

*Please note this is a very early, partially-completed preliminary draft that is subject to revision based on further research.

Ketamine: a promising, potential treatment in late-stage Lyme neuroborreliosis
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I. Introduction

There is a general consensus that Lyme disease symptoms, whether acute or chronic, are driven largely by inflammation. In late-stage Lyme disease, the inflammatory cytokines of the early (innate) immune response – particularly tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) – are chronically activated, causing direct damage both within and outside the central nervous system (Habicht 1992; Ramesh et al. 2005; Kisand et al. 2007; Ramesh et al. 2008; Rupprecht et al. 2008). A high percentage of patients in the advanced stages of disease suffer from inflammation of white matter and cerebral hypoperfusion (Fallon & Nields 1994; Fallon et al. 1995; Sumiya et al. 1997; Fallon et al. 1997; Logigian et al. 1997; Plutchok et al. 1999; Heinrich et al. 2003; Fallon et al. 2003; Donta et al. 2006; Fallon et al. 2009). Besides direct damage, chronic inflammation also triggers excessive and imbalanced catabolism of tryptophan, causing tryptophan depletion, neurotoxicity, and a form of immunosuppression -- also found several forms of cancer and HIV infection -- that significantly impairs the effector T cell response required to attack both intracellular and extracellular infection (cites).

To date, no highly-effective means of rapid symptom relief and damage reduction has been available in late-stage Lyme disease. Although the disease appears at present to be incurable in its more advanced stages, symptom improvement can sometimes be achieved with antimicrobials. Yet such treatment often requires months or years of antimicrobial therapy (Cameron et al. 2004; Stricker 2007), causing Jarisch-Herxheimer reactions and general symptom exacerbation before any improvement is seen. In the most advanced cases of illness, antibiotics can be intolerable or even fatal (cites). And because lysis of *B. burgdorferi* triggers inflammation, the use of antibiotics without a potent cerebral anti-inflammatory adjunct is likely to cause significant impairment of effector T cell response in advanced, long-term Lyme neuroborreliosis.

Low-dose, IV ketamine is a promising option for rapid, highly-effective symptom relief, damage reduction, and prevention of T cell suppression in late-stage Lyme disease. Even in low doses, ketamine is a potent anti-inflammatory, inhibiting TNF-alpha and IL-6 (Royblat et al. 1998; Shapira et al. 2004; Bartoc et al. 2006; Yang et al. 2006; Beilin et al. 2007). Ketamine easily crosses the blood-brain barrier (Pai & Heining 2007), and has been shown using brain SPECT scans in human studies to improve cerebral blood flow in patients suffering from cerebral hypoperfusion (Wu et al. 2006; Guedj et al. 2007a; Guedj et al. 2007b).

Phase II clinical trials, small studies, and individual case reports have shown low-dose IV ketamine to be remarkably effective in reducing symptoms of several conditions that

appear in late-stage Lyme disease, including refractory depression (Berman et al. 2000; Kudoh et al. 2002; Zarate et al. 2006; Correll & Futter 2006; Liebrezn et al. 2007a; Liebrezn et al. 2007b; Goforth & Holsinger 2007; Paul et al. 2008; Stefanczyk-Sapieha et al. 2008; Matthew et al. 2009), fibromyalgia (Sørensen et al. 1995; Sørensen et al. 1997; Graven-Nielsen et al. 2000; Guedj et al. 2007a; Guedj et al. 2007b), and chronic regional pain syndrome (CRPS) (Harbut & Correll 2002; Correll et al. 2004; Goldberg et al. 2005; Wu et al. 2006; Kiefer et al. 2007; Villanueva-Perez et al. 2007; Jeffreys & Woods 2007; Koffler et al. 2007; Shirani et al. 2008) – although the most advanced cases of refractory CRPS may require anesthetic dosing (Kiefer et al. 2008a; Kiefer et al. 2008b; Becerra et al. 2009). Case reports have also shown ketamine to be effective in other syndromes that appear in Lyme disease, including status epilepticus, explosive disorder, MS-like syndrome, Parkinsonism, and stroke. [Add references for ketamine case reports and for appearance of these symptoms in Lyme disease. Explain why there is no basis for statements in some studies that these manifestations occur only rarely in Lyme disease]

Ketamine by IV infusion is the most effective delivery method. At subanesthetic doses, there is no respiratory depression. Subanesthetic doses are far lower than dosages used for anesthesia. The dissociative side-effects with subanesthetic dosing are minimal and transient, especially during short-duration infusions, such as used for depression. Some fluctuations in blood pressure are common. No serious adverse events have been reported in at least thousands of people who have received short duration, low-dose infusions.

In some cases, however – such as long-standing and severe chronic regional pain syndrome – a prolonged anesthetic dose infusion is required.

The published studies have demonstrated that ketamine does not broadly suppress the immune response unless infused in massive doses that have no clinical application. Ketamine rapidly concentrates in the brain, heart, and lungs, and is not associated with new infections or malignancies when infused at low doses, or for anesthesia. Upper respiratory tract infections that are manageable with antibiotics have been reported in prolonged high-dose infusions, i.e., the multi-day anesthetic dose ketamine comas that are sometimes required for long-standing and severe CRPS. Thus, unlike systemic steroids or various non-steroidal anti-inflammatory drugs, ketamine does not broadly suppress the immune response, and is not contraindicated in Lyme disease.

Animal studies demonstrate that ketamine is not neurotoxic except in massive doses that have no clinical application. Anesthetic doses, or prolonged subanesthetic doses, might be neurotoxic to human brain cells during the brain-growth spurt, when these cells are particularly vulnerable, i.e., during the third trimester through three years of age, but the significance of these studies is currently being debated.

II. The Clinical Evidence

A. Refractory depression

In 2000, Berman et al. first reported that nine patients meeting DSM-IV criteria for major depressive episodes ($n = 8$, recurrent unipolar major depression; $n = 1$, bipolar disorder, depressed) had significant improvement of symptoms within 72 hours after a low-dose ketamine infusion. Patients had one infusion of .5 mg/kg ketamine over 40 minutes, and one sham infusion of saline, separated by at least one week, in a randomized, double-blinded manner. Robust decreases in the Beck Depression Inventory (BDI) were

observed during active but not control treatment. The mean baseline BDI score was 29.5 (± 8.2 SD), and mean final score was 16.8 (± 10.5). Four of eight patients demonstrated 50% or greater decreases in Hamilton Depression Rating Scale (HDRS) scores during the 3-day follow-up period (i.e., 7, 30, 45, 47, 52, 52, 63, and 83% decreases), whereas only one of eight subjects undergoing sham infusion demonstrated a similar response (i.e., 3, 6, 7, 8, and 74% decreases and three subjects remained 4, 22, and 33% above baseline during the follow-up period; Fisher Exact, $p > .05$). Ketamine-induced mood improvement returned to baseline levels (i.e., clinical impression and HDRS within 5 points of baseline) one to two weeks after infusion. An exception, one subject demonstrating marked mood improvement (i.e., baseline HDRS of 41 points; Day 3 HDRS of 7 points), was started on antidepressant medication without having returned to his baseline level of depression two weeks after the ketamine infusion (HDRS, 15 points). Another patient, who was excluded from analyses because of completing only active treatment, experienced marked improvement in depressive symptoms (baseline HDRS 33, final HDRS 16).

In 2006, Zarate et al. reported results in a trial involving 18 subjects with DSM-IV treatment-resistant major depression. The mean length of illness was 23.7 years (± 12.5 SD). The HDRS was used as the primary outcome measure. Within 110 minutes after injection, subjects receiving .5 mg/kg ketamine over 40 minutes showed significant improvement in depression compared with subjects receiving placebo. One day after infusion, 71% of subjects (12 of 17) met response criteria of 50% or greater reduction in symptoms of depression, and 29% (5 of 17) were in remission. One week after infusion, 35% (6 of 17) maintained response. Two weeks after infusion, 12% (2 of 17) maintained response

Significant but less robust results were reported in 2009 from a double-blind, randomized trial involving 26 patients at the same dose/rate as in the prior trials (Mathew et al. 2009). Seventeen patients (65%) met response criterion ($\geq 50\%$ reduction from baseline on the Montgomery–Asberg Depression Rating Scale) 24 h following ketamine. Lamotrigine failed to attenuate the mild, transient side-effects associated with ketamine and did not enhance its antidepressant effects. Fourteen patients (54%) met response criterion 72 h following ketamine and proceeded to participate in a 32-d, randomized, double-blind, placebo-controlled, flexible-dose continuation trial of riluzole (100–200 mg/d). The main outcome measure was time-to-relapse. An interim analysis found no significant differences in time-to-relapse between riluzole and placebo groups, with 80% of patients relapsing on riluzole vs. 50% on placebo.

Several case reports have demonstrated the same, remarkable antidepressant effect as in the trials (Kudoh et al. 2002; Correll & Futter 2006; Liebreuz et al. 2007a; Liebreuz et al. 2007b; Goforth & Holsinger 2007; Paul et al. 2008; Stefanczyk-Sapieha et al. 2008).

In 2007, Charney et al. reported remarkable and sustained benefits in three highly-refractory depressed patients after four or five ketamine infusions over successive days, with benefits lasting up to 28 days. Kollmar et al. reported in 2008 that a refractory, psychiatric in-patient with ten recent suicide attempts, no response to pharmacological agents, and only partial response to ECT, obtained symptom relief for three days after one low-dose ketamine infusion. Two weeks after the first infusion, she was given a

second low-dose infusion, followed by regular dosing with oral memantine. The patient experienced remission shortly after the second infusion. She remained in remission six months later, when her case report was submitted for publication.

