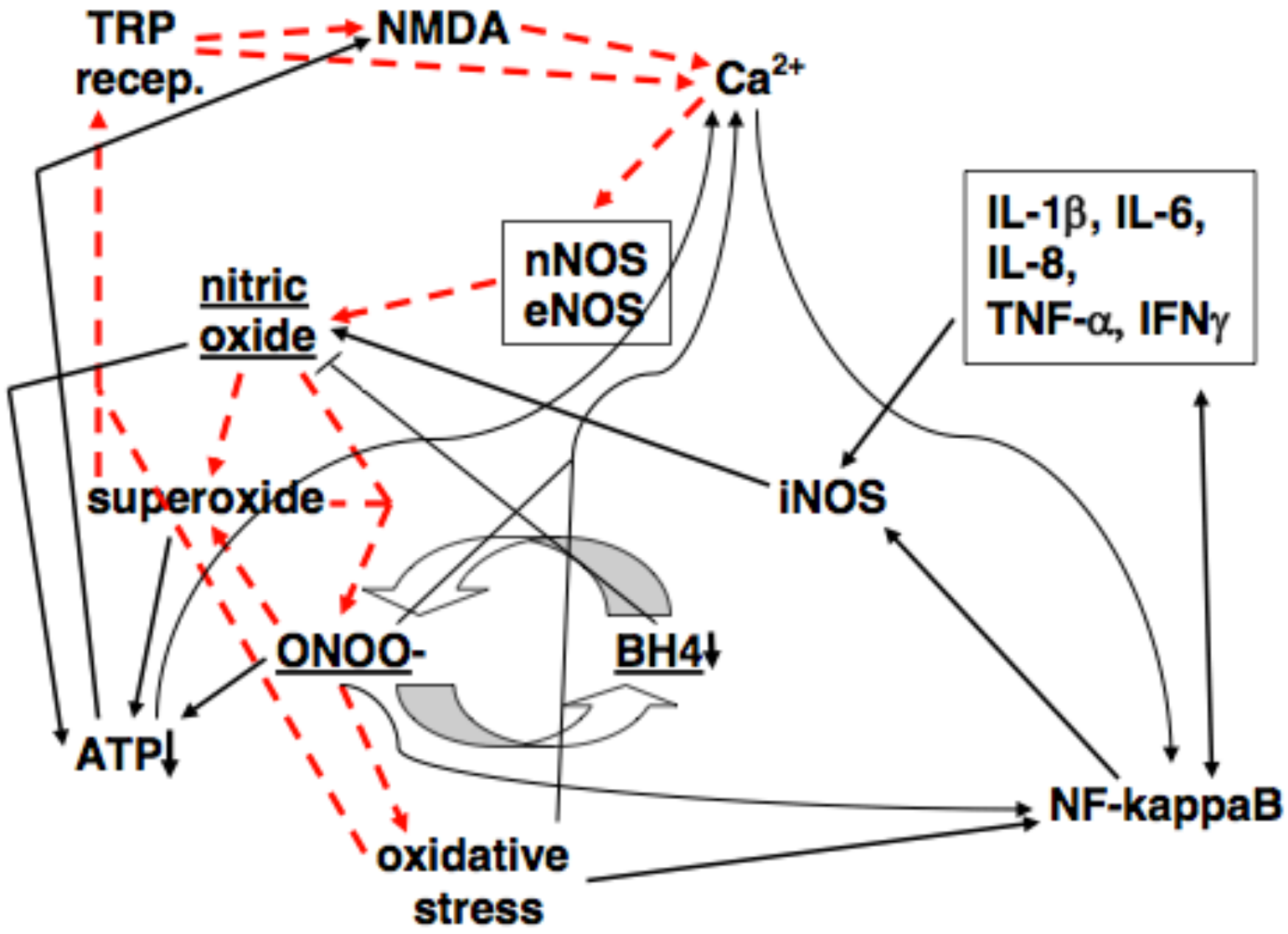
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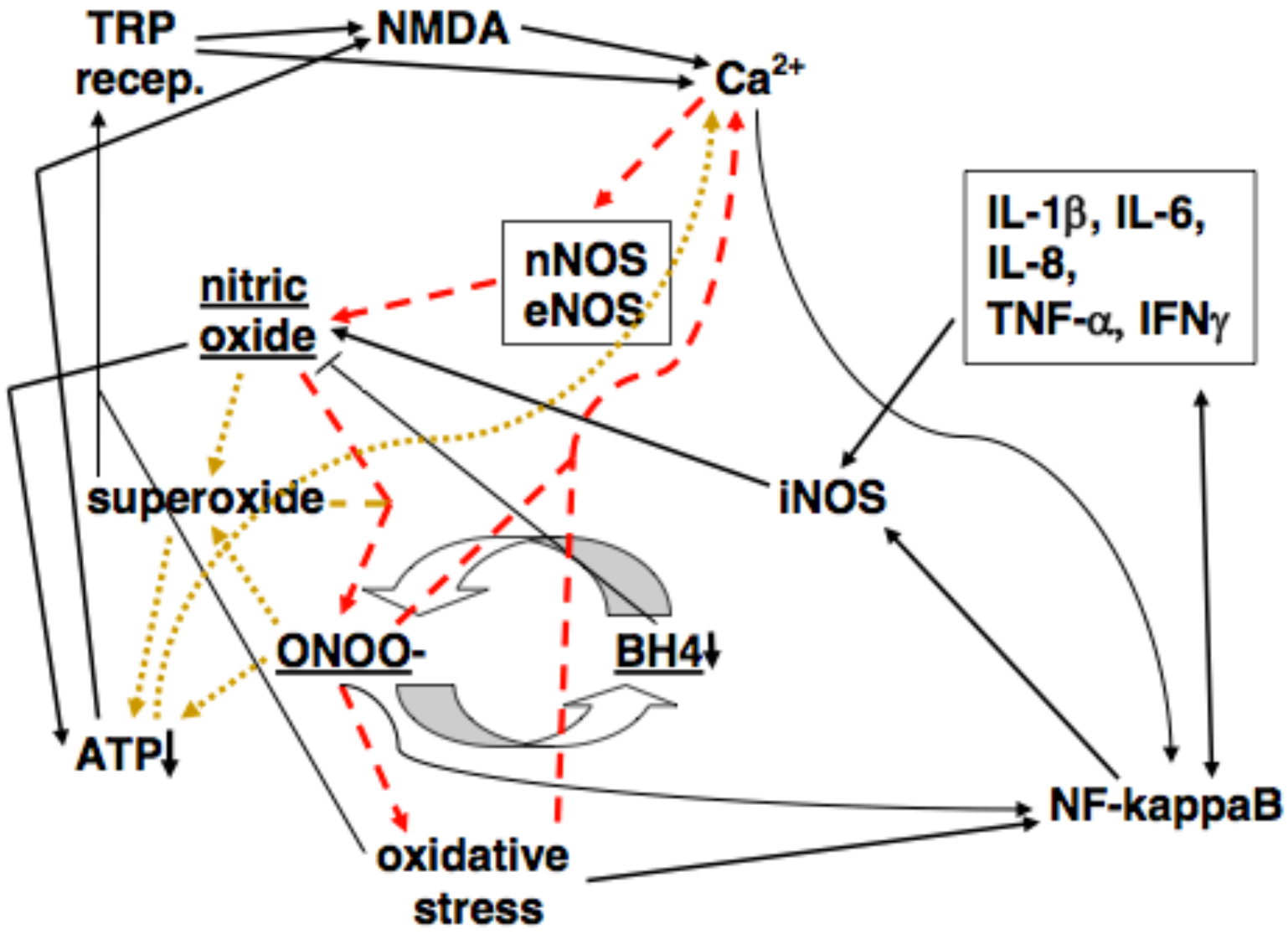
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Each of the elements of the cycle have been shown to have roles in causation of autism except possibly the TRP receptors where I am unaware of any data.

