



“Our mission is to provide evidence that autism is a set of symptoms caused by a medical disease.”

Stop Calling It Autism! Nonprofit organization

“We are showing a direct relationship between psychiatric disorders and the immune system”

Nobel Prize Winning Geneticist Mario Capecchi (2010)

“Our findings reinforce the theory that immune response in the brain is involved in autism”

Johns Hopkins School of Medicine (2004)



SCIA Medical Treatment Protocol for Autism



General Edition

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Medical Professionals can obtain a copy of the SCIA Medical Treatment Protocol for Autism **Physician's Edition** for free by joining the [SCIA for Doctors group](#). More information can be found on the [SCIA for Doctors page](#) in the SCIA website.



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Table of Contents

Introduction to the SCIA Medical Treatment Protocol.....	4
Autism Disease Process Diagram.....	5
Medical Treatment Protocol.....	6
Diagnosis.....	6
ICD-9 Diagnosis Codes	6
Clinical Presentation	6
Routinely Laboratory Tests.....	6
Treatment Instructions.....	7
Medications, Supplements and Diet Details	7
NSAIDS & Probiotics	7
Imunovir.....	8
Low Dose Naltrexone (LDN).....	8
GamaSTAN S/D, Immune Globulin (Human) - Intramuscular.....	8
Topical Glutathione	8
Antivirals.....	9
Antifungals.....	9
Diet	9
Multivitamins.....	9
Follow up Appointments	10
Laboratory Test Codes.....	11
Background and Rational.....	12
Evidence of Brain Inflammation in Autism.....	12
Evidence of Microglial Activation in Autism	13
Microglia and Their Role in Brain Inflammation.....	13
Evidence of Astrocytic Activation in the Brain in Autism	14
Results of Extended Microglial and Astrocytic Activation.....	15
Microglial Activation and Astrogliosis and Its Effect on Connectivity in the Brain	15

Evidence of increased Nitric Oxide production and related medical symptoms in autism	16
Evidence of Abnormal Brain Connectivity in ASD.....	18
NSAIDs, Microglial Activation and Nitric Oxide	19
Effects of a Probiotic Mixture on Non-steroidal Anti-inflammatory Drug Enteropathy	20
References	22
Medical Disclaimer	32

Introduction to the SCIA Medical Treatment Protocol

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Recently, Mario Capecchi, a distinguished professor of human genetics at the University of Utah School of Medicine and 2007 Nobel laureate in physiology and medicine showed evidence that there is a direct relationship between psychiatric disorders and the immune system, specifically cells named microglia that are derived from bone marrow. Microglia defends the brain and spinal cord, attacking and engulfing infectious agents. The findings – published in the journal *Cell* – should inspire researchers "to think about potential new immune-based therapies for psychiatric disorders," says Capecchi (e Science News, 2010).

Several studies now provide evidence that children with autism suffer from an ongoing neuroinflammatory process in different regions of the brain involving microglial activation (Pardo et al., 2005; Vargas et al., 2005; Zimmerman et al., 2005; Enstrom et al. 2005). Research also suggests that microglial activation can bring about a loss of connections or underconnectivity. Underconnectivity has been reported in many studies in autism (Wass, 2010). One way to control neuroinflammation is to reduce or inhibit microglial activation (Wood, 2003). Also, once activated, microglia release large amounts nitric oxide (NO) and superoxide as a cytotoxic attack mechanism (Colton and Gilbert 1987). Reactive oxygen and nitrogen species (ROS and RNS) derived from NO and superoxide may also cause local cellular damage by reacting with proteins, lipids, and nucleic acids (Valko et al. 2007). These chemicals can directly damage cells and lead to neuronal cell death.

As depicted in the Autism Disease Process diagram in the next section, microglial activation and elevated levels of nitric oxide are associated with many common neurological and medical symptoms in Autism. By inhibiting microglial activation and modulating the levels of nitric oxide many of these symptoms could be successfully treated.