This author – who is being treated by an out-of-state doctor for severe Lyme-depression – has found that co-administration of memantine at a dose above 20 mg daily might interfere with ketamine's antidepressant action. This author has also found that taking 5 mg diazepam prior to a ketamine infusion prevents dissociative side-effects during infusion, and results in longer duration of antidepressant action. It is not uncommon to experience vivid nightmares for 1-3 nights after a ketamine infusion. Because stress induces inflammatory cytokine production, vivid nightmares likely interrupt ketamine's anti-inflammatory effects. After his first three infusions, this author found that although ketamine provided symptom relief within hours of infusion, the effect was aborted within one or two days if followed by stressful sleep. The author experiences almost no post-infusion nightmares by taking 5 mg diazepam at bedtime on the evening of an infusion and the following two evenings – with full remission from depression lasting for a week. This author was no longer taking memantine upon discovering that diazepam prevents ketamine-induced nightmares. It is not clear, therefore, whether memantine above 20 mg daily interfered with ketamine efficacy, or whether post-infusion nightmares were responsible for loss of efficacy during co-administration of memantine, prior to the addition of diazepam, in this sample-of-one.

B. Refractory fibromyalgia

Abstracts or partial abstracts with excerpts from articles and some of my preliminary comments – will add more analysis...

- Sörensen J, Bengtsson A, Bäckman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol.* 1995;24(6):360-5.

Pain intensity, muscle strength, static muscle endurance, pressure pain threshold, and pain tolerance at tender points and control points were assessed in 31 patients with fibromyalgia (FM), before and after intravenous administration of morphine (9 patients), lidocaine (11 patients), and ketamine (11 patients). The three different studies were double-blind and placebo-controlled. The patients were classified as placebo-responders, responders (decrease in pain intensity by > 50%) and non-responders. The morphine test did not show any significant changes. The lidocaine test showed a pain decrease during and after the infusion. The ketamine test showed a significant reduction in pain intensity during the test period. Tenderness at tender points decreased and endurance increased significantly, while muscle strength remained unchanged.

Twelve female fibromyalgia patients were included in the ketamine component of the study, but one patient was subsequently excluded because she did not complete the study. The mean age was 39 (range 23-53) years. The median duration of the fibromyalgia symptoms was 3 (range 3-28 years). Six patients regularly used analgesic drugs such as paracetamol or dextropropoxyphene. Eight patients were at work full- or half-time, one studied and two had a disability pension.

During a one-week period before the first infusion (ketamine or saline) was given, during the one-week between the two infusions, and during one-week after the second infusion was given, the patients scored global pain once a day, on a vertical Visual Analogue Pain scale (VAS), length 100 mm anchored at “No pain” and “Worst imaginable pain” An intravenous cannula was inserted on the dorsum of the hand or the forearm. The patients were given either 0.3 mg ketamine per kg body weight or the same volume of isotonic saline by infusion pumps over a ten minute period. [Low-dose and very short duration – I wouldn't expect results with this dosing regimen].

Pain intensity was scored one week before and after the infusion of saline and ketamine, respectively. Median (range) pain intensity score was 46 (range 2-93) and 50 (range 2-100) for saline. The corresponding scores for ketamine were 58 (range 2-100) and 53 (range 2-95).

There was a significant reduction of pain at the end of the ketamine injection ($p < 0.05$), and 20-80 min after the end of the injection compared to placebo ($p < 0.01$ - $p < 0.001$). The patients were classified as follows: 1 placebo responder, 8 responders, and 2 non-responders. Six of the responders had a reduction in pain for 2-7 days. Statistically significant differences were seen in pressure pain threshold and pain tolerance at tender points, control points, and muscle endurance. No statistically significant differences were seen in muscle strength after ketamine or after placebo. RPE scores at the end of the endurance tests were unchanged. No spontaneous adverse effects were reported during and after the placebo infusion. During ketamine administration, 10 of the patients reported side effects. These included a feeling of unreality in five patients, dizziness in four, and changes in hearing in three. These symptoms began shortly before the end of the injection and had disappeared after 15 min. [No benzodiazepine was used to reduce dissociative effects].

- Sörensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M. Fibromyalgia--are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. *J Rheumatol.* 1997 Aug;24(8):1615-21. [Need to get full article].

Pain was analyzed in patients with fibromyalgia (FM) in a randomized, double blind, crossover study using intravenous (i.v.) administration of different drugs. METHODS: In 18 patients with FM muscle pain to i.v. administration of morphine (0.3 mg/kg), lidocaine (5 mg/kg), ketamine (0.3 mg/kg) [low dose – duration?], or saline was studied. Spontaneous pain intensity, muscle strength, static muscle endurance, pressure pain threshold, and pain tolerance at tender points and non-tender point areas were followed. Drug plasma concentrations and effects on physical functioning ability score (FIQ) were recorded. A personality inventory (KSP) was used to related pain response to personality traits. RESULTS: Thirteen patients responded to one or several of the drugs, but not to placebo. Two patients were placebo responders responding to all 4 infusions. Three were nonresponders to all infusions. Seven of the responders had a reduction in pain for 1-5 days. Pressure pain threshold and pain tolerance increased significantly in responders. Plasma concentrations were similar in responders and nonresponders. FIQ values improved significantly after the ketamine infusion. Responders scored higher on KSP scales for somatic anxiety, muscular tension, and psychasthenia compared with healthy

controls. CONCLUSION: FM diagnosed according to the American College of Rheumatology criteria seems to include patients with different pain processing mechanisms. A pharmacological pain analysis with subdivision into responders and nonresponders might be considered before instituting therapeutic interventions or research.

- Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, Bengtsson M, Sørensen J, Johnson A, Gerdle B, Arendt-Nielsen L. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain*. 2000 Apr;85(3):483-91.

Fibromyalgia patients received either i.v. placebo or ketamine in two experiments. [Saline is not a “placebo” in a ketamine study, since it has no psychoactive effects.] Habitual pain intensity was assessed on a visual analogue scale (VAS). In the first experiment, 29 FMS patients received ketamine (0.3 mg/kg or isotonic saline to determine which patients were ketamine responders (>50% decrease in pain intensity at rest by active drug on two consecutive VAS assessments). [Too low a dose and too short duration of infusion for reducing FM effectively in many patients.] The screening involved two sessions separated by one week, during which the FMS patients received either placebo or ketamine. Before, 10, 20, 30, 40, 50, 60, 75, 90 and 150 min after infusion start, the patients gave VAS scores of their pain at rest. Fifteen out of 17 ketamine-responders were included in the second experiment, which assessed the effect of ketamine on somatosensory sensibility and referred pain. This experiment also involved two sessions separated by one week, in which 15 of the ketamine responders received either placebo or ketamine given over 30 min. The investigators were blinded as to infusion drug. Before, 10, 20, and 30 min after infusion start, the patients gave VAS scores of the ongoing pain. Somatosensory sensibility assessments (pressure algometry, cutaneous and i.m. electrical stimulation and saline-induced muscle pain) were performed before and after completed medication and took maximum 30 min (i.e. no assessment of somatosensory sensibility during infusion of ketamine or placebo). Before and after ketamine or placebo, experimental local and referred pain was induced by intramuscular (i.m.) infusion of hypertonic saline (0.7 ml, 5%) into the tibialis anterior (TA) muscle. The saline-induced pain intensity was assessed on an electronic VAS, and the distribution of pain drawn by the subject. In addition, the pain threshold (PT) to i.m. electrical stimulation was determined for single stimulus and five repeated (2 Hz, temporal summation) stimuli. The pressure PT of the TA muscle was determined, and the pressure PT and pressure pain tolerance threshold were determined at three bilaterally located tenderpoints (knee, epicondyle, and mid upper trapezius). VAS scores of pain at rest were progressively reduced during ketamine infusion compared with placebo infusion. Pain intensity (area under the VAS curve) to the post-drug infusion of hypertonic saline was reduced by ketamine (-18.4±0.3% of pre-drug VAS area) compared with placebo (29.9±18.8%, P<0.02). Local and referred pain areas were reduced by ketamine (-12.0±14.6% of pre-drug pain areas) compared with placebo (126.3±83.2%, P<0.03). Ketamine had no significant effect on the PT to single i.m. electrical stimulation. However, the span between the PT to single and repeated i.m. stimuli was significantly decreased by the ketamine (-42.3±15.0% of pre-drug PT) compared with placebo (50.5±49.2%, P<0.03) indicating a predominant effect on temporal summation. Mean pressure pain tolerance from the three paired tenderpoints was increased by ketamine (16.6±6.2% of pre-drug thresholds) compared with placebo (-2.3±4.9%, P<0.009).

The pressure PT at the TA muscle was increased after ketamine (42.4+/-9.2% of pre-drug PT) compared with placebo (7.0+/-6.6%, P<0.011). The present study showed that mechanisms involved in referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest were attenuated by the NMDA-antagonist in FMS patients.

- Guedj E, Cammilleri S, Colavolpe C, Taieb D, de Laforte C, Niboyet J, Mundler O. Predictive value of brain perfusion SPECT for ketamine response in hyperalgesic fibromyalgia. *Eur J Nucl Med Mol Imaging*. 2007a Aug;34(8):1274-9. Epub 2007 Mar 13.

We evaluated brain SPECT perfusion before treatment with ketamine, using voxel-based analysis. The objective was to determine the predictive value of brain SPECT for ketamine response.