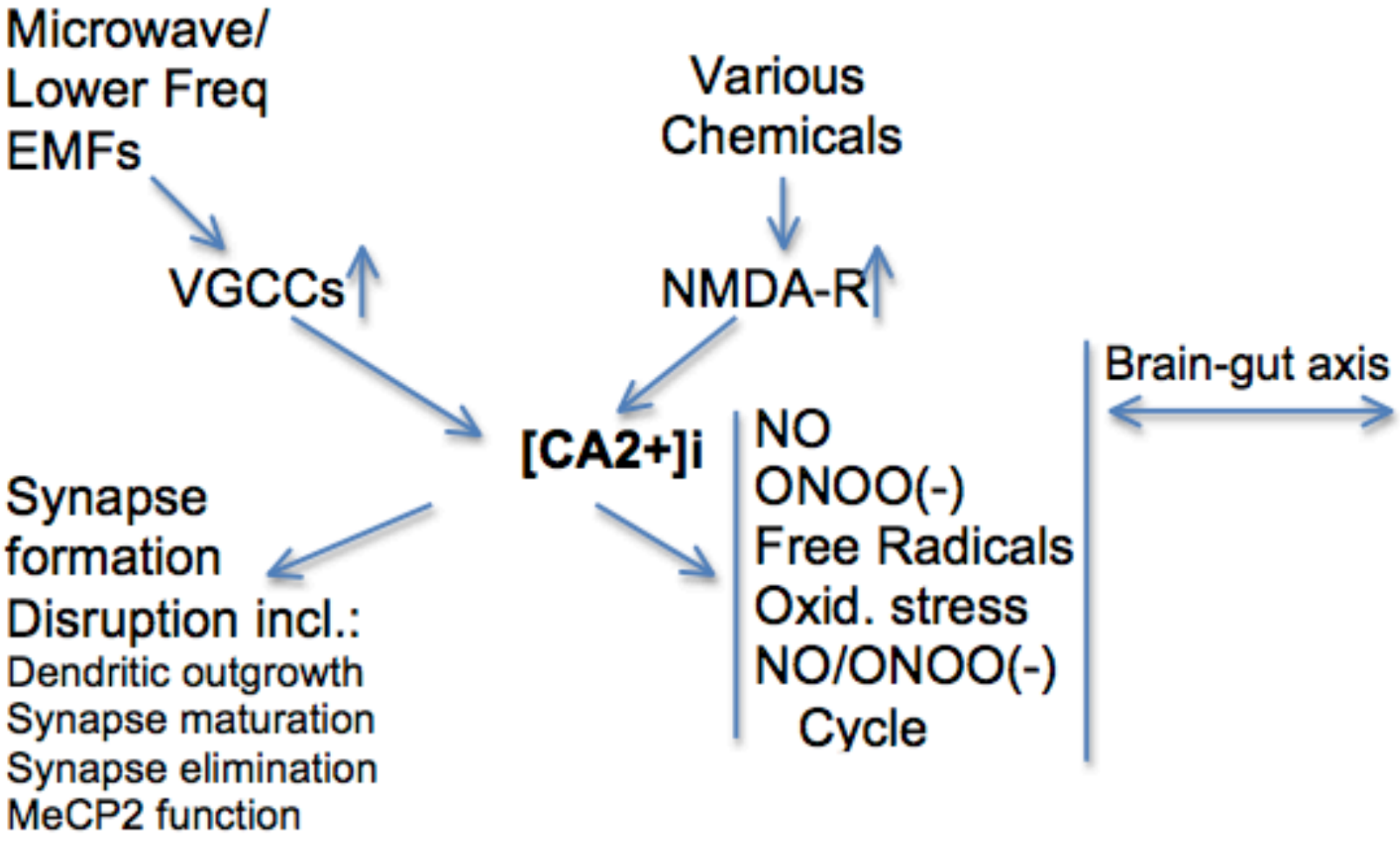
And lowering NO/ONOO(-) cycle elements is reported to be useful in therapy. For example, James et al reported that reduced folates and high concentrations of vitamin B12 are useful in autism treatment (Am J Clin Nutr 2009;89:425). This may be because reduced folate raises the powerful peroxynitrite scavenger 5-methyltetrahydrofolate (5-MTHF) **(see Rezk,** *FEBS Lett* 2003;555:601–605; **Antoniades**, *Circulation* 2006;114:1193–1201) . It may also be because the hydroxocobalamin form of B12 is a potent scavenger of NO and superoxide. (Has previously interpreted in terms of methylation.

Tetrahydrobiopterin (BH4) supplements have been shown to be useful in autism treatment (see Frye, N Amer J Med Sci 2014;7:93-96).

Raising Nrf2 activity may be a general way of lowering the NO/ONOO(-) cycle.

In general, then autism should be treated by lowering the NO/ONOO(-) cycle as well as by avoiding both EMF and chemical causal exposures.

Prevention should focus mainly on avoiding both EMF and chemical causal exposures.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