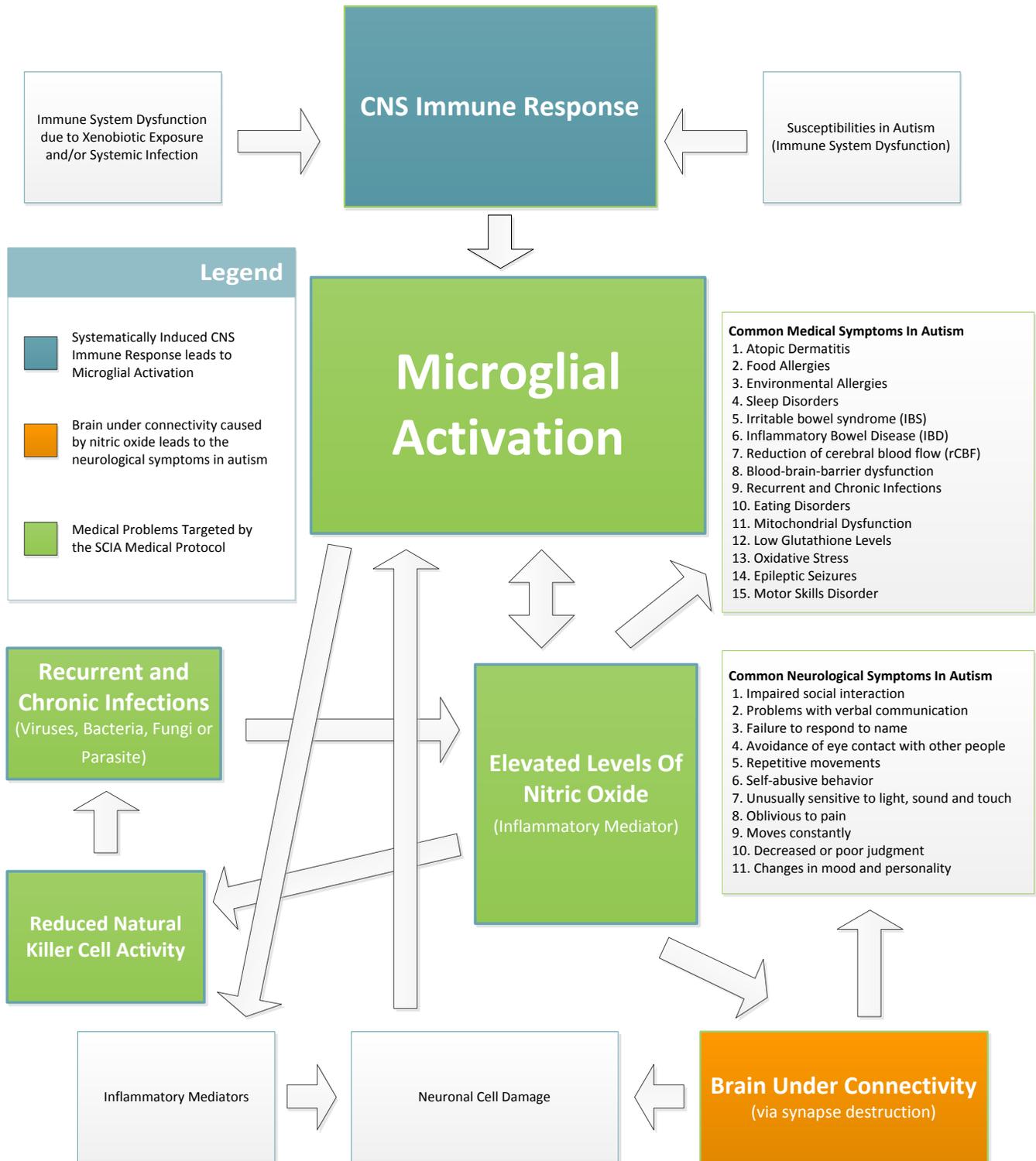
Research findings indicate that NSAIDs can be used to effectively reduce neuroinflammation and microglial activation. NSAIDs in particular Ibuprofen has been shown to modulate production of nitric oxide. In addition, anecdotal reports have indicated that NSAID treatment can improve symptoms in autism. The SCIA medical treatment protocol described in this document has been designed to help inhibit microglial activation, reduce neuroinflammation, modulate nitric oxide production, support the immune system and treat infections known to cause microglial activation. These areas of treatment are depicted in the [Autism Disease Process diagram](#) in the next section.

The SCIA medical treatment protocol could easily be used as an adjunct to current early behavioral and developmental interventions in a supportive role. By reducing brain inflammation and microglial activation, the neurodestructive effects of chronic inflammation could be reduced and allow for these early intervention measures to be more effective, and ultimately enhance developmental outcomes.

Autism Disease Process Diagram

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Medical Treatment Protocol

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Diagnosis

Autism, PDD-NOS, Asperger's Syndrome

ICD-9 Diagnosis Codes

279.3 Unspecified Immunity Deficiency

279.9 Unspecified Disorder of Immune Mechanism

Clinical Presentation

Speech Disorders, Motor Skills Disorders, Sleep Disorder, Behavior Disorders, Impaired Social Interaction, Self-Abusive Behavior, Mood Disorders, Sensory Integration Disorders, Memory Loss, Challenges in planning or Solving Problems, Difficulty Completing Familiar Tasks, Confusion With Time or Place, Trouble Understanding Visual Images and Spatial Relationships, Decreased or Poor Judgment, Eating Disorders, Obsessive Compulsive Disorder, Food and/or Environmental Allergies, Atopic Dermatitis, Constipation, Chronic Diarrhea, Irritable Bowel Syndrome, Inflammatory Bowel Disease, Frequent and/or Chronic Infections (i.e.. Yeast, Viral, Bacterial or Parasital) or Epileptic Seizures.