Seventeen women with FM (48±11 years; ACR criteria) were enrolled in the study. Brain SPECT was performed before any change was made in therapy in the pain care unit. We considered that a patient was a good responder to ketamine if the VAS score for pain decreased by at least 50% after treatment. A voxel-by-voxel group analysis was performed using SPM2, in comparison to a group of ten healthy women matched for age.

Patients were treated for 10 days in the pain care unit with rising doses of subcutaneous ketamine (average maximum dose: 100 mg) [very unlikely to be as effective in reducing cerebral hypoperfusion as i.v. ketamine]. Eleven patients were considered as “good responders,” with a decrease in pain intensity, evaluated by visual analog scale (VAS), greater than 50%. On the other hand, six patients were considered as “poor responders”. Responder and non-responder subgroups were similar in terms of pain intensity before ketamine.

In comparison to responding patients and healthy subjects, non-responding patients exhibited a significant reduction in bilateral perfusion of the medial frontal gyrus. This cluster of hypoperfusion was highly predictive of non-response to ketamine (positive predictive value 100%, negative predictive value 91%). Conclusion: Brain perfusion SPECT may predict response to ketamine in hyperalgesic FM patients.

[But see companion study below – another analysis of the same patients. A plausible explanation is simply that the nonresponders had more widespread hypoperfusion, and that subcutaneous ketamine did not adequately penetrate all affected areas of the brain in the nonresponders].

- Guedj E, Cammilleri S, Colavolpe C, de Laforte C, Niboyet J, Mundler O. Follow-up of pain processing recovery after ketamine in hyperalgesic fibromyalgia patients using brain perfusion ECD-SPECT. *Eur J Nucl Med Mol Imaging*. 2007a Dec;34(12):2115-9. Epub 2007 Sep 21.

The aim of this study was to determine whether the follow-up of pain processing recovery in hyperalgesic fibromyalgia (FM) could be objectively evaluated with brain perfusion ethyl cysteinate dimer single photon computerized tomography (ECD-SPECT) after administration of ketamine.

In comparison to baseline brain SPECT, midbrain rCBF showed a greater increase after ketamine in the responder group than in the nonresponder group ($p_{cluster}=0.016c$) in the 17 subjects described in our companion study. In agreement with the clinical response, the change in midbrain rCBF after ketamine was highly correlated with the reduction of VAS pain score ($r=0.7182$; $p=0.0041$).

This prospective study suggests that blockade of facilitatory descending modulation of pain with ketamine can be evaluated in the periaqueductal grey with brain perfusion SPECT.

C. Refractory chronic regional pain syndrome

In individual case reports and small studies, chronic regional pain syndrome has been treated successfully with prolonged infusions of subanesthetic dose ketamine, and with prolonged anesthetic dose infusions in the most severe cases.

One of the first case reports, published in 2002, involved a 44-year old woman with a nine-year history of chronic right leg and foot pain that began without any apparent triggering event. The patient required a walking cane, and had been on permanent disability for the previous seven years. The patient had tried numerous therapies, some of which provided partial and merely ephemeral relief. When presenting for her consult regarding ketamine treatment, she described a constant burning pain in her right leg and foot that ranged in intensity from 4–8/10. She stated that the pain was prominent on the anterior surface of her ankle and lower leg, and the dorsal and plantar surfaces of her right foot and toes. Walking any distance was stated to be difficult because, “the percussion” of her foot to the floor “was extremely painful.” While riding in a car, the patient needed to cushion her leg to ease the vibration. Her car was altered to have the accelerator pedal moved to the left side, even though she did not drive very often. She described a “deep bone-crushing pain” in her affected area. She also reported that the following experiences were very painful for her: “a dog licking her leg,” “a child touching her skin,” “shaving her leg,” and “a gentle wind blowing on her skin.” She also noted that clothes rubbing against her skin were very painful and that she preferred to have her blanket supported above her leg while she was sleeping. She also preferred to roll up her right pant leg so it was not touching her skin. She also commented that loud noises made her pain worse, and that she was unable to wear closed-in shoes. Her right ankle was notably swollen and about 20% larger than her left ankle. She stated this swelling was common and was reduced in the early morning when she awoke after having had her feet up in bed.

An infusion of ketamine was started at a rate of 10 mg/hr and increased by 10 mg/hr every 2 hours as tolerated up to a maximum infusion rate of 30 mg/hr. The infusion was continuous during daytime and nighttime for six days, with tapering down of dose to zero on the sixth day. Given the patient’s weight of 306 pounds, the i.v. infusion rate of 30 mg/hr equaled 0.22 mg per kilogram body weight per hour. Further increases were not pursued as the patient wished to remain “in control” and was beginning to perceive a mild feeling of inebriation. Overall, the patient’s pain level remained unchanged the first day with a VAS score of 4.5–5/10. Her medications included sustained-release

oxycodone 40 mg twice daily, and warfarin 10 mg daily. She remained on i.v. ketamine 30 mg/hr for seven days. At the end of the third day, her VAS score was 3/10. At the end of the fourth day, her VAS score was 0.4/10, and she had reduced oxycodone to 10 mg twice daily. During the fifth day, her VAS score reached 0/10, and remained at that level for the rest of the infusion. During day 6, the rate of infusion was reduced to 20 mg per hour, and then 10 mg per hour, and then to zero. Five months later, the patient was still pain-free

In this case report, the patient did not experience dysphoria, sedation, or hallucinations. The patient was carefully titrated with slowly increasing doses of ketamine up to that level which just began to make her feel mildly inebriated (Harbut et al. 2002).

In 2004, Correll et al. published a retrospective study of 33 patients with diagnoses of CRPS patients who had undergone ketamine treatment at least once. Due to relapse, 12 of 33 patients received a second course of therapy, and two of 33 patients received a third. Generally, the ketamine infusions were started at a rate of 10mg/hr. The rate was increased in small increments, as tolerated, until the onset of what patients typically describe as a feeling of inebriation or its equivalent. The onset of this particular CNS symptom appeared to be necessary to help guide the authors to reach what they believe is, or is close to, the minimally effective infusion rate for ketamine. Once the effective rate was achieved, it was continued as long as the patient tolerated the drug and continued benefit was observed. If unacceptable side effects were noted, the rate was decreased or the infusion was temporarily discontinued. The highest tolerated dose producing analgesia (i.e., without unacceptable side effects) was continued for the duration of the infusion. The average maximum infusion rate was 23.4mg/hr. During 78% of all infusion cycles, patients received ketamine at a rate ≤ 25 mg/hr. Comparing the percentage distribution of the maximum ketamine dosing, patients given a second infusion cycle received a slightly higher infusion rate of ketamine than during the first round of therapy, that is, a slight shift of the maximum from 15–20 to 20–25mg/hr. Due to insufficient responses in three of the patients, the maximum infusion rates were increased to 50, 46, and 40mg/hr, respectively. This increase was done in an attempt to maximize any potential benefit for the patients. In two other patients, there was no response to therapy despite ketamine titration up to 50 mg/hr. These two patients, who were the only non-responders, were the only patients in the study who were taking morphine -- in high doses.

The degree of relief obtained following the initial course of therapy was impressive (N = 33); there was complete pain relief in 25 (76%), partial relief in six (18%), and no relief in two (6%) patients. The degree of relief obtained following repeat therapy (N = 12) appeared even better, as all 12 patients who received second courses of treatment experienced complete relief of their CRPS pain. The duration of relief was also impressive, as was the difference between the duration of relief obtained after the first and after the second courses of therapy. In this respect, following the first course of therapy, 54% of 33 individuals remained pain free for ≥ 3 months and 31% remained pain free for ≥ 6 months. After the second infusion, 58% of 12 patients experienced relief for ≥ 1 year, while almost 33% remained pain free for >3 years. The most frequent side effect observed in patients receiving this treatment was a feeling of inebriation. Hallucinations occurred in six patients. Less frequent side effects also included complaints of

lightheadedness, dizziness, and nausea. In four patients, an alteration in hepatic enzyme profile was noted; the infusion was terminated and the abnormality resolved thereafter.

In 2005, Goldberg et al. published an open label, prospective study involving 40 patients (36 female; four male) diagnosed with CRPS I or II, demonstrating that a daily four-hour ketamine infusion escalated from 40-80 mg per infusion (i.e., from 10 to 20 mg per hour) over ten days (during a two week period, excluding weekends) can result in a significant reduction of pain with increased mobility and a tendency to decreased autonomic dysregulation. [Low dose and short infusions, considering the patient population] The patients in this study had a history of longstanding or rapidly spreading CRPS, refractory to conventional therapy which included: a) physical therapy; b) drug combinations of NSAIDS, tricyclic antidepressants, anticonvulsants, and opioids; c) sympathectomy either by intermittent superior cervical or paravertebral block, or five days intrapleural or epidural block. Four patients had failed a therapeutic trial of dorsal column stimulation. The patients referred for therapy were diagnosed to have persistent and/or progressive severe disease, and no known contraindications to ketamine, clonidine, or midazolam. Prior to entering the ketamine protocol, these patients had been treated for a period of three months to three years.

On a 0-10 point scale, the mean reduction in pain intensity was 7.54 ± 1.93 , and the mean percentage of overall pain relief was 43.61 ± 27.79 [why such a large standard deviation?] by the tenth day compared to baseline.

Each patient also received clonidine 0.1 mg orally prior to the infusion to prevent a hypertensive response and possible muscle pain, as well as midazolam (2-4 mg) to relieve anxiety. Overall, side effects were minimal with 4/40 and 5/40 patients reporting headaches and restlessness respectively with infusion. There were no episodes of desaturation ($SpO_2 < 93\%$) and 3/40 patients experienced a 20% increase over their baseline heart rate during the infusion of ketamine. None of these side effects required intervention. No patient reported hallucinations or nightmares over the duration of exposure to ketamine.

At the time of publication, four patients (10%) had a return of “worst” and “punishing” pain to pre-infusion levels by two weeks post treatment. Twenty-five patients (62%) had at least a 70% reduction of “worst” and “punishing” pain for six weeks and were back to baseline pain levels by nine weeks post treatment. Eight patients (20%) had a >70% reduction in those same pain measures for 11-12 weeks. Three patients remained CRPS free at 15 months following treatment.

[Finish summarizing the studies...]

In another study, 16 of 20 CRPS patients remained symptom-free six months after a five-day anesthetic-dose infusion (Kiefer et al. 2008). . . Many of these patients developed chronic CRPS after trauma or surgery. Both trauma and surgery are known to activate latent infection (cites), while the latter, of course, is associated with high infection rates. One possible explanation is that by reducing immunosuppression, ketamine enabled these patients to mount an adequate immune response to clear undiagnosed, intracellular CNS infections. Another possible explanation is that a high dose of ketamine suppresses

inflammatory mediators for lengthy periods. To be expanded... [Need to follow up to see whether these patients did in fact relapse at some point. If that is the case, will revise this section...]

D. Case reports in other psychiatric and neurodegenerative disorders

Case reports have also demonstrated ketamine's efficacy in several other psychiatric and neurodegenerative disorders, including status epilepticus, explosive disorder, multiple sclerosis, Parkinsonism, traumatic brain injury, and post-ischemic stroke (cites).

* * * * *

E. Dosing

Ketamine by IV infusion is the most effective delivery method. The dose for refractory depression is usually 0.5 mg/kg over 40 minutes. This is much lower than the anesthetic dose, which is usually started in the range of 1-4.5 mg/kg over 60 seconds. At the subanesthetic dose, there is no respiratory depression, and there is no need for an anesthesiologist. The dissociative side-effects at the subanesthetic dose are minimal and transient in short-duration infusions, such as used for depression. Dissociative effects increase with duration of low-dose infusion. Some fluctuation in blood pressure is common. No serious adverse events have been reported in at least 500 people who have received low-dose infusions.

Repeating low-dose infusions over several successive days, increasing the dosing time of infusions, or increasing dosage has a cumulative effect on duration of symptom relief (aan het Rot et al. 2010). Patients with refractory depression ...

Ketamine dosing varies widely depending on symptoms being addressed. 0.5 mg/kg over 40 minutes often works for depression, with anti-depressant action lasting between 3 days and two weeks. In chronic regional pain syndrome, continuous infusion between .25mg/kg and .5mg/kg per hour, for ten hours a day, over a five day period, is often required, and can result in months of symptom relief.

Oral ketamine is only 25% bioavailable, as compared to 100% bioavailability for IV ketamine. But oral ketamine is also somewhat effective ... It appears, however, that oral dosing of 800 mg or more daily over several months presents a risk of urinary tract damage (Storr & Quibell 2009).

III. Pathogenicity in Advanced Lyme Disease

A. Inflammation

The recently-discovered toll-like receptors (TLRs) play a critical role in pathogenesis in advanced Lyme disease. TLRs are one of the key mechanisms used by the innate immune response to detect the invasion of pathogenic microorganisms. However, TLRs are also located on T cells, and play a role in the adaptive immune response (Kabelitz 2007), including chronic inflammatory joint disease caused by *B. burgdorferi* in mice (Sobek et al. 2004). TLRs

recognize specific molecular patterns that are present in microbial components. To date, 13 TLRs have been identified in mammals (Akira et al. 2004; Gay et al. 2006; Takeda et al. 2005; Liew et al. 2005).

Over-expression of TLR2 is strongly implicated in late-stage Lyme disease. Surface lipoproteins of *B. burgdorferi* interact with TLR2/TLR1 heterodimers (Dennis et al. 2009; Alexopoulou et al. 2002; Takeda et al. 2001) activating genetic transcription by nuclear factor kappaB (NF-kappaB), which results in release of inflammatory cytokines, including TNF-alpha and IL-6 (Dennis et al. 2009; Hirschfeld et al. 1999). TLR2 knockout mice, and humans with the Arg753Gln polymorphism in the TLR2 gene, are protected from developing late-stage Lyme disease due to reduced signaling via TLR-2/TLR-1 (Schröder et al. 2005). Moreover, monocytes from patients with chronic Lyme disease exhibit a significantly stronger TNF-alpha response to LPS as well as to borrelia antigen than monocytes from patients with early Lyme disease and healthy controls (Kisand et al. 2007) [double check to see if this study involved TLR2 analysis].

TLR2 is required for the innate, but not the acquired host defense to *B. burgdorferi* in mice. (Wooten et al. 2002). Inflammatory cytokine production predominates in early Lyme disease in patients with erythema migrans, with low levels of the anti-inflammatory cytokine IL-10 (Glickstein et al. 2003). Yet *B. burgdorferi* can also suppress the early inflammatory response by upregulating IL-10, helping enable the infection to disseminate (Lazarus et al. 2008; Diterich et al. 2001; Giambartolomei et al. 1998).

Although *B. burgdorferi* does not contain LPS, phagocytosis of *B. burgdorferi* by primate microglia enhances not only the expression of TLR1, -2, and -5, but also that of TLR4 -- perhaps as a result of TLR cross-talk -- all of which elicits an inflammatory response (Bernardino et al. 2008).

A recent in vitro mouse macrophage study may explain why TLR2 remains chronically activated in advanced Lyme disease. (Sahay et al. 2009). Current thinking emphasizes the primacy of CD14 in facilitating recognition of microbes by certain TLRs to initiate proinflammatory signaling events and the importance of p38-MAPK in augmenting such responses. CD14 is expressed by macrophages and neutrophils. Yet live *B. burgdorferi* triggers an inflammatory response in CD14-deficient mouse macrophages. The deficiency of CD14 alters PI3K/AKT/p38-MAPK signaling, compromising the induction of tolerance and impairing negative regulation of TLR2 in mouse macrophages. Impairment of this signaling may underlie chronic inflammation and activation of TLR2 in humans. Inhibiting PI3K in CD14-deficient mouse macrophages reduces TNF-alpha response to *B. burgdorferi*.

Moreover, CD14-deficient macrophages are able to internalize live *B. burgdorferi*, but killing of the internalized microbe is impaired.

CD14 deficiency results in increased localization of PI3K to lipid rafts, hyperphosphorylation of AKT, and reduced activation of p38. Such aberrant signaling leads to decreased negative regulation by SOCS1, SOCS3, and CIS, thereby compromising the induction of tolerance in macrophages and engendering more severe and persistent inflammatory responses to *B. burgdorferi*.

B. Kynurenine pathway-mediated excitotoxicity and oxidative stress

Aside from causing direct inflammatory damage, inflammatory cytokines fuel neurotoxicity by activating enzymes that cause excessive or pathogenically imbalanced catabolism of CNS L-tryptophan (TRP) and its metabolites -- known as kynurenines -- via the kynurenine pathway. TRP is one of the ten essential amino acids, is involved in protein synthesis, and acts as a precursor of many biologically active substances (Robotka et al. 2008). When significantly elevated in the CNS, the tryptophan metabolite quinolinic acid (QUIN) is neurotoxic (Guillemin et al. 2005; Halperin & Heyes 1992). And even moderate elevation of the tryptophan metabolite 3-hydroxykynurenine (3-OH-KYN) causes neurotoxicity (Wichers & Maes 2004; Moroni et al. 1999; Okuda et al. 1998). Cerebrospinal fluid levels of QUIN are significantly elevated in disseminated and late-stage Lyme disease -- dramatically in Lyme neuroborreliosis, and to a lesser degree in Lyme encephalopathy without intra-CNS inflammation (Halperin & Heyes 1992). Likewise, increased concentrations of neopterin and of the tryptophan degradation product, L-kynurenine, are detected in the cerebrospinal fluid of patients with acute Lyme neuroborreliosis (Gasse et al. 1994; Fuchs et al. 1991). No studies of CNS levels 3-OH-KYN in *B. burgdorferi* infection have been published.

CNS inflammation and kynurenine imbalances are found in several psychiatric and neurodegenerative syndromes, including depression (Raison et al. 2010; Maes et al. 2009; Myint et al. 2007; Wichers et al. 2005;), schizophrenia (cites), Parkinsonism (elevated 3-OH-KYN, reduced KYNA) (Mogi et al. 1994a; Mogi et al. 1994b; Blum-Degen et al. 1995; Muller et al. 1998; Mirza et al. 2000; Nagatsu et al. 2000; Hald & Lotharius 2005; Mosley et al. 2006), early-stage Huntington's disease (elevated 3-OH-KYN and QUIN) (Heyes et al. 1992a; Guidetti & Schwarcz 2003;), AIDS dementia (elevated QUIN) (Heyes et al. 1992a), autism and autistic spectrum disorders (elevated brain levels of TNF- α , IL-6, IL-8, and IFN- γ (cites). . .

Parkinsonism typically involves CNS inflammation (Mirza et al. 2000), with increased levels of TNF- α , IL-1 beta, IL-3, and IL-6 in CSF, and in the postmortem striatum and substantia nigra.50-56 Likewise, elevated levels of 3-OH-KYN are found in the CSF, and in the postmortem brain.59-66 Excitotoxic overactivation of the NMDA receptors in Parkinsonism is mediated in large part by low levels of kynurenic acid, a tryptophan metabolite that is the only known endogenous NMDA receptor antagonist. (Ogawa et al. 1992; Stone 2001a; Erhardt et al. 2009; Stone 1993; Stone 2001b; Sas et al 2007; Németh et al. 2006; Borlangan et al. 2000). Kynurenic acid and 3-OH-KYN are both synthesized from N-formylkynurenine (N-formyl-KYN), but involving different enzymes.

[Will add more detail for several psychiatric and neurodegenerative disorders].

Tryptophan is metabolized in several pathways. The most widely known is the serotonergic pathway, which is active in platelets and neurons, and yields 5-hydroxy-TRP, and then serotonin. TRP is also the precursor of the pineal hormone, melatonin. But ninety five percent of TRP within the brain is catabolized through the kynurenine pathway (Robotka et al. 2008). In this pathway, the enzyme indoleamine-2,3-dioxygenase (IDO) catalyzes the first step in tryptophan degradation. (See figure 1).

Elevated TNF- α increases production of the cytokine IFN- γ , which exerts a powerful stimulus on IDO. Excessive or pathogenically imbalanced catabolism through

the kynurenine pathway results in production of neurotoxic levels of 3-OH-KYN and QUIN (Robotka et al. 2008; Vamos et al. 2009; Guillemain et al. 2003; Guillemain et al. 2001), and insufficient levels of the only known endogenous NMDA receptor antagonist, kynurenic acid (KYNA).

[Expand to include other inducers of IDO]

In the human brain, IDO is expressed in microglia (Guillemain et al. 2003; Wichers et al 2005; Vamos et al. 2009) and in part in the astrocytes (Guillemain et al. 2001; Vamos et al. 2009). Infiltrating macrophages and resident microglia are the major source of QUIN within the brain (Heyes et al. 1992b; Espey et al. 1997; Guillemain et al. 2001; Guillemain et al. 2005). Although the kynurenine pathway is fully expressed in both microglia and macrophages, for unknown reasons, macrophages have a much greater capacity of producing QUIN than microglia (Guillemain et al. 2003; Guillemain et al. 2005). Human astrocytes are not able to produce QUIN, but are capable by themselves of producing L-kynurenine, which is the substrate for 3-OH-KYN synthesis. IDO activation by infiltrating macrophages is particularly damaging because IL-4, which downregulates IDO activity, is found in low levels in the brain [verify with more research] (Wesselingh et al. 1993).

The role of 3-OH-KYN in brain physiology is unknown, but in primate lenses it appears to play a role in protecting the retina from UV radiation (Vamos et al. 2009; Vasquez et al. 2002). Even relatively low levels of 3-OH-KYN may cause neurotoxicity by inducing oxidative stress and neuronal apoptosis (Wichers et al. 2004; Moroni et al. 1999; Okuda et al. 1998). QUIN acts as an agonist at the *N*-methyl-D-aspartate (NMDA) receptor subgroup containing subunits NR2A and NR2B. Significant elevation of CNS QUIN causes a form of neurotoxicity -- known as excitotoxicity -- by over-activating NMDA receptors in the brain hippocampus. This allows excessive influx of calcium into neurons (Robotka et al. 2008; Vamos et al. 2009), inhibits glutamate uptake into the synaptic vesicle, leading to excessive microenvironment glutamate concentrations (Robotka et al. 2008; Vamos et al. 2009), and promotes lipid peroxidation (Robotka et al. 2008; Rios & Santamaria 1991; Behan & Stone 2002). Elevated QUIN might also potentiate its own neurotoxicity and that of other excitatory amino acids in the context of energy depletion (Robotka et al. 2008; Schurr & Rigo 1993; Bordelon et al. 1997; Schuck et al. 2006). Moreover, 3-OH-KYN and QUIN appear to cause neurotoxicity in a synergistic manner: co-injection of these kynurenines into the striatum of rats causes substantial neuronal loss in doses that cause no or minimal neurodegeneration when injected alone (Robotka et al. 2008; Guidetti et al. 1991). QUIN-induced damage is also potentiated by reactive oxygen radicals (Behan et al. 2002; Stone & Darlington 2002). Because KYNA is an NMDA receptor antagonist, insufficient levels of this kynurenine are functionally similar to elevated levels of QUIN.

Glutamate, like QUIN, is an NMDA receptor agonist. In the mammalian CNS, glutamate is the main excitatory neurotransmitter, and is essential for normal brain functions (Ozawa et al. 1998). Glutamate accumulation into synaptic vesicles is the initial critical step for physiologic glutamatergic neurotransmission (Özkan & Ueda 1998). However, overstimulation of the glutamatergic system, which occurs when extracellular glutamate levels increase over the physiological range, is involved in many acute and chronic brain diseases due to excitotoxicity (Maragakis & Rothstein 2004). elevated extracellular QUIN stimulates synaptosomal glutamate release (Tavares et al. 2002) and inhibits glutamate uptake into astrocytes (Tavares et al. 2002). Moreover, extracellular elevation of excitotoxic QUIN results in overlapping glutamate excitotoxicity. Elevated extracellular QUIN and

glutamate are found in ., including epilepsy (Meldrum 1994), amyotrophic lateral sclerosis (ALS) (Spreux-Varoquaux et al., 2002), probably Parkinsonism (Maragakis & Rothstein 2004), perhaps Huntington's (Maragakis & Rothstein 2004). In order to avoid excessive increases of extracellular glutamate and glutamatergic excitotoxicity, glutamate must be taken up from synaptic cleft to the cytosol of glial and neuronal cells to be stored into synaptic vesicles on neuronal terminals (Robinson & Dowd, 1997; Anderson and Swanson, 2000; Fykse & Fonnum, 1996; Wolosker et al., 1996). The most significant mechanism for maintaining extracellular glutamate levels below neurotoxic concentrations is uptake by astrocytes. (Rothstein et al., 1996). However, elevated extracellular QUIN stimulates synaptosomal glutamate release (Tavares et al. 2002) and inhibits glutamate uptake into astrocytes (Tavares et al. 2002). Thus, excessive extracellular concentration of excitotoxic QUIN results in overlapping glutamate excitotoxicity.

IV. IDO/kynurenine pathway-mediated immune dysregulation

A. Simplified and selective overview of some key components in adaptive immune response

Suppression of CD4+ and CD8+ effector T cells and/or induction of T regulatory cells caused by overactivation of IDO and concomitant activation of the kynurenine pathway is likely to be a significant immunosuppressive mechanism in advanced Lyme disease, and may also contribute to autoimmune reactions.

A simplified overview of some key components in the adaptive immune response helps in understanding the potential effects of IDO/kynurenine pathway-mediated dysregulation of the immune system.

During the early (innate) immune response, macrophages and dendritic cells phagocytize extracellular pathogens and also cells that are infected by microbial pathogens (intracellular infection). Dendritic cells are an important link between the innate and adaptive immune response. They present antigen-derived molecules from phagocytized microbes to T cells in the peripheral lymphoid organs, i.e., the lymph nodes, the spleen, and the mucosal and cutaneous immune systems. For this reason, they are one of the most important types of antigen presenting cells (APCs).

Dendritic cells carrying class I major histocompatibility (MHC-I) molecules from phagocytized intracellular microbes are recognized only by cytotoxic CD8+ T cells. Cytotoxic T cells recognize and attack only intracellular infections.

[How are CD8+ Tregs differentiated? By characteristics of dendritic cells carrying MHC-I molecules?]

Dendritic cells carrying MHC-II molecules from phagocytized extracellular microbes are recognized only by CD4+ T cells. Depending, among other things, on characteristics of the dendritic cells that deliver MHC-II molecules to the peripheral lymphoid organs, CD4+ T cells differentiate into T helper 1 (Th1) cells, T helper 2 (Th2) cells, T helper 17 (Th17) cells, or T regulatory cells (Tregs).

Th1 lymphocytes produce inflammatory cytokines that assist macrophages in phagocytosis of cells harboring intracellular infection.

Th2 lymphocytes produce anti-inflammatory cytokines that assist B cells in producing antibodies to attack extracellular infection. Th2 lymphocytes also promote the IgE and eosinophilic response to helminths (parasitic worms), which are too large to be phagocytized by macrophages, dendritic cells, or other phagocytes.

Th17 lymphocytes were discovered fairly recently, and are not as well understood as Th1 and Th2 lymphocytes.

Th lymphocytes (CD4+) and cytotoxic T cells (CD8+) are all known as effector T cells, in contrast to Tregs.

Tregs are usually described as CD4+ T lymphocytes that suppress Th1 and/or Th2 lymphocytes (CD4+) to maintain a properly balanced response to the pathogen being encountered. Nonetheless, CD8+ Tregs also exist, though they remain poorly characterized (Smith & Kumar 2008; Bilsborough et al 2003; Gilliet & Liu 2002). Obviously, when the ratios of these T cells are out of balance, the adaptive immune response is impaired (Abbas & Lichtman 2008; Berger 2000).

[Incorporate natural killer cells into basic summary...]

Inflammatory cytokines play a crucial role in the innate immune response to various infections, and are also required for the adaptive immune response. Thus, inhibiting inflammatory cytokines renders the host more susceptible to new infections (cites), including new infection by *B. burgdorferi* (Wooten et al. 2002; Lazarus et al. 2008; Diterich et al. 2001; Giambartolomei et al. 1998).

Likewise, IDO and kynurenine pathway activation have multiple protective functions in immune system regulation. On the one hand, induction of IDO plays an important role in the innate immune response during early stages of several infections (Njau et al. 2009; Müller et al. 2008; Hainz et al. 2007; Popov & Schultze 2008). On the other hand, elevation of IDO and kynurenine pathway activation may play a role in protecting the fetus from immune system attack by fostering fetomaternal tolerance (Sedlmayr 2007).

B. HIV- and cancer-like immunosuppression by overactivation of IDO and kynurenine pathway

However, in several forms of cancer and in several chronic infectious diseases, overactivation of inflammatory cytokines and IDO, depletion of tryptophan, and synthesis of kynurenines – individually or in combination – suppress the adaptive immune response by affecting either T cells, antigen-presenting cells, or both. (MacKenzie et al. 2007).

Elevated IDO appears to play a role in upregulating Tregs in human lymphatic filariasis (Babu et al. 2006), a significant role in CD4+ T cell dysregulation in chronic human HCV infection (Larrea et al. 2007), causes significant suppression of CD4+ and cytotoxic T cells in the peripheral blood in chronic human HBV (Chen et al. 2009), appears to downregulate CD4+ effector T cells, increase Tregs, and increase the rate of apoptosis in CD8+ T cells in SIV infection (Boasso et al. 2007; Boasso et al. 2009), inhibits CD4+ T-cell proliferation that characterizes HIV disease progression, and appears to limit proliferative and cytotoxic capacity of CD8+ T cells in HIV infection (Boasso et al. 2007b; Boasso et al. 2007c; Persidsky et al. 2006). This same form of immunosuppression occurs in several malignancies, including breast

cancer (Mansfield et al. 2009); acute myeloid leukemia (Curti et al. 2007; Curti et al. 2008; Chamuleau et al. 2008), ovarian carcinoma (Inaba et al. 2009), lung cancer (Suzuki et al. 2009), endometrial cancer (Ino et al. 2008), pancreatic cancer (Witkiewicz et al. 2008), hepatocellular carcinoma (Pan et al. 2008), cutaneous melanoma (Polak et al. 2007).

[Add studies on effects of natural killer cells].

The mechanisms involved in IDO/kynurenine pathway-mediated immunosuppression are being studied intensively, and are partially understood.

Human dendritic cells that differentiate under elevated-IDO and/or low-tryptophan conditions show a reduced capacity to stimulate T helper (Th) cells (CD4+), and favor induction of Tregs (Brenk et al. 2009; Chen et al. 2008; Hill et al. 2007). The reduced proliferation of CD4+ T cells and increased induction of Tregs would be systemic (Brenk et al. 2009), and therefore measurable in the peripheral serum. Similarly, in human fibroblasts, elevated IDO and kynurenine pathway activation suppresses proliferation of CD8+ T cells, and to a lesser extent CD4+ T helper cells (Forouzandeh et al. 2008).

The molecular effect of tryptophan depletion and/or exposure to tryptophan catabolites on CD8+ T cells appear to be associated with limited proliferative response and ability to exhibit cytotoxic function (Boasso et al. 2007b).

The reduced proliferation of CD8+ cytotoxic T cells is only partially measurable in peripheral serum, because it also occurs in the local microenvironment where elevated IDO activates the kynurenine pathway (Brenk et al. 2009; Chen et al. 2008; Hill et al. 2007).

Liu et al. have recently shown that while elevated IDO significantly reduced the number of proliferating CD3+ and CD8+ T cells in an experimental rat lung allograft, those levels were still significantly higher than found in normal lungs. Yet the CD8+ T cells that did proliferate were significantly stripped of their cytotoxic capacity in microenvironments with elevated IDO, despite remaining viable (Liu et al. 2009).

In patients with chronic hepatitis B, elevated IDO is responsible for immunotolerance against HBV, closely correlates with HBV viral load, and is negatively correlated with CD4 (+) and CD8 (+) T cells, and with the ratio of CD4/CD8 (Liu et al. 2009). In patients with chronic hepatitis C -- which is characterized by weak T-cell responses -- IDO expression in liver tissue, and serum kynurenine-tryptophan ratio -- a reflection of IDO activity -- are significantly elevated (Larrea et al. 2007). In hepatitis C-infected chimpanzees, hepatic IDO expression decreased in animals that cured the infection, while it remained high in those that progressed to chronicity (Larrea et al. 2007). Elevated IDO and kynurenine-tryptophan ratio are strongly correlated to viral load and immunosuppressive regulatory T cell (Treg) levels in the spleen and gut during progressive simian immunodeficiency virus (SIV) infection (Boasso et al. 2007). Elevated IDO and depleted tryptophan also induce suppression of cytotoxic T-cells in mice infected with malaria (Tetsutani et al. 2007).

Inhibition of IDO as an adjunct to treatment has proven remarkably effective in animal studies of SIV and HIV infection, and several forms of cancer. In SIV-infected monkeys experiencing only a partial response to retroviral therapy, partial blockade of IDO with retroviral therapy reduced plasma and lymph node SIV to undetectable levels (Boasso et al. 2009). In a murine model of HIV-1 encephalitis, the IDO inhibitor 1-methyl-DL-

tryptophan (1-MT) enhances the generation of HIV-1-specific cytotoxic T lymphocytes, leading to elimination of HIV-1-infected macrophages in brains of the treated mice (Potula et al. 2005). In mouse models of transplantable melanoma and breast cancer, 1-MT, in combination with chemotherapeutic agents, significantly inhibited tumor growth and enhanced survival of treated mice (Hou et al. 2007). Yet because of its poor solubility, 1-MT has restricted clinical application (Hou et al. 2007, van der Sluijs et al. 2006, Popov et al. 2008). Inhibition of IFN-gamma, with resulting inhibition of IDO, also reverses T cell unresponsiveness in mice injected with staphylococcal enterotoxin A (Kim et al. 2009).

This same immunosuppressive mechanism is likely occurring in advanced Lyme disease of long-term duration, since tryptophan is depleted, IDO is very likely overactivated, and CNS QUIN is significantly elevated – “dramatically” so in neuroborreliosis where “the severity of the infection and [inflammatory] immune stimulation [was not yet] intense.” (Halperin & Heyes 1992). [Cite studies on Th1/Th2, Treg, and CD8+ ratios in chronic Lyme]. Because cytotoxic T cells, natural killer cells, and macrophages play a central role in attacking intracellular infection, systemic or local microenvironment suppression/deactivation of CD8+ and CD4+ Th1 lymphocytes may largely explain the persistence of intracellular *B. burgdorferi*. Likewise, suppression of CD4+ Th2 cells would help explain the persistence of extracellular *B. burgdorferi*.

This could also explain the poor sensitivity of the CD57+ NK T-cell count as a diagnostic and prognostic indicator, despite its apparent specificity in Lyme disease and/or TBIs. [Elaborate further...]

Moreover, because lysis of *B. burgdorferi* provokes inflammation (cites), antibiotics are likely to cause further activation of IDO and the kynurenine pathway, which would compromise the immune response against both intracellular and extracellular infection. Of course, antimicrobials can be effective in Lyme disease that is not too far advanced, as demonstrated by Halperin & Heyes (1992). But in cases of long-term infection, this would help explain why advanced Lyme disease is incurable using antimicrobials without a targeted, anti-inflammatory adjunct.

Plenty of anecdotal evidence for herx-like reactions in treating babesiosis. Look for studies on this in treating babesiosis and malaria. Elevated IDO and depleted tryptophan induce suppression of cytotoxic T-cells in mice infected with malaria (Tetsutani et al. 2007).

C. Role of IDO and kynurenine pathway in autoimmunity

It is well-established that in experimental animal models, activation of IDO often inhibits proliferation of autoreactive T-cells and development of autoimmune disease. In mouse models of experimental autoimmune conditions, inhibiting IDO actually exacerbates disease by causing an increase in autoreactive CD8+ T cells.

On the other hand, Scott et al. recently demonstrated that inhibiting IDO in the earliest stages of joint inflammation delayed the onset of autoreactive B cell-mediated arthritis and alleviated disease severity in genetically-prone mice. In contrast, if 1MT was administered after this time point, it was no longer effective in treating joint inflammation. The alleviation of joint inflammation with 1MT was not due to a reduction in Tregs or an altered Th cell cytokine profile, yet it did result from a diminished autoreactive B cell response (Scott et al. 2009). Since this study used mice that are genetically

predisposed to rheumatoid arthritis, it does not support or detract from the hypothesis of a post-Lyme autoimmune syndrome, i.e., that autoimmune Lyme arthritis is self-perpetuating in the absence of infection after “adequate” treatment. No studies have yet been published concerning the role of IDO in autoimmune B cell pathogenicity in humans.

Research on the role of IDO/kynurenine pathway activation involvement in human autoimmunity is in its infancy, yet it is becoming clear that the experimental mouse models involving autoreactive T cells have not held true in *ex vivo* and *in vitro* human cell studies.

Researchers have recently discovered that at least one subset of IDO-negative dendritic cells stimulate myelin basic protein (MBP)-specific T cells extracted from the blood of MS patients, but that dendritic cells treated with IFN-gamma produced significant IDO, and these IDO-positive dendritic cells did not suppress autoreactive, MBP-specific T cells from MS patients (Terness et al. 2005).

Likewise, autoreactive T cells derived from the joint fluid of rheumatoid arthritis patients proliferated in response to IDO-positive dendritic cells, which was not affected by inhibition of IDO by 1-MT in the presence of IFN-gamma (Zhu et al. 2006).

In a study of Grave’s disease, the serum kynurenine to tryptophan ratio was increased, which was associated with increased IDO expression in B cells and dendritic cells. Since IDO is mainly expressed in antigen-presenting cells (APCs), such as macrophages and dendritic cells, the activation of IDO in APCs may cause a local decrease in tryptophan concentration, suppressing the activation of the surrounding T lymphocytes, whereas tryptophanyl-tRNA synthetase (TTS) works in the opposite way. CD4+ T cells derived from GD patients showed an enhanced expression of TTS, and their proliferation was not inhibited in the presence of IDO-expressing dendritic cells from these patients. IFN-gamma increases TTS expression in CD4+ T cells, and the increased TTS expression in CD4+ T cells from these patients was IFN-gamma dependent (Wang et al. 2009).

D. Risks of suppressing TNF-alpha and IDO

Ketamine as anesthetic not associated with new infections or malignancies, or with activation of latent infections or malignancies.

Inflammation may have a protective role and promote regeneration of damaged neurons. We do not yet know how to achieve a “balanced” inflammation. Because some novel anti-inflammatory treatment might have detrimental consequences, carefully monitoring disease progress in patients treated with this category of drugs is indispensable (Aktas et al. 2007; Bransfield). However, as inflammation, IDO activation, and CNS QUIN levels subside, so do Lyme disease symptoms. Since short-course, low-dose ketamine infusions suppress inflammation for days or weeks, and if ketamine is infused only symptomatically, the immune balance should not be skewed in an anti-inflammatory direction for any extended period.

Role of tryptophan starvation in controlling specific infections. Higher degree of tryptophan depletion required to deactivate T cells than to fight off these infections.

Increased susceptibility to new infections and malignancies

Escape of infections and malignancies contained by granulomas...] (Popov & Schultze 2008)
Related to enzymatic activity, e.g., infliximab vs etanercept (Furst et al. 2006), and also distribution in areas most crucial to innate immune response.

Superior profile of ketamine...

V. Ketamine's mechanisms of action

A. Anti-inflammatory effects and neuroprotective mechanisms in excitotoxicity and oxidative stress

Ketamine is an NMDA receptor antagonist. But in vitro studies suggest that ketamine is not a strong enough antagonist to overcome the agonistic effects of highly-elevated QUIN at the NMDA receptor (Henschke et al. 1993). Of the non-competitive inhibitors which bind within the ion channel of the NMDA receptor, dizocilpine (MK 801) is the most potent, whereas ketamine is one of the least active (Lees 1995). Ketamine is effective in preventing excitotoxicity because works at both ends of the neurotoxic cascade: primarily by preventing inflammation that activates IDO and synthesis of neuroactive kynurenines, and secondarily by blocking the overactivated NMDA receptor.

Ketamine's anti-inflammatory mechanisms have not been studied in the context of *B. burgdorferi* infection. But studies in the context of LPS-induced inflammation of murine macrophage-like Raw 264.7 cells reveal several mechanisms of action.

Treatment with ketamine at a therapeutic (anesthetic) concentration significantly reduces LPS-stimulated IL-1 β gene expressions in Raw 264.7 cells. LPS provokes inflammation in the following manner: LPS binds to the LPS-binding protein (LBP) in the bloodstream, then alters TLR4's conformation on macrophage-like cells, activating Ras protein. Ras protein phosphorylates Raf kinase. Raf kinase sequentially triggers mitogen-activated protein kinase kinases (MEK) 1/2 and extracellular signal-regulated kinases (ERK) 1/2. ERK 1/2 activates inhibitor kappaB kinase (IKK). IKK stimulates the translocation of nuclear factor- κ B (NF κ B) from the cytoplasm to the nucleus, and the transactivation of NF κ B. NF κ B induces the expressions of certain inflammatory genes, including the genes for TNF- α , IL-6, and IL-1 β . Ketamine decreases the extracellular binding affinity of LPS to LBP in the bloodstream. Sequentially, a therapeutic concentration of ketamine downregulates LPS-induced increases in Ras activity and Raf phosphorylation. In parallel with these decreases in Ras/Raf activations, ketamine ameliorates LPS-induced phosphorylations of MEK1/2, ERK1/2, and IKK, significantly reducing translocation and transactivation of NF κ B, and therefore significantly reducing expression of genes for TNF-alpha, IL-6, and IL-1 β . Ketamine targets this activity at toll-like receptors 2 and 4. (Wu et al. 2009).

Treatment with ketamine at a therapeutic (anesthetic) concentration significantly reduced LPS-stimulated TNF- α and IL-6 gene expressions in Raw 264.7 cells. LPS binds to the LPS-binding protein (LBP) in the bloodstream. Alteration of TLR4's conformation on macrophage-like cells activates phosphorylation of c-Jun N-terminal kinase (JNK). JNK

activation phosphorylates c-Jun and c-Fos, two major components in the heterodimeric structure of the AP-1 activator protein. Phosphorylation causes c-Jun and c-Fos to translocate from the cytoplasm to the nuclei of macrophage-like cells, resulting in AP-1 activation. AP-1 induces the expressions of the genes for TNF- α and IL-6. Ketamine significantly and sequentially decreases LPS-induced activation of c-Jun N-terminal kinase, and translocation and transactivation of c-Jun and c-Fos in Raw 264.7 cells. Jun and Fos are two major components in the heterodimeric structure of AP-1 transcription factor. Ketamine-induced suppression of c-Jun and c-Fos translocation from the cytoplasm to nuclei means that this ketamine can decrease AP-1 activation in LPS-stimulated macrophages. The AP-1 activator protein induces the expressions of certain inflammatory genes, including TNF-alpha and IL-6. Ketamine targets this activity originating at toll-like receptor 4 (Chen et al. 2009).

Ketamine also acts on a wide range of receptors...

B. Likelihood of reducing immunosuppression and possibility of terminating autoimmunity in advanced Lyme disease

By reducing CNS inflammation, ketamine should counteract IDO/tryptophan/kynurenine-mediated induction of Tregs, suppression of CD4+ and CD8+ effector T cells.

Autoimmunity in Lyme-MS, Lyme-arthritis after “adequate” antibiotic therapy...

Only one in vivo mouse study so far to support this, but possibility that lysis-induced inflammation can trigger or exacerbate autoimmune response by further activating IDO and kynurenine pathway... ..

VI. Low-dose ketamine safety profile

A. Side-effects

Dissociative effects...

Midazolam, diazepam, etc. for reduction of dissociative effects during infusion, and prevention of post-infusion nightmares. Include info in drug-drug interactions re. ketamine increasing sedating effects of benzodiazepines.

...

Thousands of people have taken low-dose ketamine infusions with no serious adverse consequences. In a retrospective study at one clinic, 500 people had taken low-dose infusions of ketamine without serious adverse incident. But these were just one-time doses...

Strong safety record as anesthetic...

B. Tolerance and addiction

Daily dosing with i.v. or i.m. ketamine for an extended period likely to result in rapid tolerance and moderate addiction. May also be true for weekly dosing. Best approach is to do a higher dose (for longer effect) as infrequently as possible.

Tolerance and addiction with daily oral dosing? Haven't seen any indication of this in studies discussing prolonged, daily oral dosing. But wouldn't be surprised if this were the case.

Buprenorphine is a mu-opioid receptor agonist that is used in treatment-resistant depression. Like ketamine, buprenorphine produces anti-inflammatory effects. Ketamine acts on a wide range of receptors, including agonism of the mu-opioid receptor. In this author's experience (sample size one), ketamine and buprenorphine act synergistically with regard to their anti-depressant effects, and buprenorphine increases ketamine's dissociative effects. On the other hand, this author stopped developing tolerance to ketamine after beginning to take buprenorphine as an adjunct to ketamine, because ketamine alone had lost efficacy at higher doses. For the past six weeks on a daily basis, this author has taken buprenorphine 1-2 hours prior to i.m. ketamine injection, and 10 mg diazepam 15 minutes prior to ketamine injection to reduce dissociative effects, with no increase in tolerance to buprenorphine or ketamine. Without this combination of medications, the author suffers extreme, life-threatening depression.

C. Neurotoxicity

To be drafted... [no risk of neurotoxicity at subanesthetic doses in adults]

D. Effects of long-term treatment with low-dose ketamine

Ketamine is gradually being incorporated into clinical treatment of several conditions, including depression, CRPS, and fibromyalgia. There are few published reports of adverse effects after several months of intermittent IV infusions or daily oral dosing. Risks...

Long-term, daily use of high-dose ketamine -- urinary tract damage, ulcerative cystitis, disabling frequent urination... Controlled effectively by author by Class IV 7.5 W, 980 nm medical near-infrared laser.

Mimicry of schizophrenic symptoms by blockage of NMDA receptor should not be an issue in Lyme disease if used symptomatically, since NMDA receptor is overactivated. However, since the NMDA receptor is generally underactivated in schizophrenia, and because the Halperin & Heyes study showing dramatically elevated quinolinic acid (NMDA receptor antagonist) in Lyme neuroborreliosis involved a small and heterogeneous group of patients, ketamine should be used very cautiously in Lyme-schizophrenia.

More to add...

E. Drug-drug interactions

Non-comprehensive list...

Morphine, at least in high doses, may block the analgesic effects of ketamine (Correl et al. 2004). Moreover, there is evidence from animal experiments that morphine-3-glucuronide (M3G), an active metabolite of morphine, activates the NMDA receptors (Correl et al. 2004; Popik et al. 1998). This would, of course, contribute to overactivation of the NMDA receptor by quinolinic acid, and would therefore increase neurotoxicity, although the effect may be masked by morphine's analgesic properties.

More to add...

VII. Conclusion

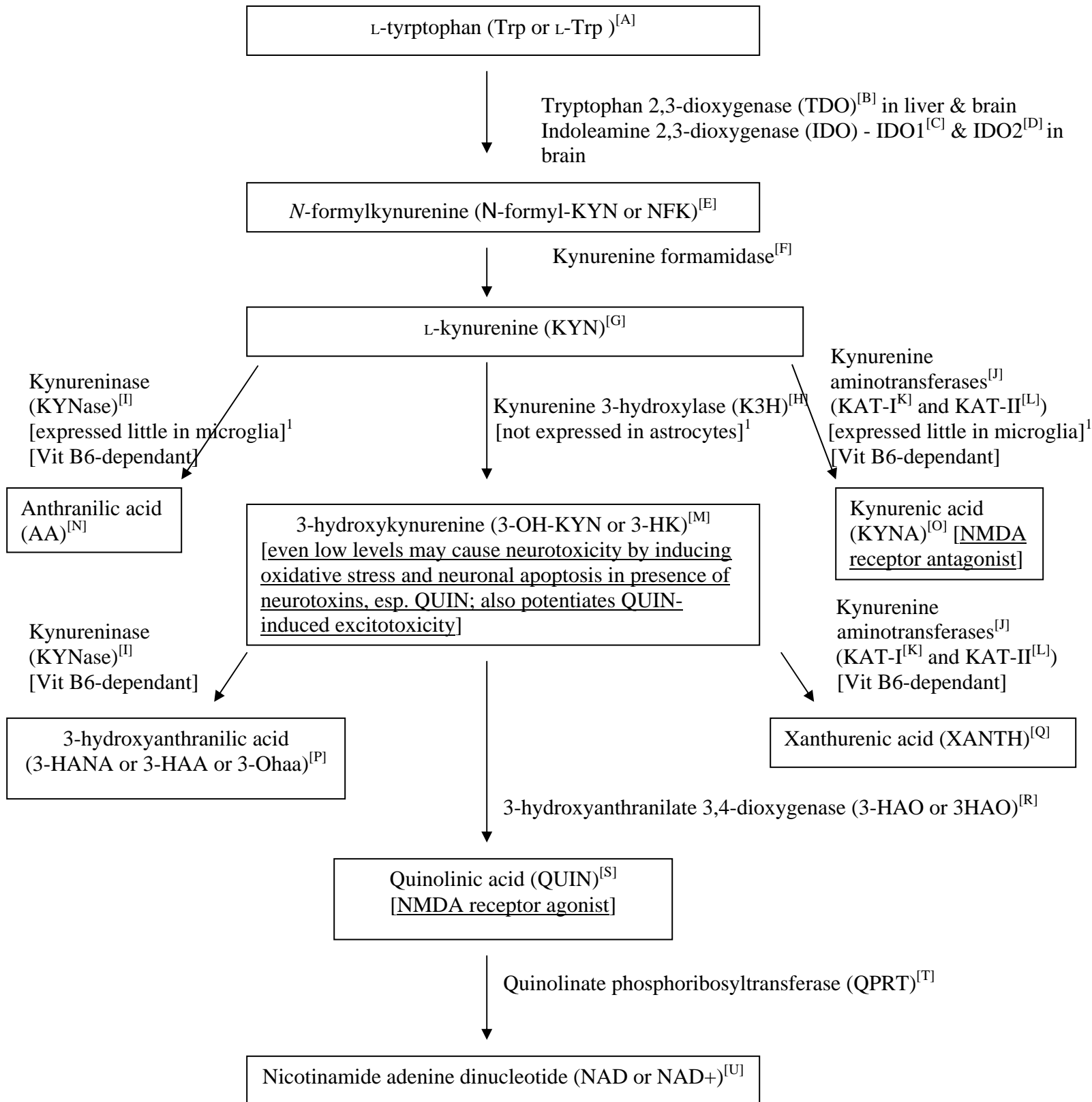
Symptom reduction, neuroprotection, etc. . . .

Because ketamine aids in cerebral delivery of IV antibiotics by ameliorating cerebral hypoperfusion, and may also ameliorate a major form of immunosuppression, the duration of antibiotic treatment and time to cure should be decreased in Lyme disease patients using ketamine. Ketamine also offers hope for late-stage patients who cannot tolerate antibiotic-induced symptom exacerbation.

Fig. 1. The kynurenine pathway – expressed primarily in infiltrating monocytes/macrophages, microglia and in part in astrocytes, with only sporadic presence of some pathway enzymes in neurons¹

Alphabetical footnotes list common synonyms

Numerical footnotes provide source references



Synonyms for Figure 1 – Kynurenine Pathway

- A. L-Tryptophan synonyms:
(L)-Tryptophan
tryptophan, L-
tryptophane
L-Tryptophane
tryptophan (H-3)
tryptophanum [Latin]
(S)-Tryptophan
tryptacin
- B. Tryptophan 2,3-dioxygenase (TDO) synonyms:
tryptamin 2,3-dioxygenase
tryptophan pyrrolase
tryptophanase
tryptophan oxygenase
Note: TDO2 is the name of the TDO gene
- C. Indoleamine 2,3-dioxygenase 1 (IDO-1) synonyms:
indoleamine-pyrrole 2,3-dioxygenase
- D. Indoleamine 2,3-dioxygenase 2 (IDO-2) synonyms:
indoleamine 2,3-dioxygenase-like protein 1
indoleamine-pyrrole 2,3-dioxygenase-like protein 1
- E. N-formylkynurenine (N-formyl-KYN) synonyms:
N-formylkynurenine
formylkynurenine
N'-formylkynurenine
- F. Kynurenine formamidase synonyms:
formamidase
- G. L-kynurenine (KYN) synonyms:
kynurenine
- H. Kynurenine 3-hydroxylase (K3H) synonyms:
kynurenine hydroxylase
kynurenine 3-monooxygenase
- I. Kynureninase (KYNase) synonyms:
L-kynurenine hydrolase
- J. Kynurenine aminotransferases synonyms:
L-kynurenine aminotransferases
aminotransferases, kynurenine
kynurenine 2-oxoglutarate transaminases
kynurenine transaminases (cyclizing)
- K. Kynurenine aminotransferase-I (KAT-1) synonyms:
kynurenine pyruvate aminotransferase

- L. Kynurenine aminotransferase-II (KAT-1I) synonyms:
kynurenine-2-oxoglutarate aminotransferase
- M. 3-hydroxykynurenine (3-OH-KYN or 3-HK) synonyms:
3-(3-hydroxyanthraniloyl)alanine
2-amino-4-(2-amino-3-hydroxyphenyl)-4-oxobutanoic acid
- N. Anthranilic acid (AA) synonyms:
anthranilate
o-Aminobenzoic acid
2-Carboxyaniline
benzoic acid, o-amino-
o-Carboxyaniline
ortho-Aminobenzoic acid
2-Aminobenzoic acid
benzoic acid, 2-amino-
1-Amino-2-carboxybenzene
2-Aminobenzoate
vitamin L1
o-Anthranilic acid
- O. Kynurenic acid (KYNA) synonyms:
kynurenate
transtorine
4-Hydroxyquinoline-2-carboxylic acid
4-Hydroxy-2-quinolinecarboxylic acid
4-hydroxyquinoline-2-carboxylic acid
quinaldic acid, 4-hydroxy-
2-Quinolinecarboxylic acid, 4-hydroxy-
- P. 3-hydroxyanthranilic acid (3-HANA or 3-HAA or 3-Ohaa) synonyms:
2-Amino-3-hydroxy-benzoic acid
2-Amino-3-hydroxybenzoic acid
3-Oxyanthranilic acid
- Q. Xanthurenic acid (XANTH) synonyms:
xanthurate
xanthurenate
oxoxanthurenate
- R. 3-hydroxyanthranilate 3,4-dioxygenase (3-HAO or 3HAO) synonyms:
3-hydroxyanthranilate 3,4-di-
3- hydroxyanthranilate oxygenase
3-hydroxyanthranilic acid oxidase
3-hydroxyanthranilic acid oxygenase
oxygenase, 3-hydroxyanthranilate 3,4-di-
- S. Quinolinic acid (QUIN) synonyms:
quinolinate
pyridine-2,3-dicarboxylic acid
2,3-Pyridinedicarboxylic acid
pyridine-2,3-dicarboxylate
- T. Quinolinate phosphoribosyltransferase (QPRT) synonyms:
QPRTase²⁷

QAPRTase
nicotinate-nucleotide pyrophosphorylase

- U. Nicotinamide adenine dinucleotide (NAD or NAD⁺) synonyms:
nicotinamide dinucleotide
beta-Nicotinamide adenine dinucleotide
codehydrase I

References for Figure 1 – Kynurenine Pathway

1. Vamos E, Pardutz A, Klivenyi P, Toldi J, Vecsei L. The role of kynurenines in disorders of the central nervous system: possibilities for neuroprotection. *J Neurol Sci.* 2009 Aug 15;283(1-2):21-7.
- 2.

Table 1 – IDO inducers

Amyloid peptide A β ₁₋₄₂ – induces IDO expression and a significant increase in the production of QUIN by human macrophages and microglia in Alzheimer's. (Guillemin et al. 2003).

Interferon- β (IFN- β) – in multiple sclerosis, pharmacologically relevant concentrations of IFN-beta are able to induce the kynurenine pathway in human macrophages. (Amirkhani et al. 2005; Gullemin et al. 2001)

Interferon- γ (IFN- γ) – very potetently activates IDO

Nef (Smith et al. 2001)

Tat (Smith et al. 2001)

Tumor necrosis factor- α (TNF- α) – strongly stimulates IFN- γ (see above)

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