Routinely Laboratory Tests

Before starting treatment protocol and every six weeks onwards

Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP)

Before starting treatment protocol and every six months onwards

Lymphocyte Subset Panel 1 (Immune Panel including NK Cell Profile), NK Cell Functional Assay, Cell Mediated Immunity Assay, Immunoglobulins A/E/G/M, Human Herpesvirus 6 Antibodies (IgG), Antistreptolysin O (ASO) Antibodies, Cytomegalovirus (CMV) Antibodies-IgG, Rubella Antibodies (IgG), Rubeola Antibodies (IgG), Mumps Antibodies (IgG), Epstein Barr Virus-EBV(IgG)

The codes for the lab tests above are located in the [Laboratory Test Codes section](#).

Treatment Instructions

Note: Always introduce or remove one medication or supplement at the time unless otherwise specified. Wait at least two weeks before introducing or removing any medication or supplement. It is recommended that the patient should not be taking any other medications or supplements while in the SCIA Medical Treatment Protocol. **For details on how to administer the medications or supplements, refer to the Physician's Edition of this document. Your child's physician can obtain a free copy by joining the SCIA for doctors group. For more details visit [the Stop Calling It Autism! website.](#)**

1. Introduce the NSAIDs, probiotics, multivitamins and the diet.
2. Introduce the antivirals seven days after finishing the first round of NSAIDs
3. Introduce the antifungals seven days after the antivirals have been introduced
4. Wait one month before the next medication is introduced
5. Introduce the Immunovir
6. Wait one month before the next medication is introduced
7. Introduce the LDN
8. Wait one month before the next supplement is introduced
9. Introduce the topical glutathione

Note: Antibiotics and GamaSTAN can be prescribed if needed by the patient.

Medications, Supplements and Diet Details

NSAIDS & Probiotics (Inhibit Microglial Activation and Reduce Nitric Oxide Levels)

Start the patient on probiotics, 50billion CFU at wake up time and 50billion CFU at bed time. On a weekly basis, increase the probiotics dose by 50billion CFU at wake up time and 50billion CFU at bed time until a dose of 200billion CFU at wake up time and 200billion CFU at bed time is reached.

Notes:

1. Probiotics must be given on an empty stomach. Patient should not eat until after 30 minutes of the administration of the probiotics. Probiotics should be taken on a daily basis.
2. The NSAIDs must be strictly given with meals, make sure the patient has as much food as possible in his/her stomach. Encourage the parents to give plenty of fluids while taking the NSAIDs.

Recommended probiotics as of December 2011

1. [Custom Probiotics D-Lactate Free](#)
2. [VSL#3](#)

Q&A regarding Probiotics & NSAIDs

1. Why is it important to take high potency probiotics with the NSAIDs?

Probiotics work by colonizing the GI tract with optimal quantities and types of probiotic bacteria. These bacteria adhere to the walls of the GI tract and form a barrier which protects the inner layer of the gut from bad bacteria and other toxic substances that can cause inflammation. Using a high concentration of multiple different strains of specially selected beneficial bacteria, the recommended probiotics produce an optimal composition of good bacteria, delivering relief from preexisting GI symptoms, enhancing the health of the GI tract and reducing any gastrointestinal side effect that the NSAIDs could cause.

Imunovir (Immunomodulator, restores cell-mediated immunity, increases NK Cell activity and can be used for the virally-induced indications indicated in the [physician information package](#)) [click here to visit product website.](#)

Dosage is determined on the basis of lean body weight of the patient. Daily administration should be divided evenly during waking hours.

Treatment duration: 90 days on; 30 days off.

Low Dose Naltrexone (LDN) (Enhances Immune Function and Increases Natural Killer Cell Activity)
[Product Website](#)

The LDN should be purchased from the [pharmacies listed](#) on the product website.

Side Effects

LDN has virtually no side effects. Occasionally, during the first week's use of LDN, patients may complain of some difficulty sleeping. This rarely persists after the first week. In some cases, individuals with casein and gluten sensitivity may experience withdraw symptoms, i.e. irritability, hyperactivity, mood swings, if they are consuming foods with these proteins. Complete avoidance of these foods is advisable in some individuals 3 to 4 weeks before starting LDN and while taking LDN is advisable.

GamaSTAN S/D, Immune Globulin (Human) - Intramuscular
[Product Insert](#)

Note: GamaSTAN S/D is recommended for patients with Immunoglobulin G deficiency

Note: The needle must be 22 gauge.

Topical Glutathione (Immune System Support, antioxidant, cell protection)

Pharmacies

- Wellness Pharmacy in Alabama (800)227-2627
- Kirkman Labs E-mail: sales@kirkmanlabs.com
- McGuff Pharmacy in California, (877) 444-1133, Email: pharmacyanswers@mcguff.com
- Lee Silsby Pharmacy in Ohio, (800) 918-8831, Email: info@leesilsby.com
- Coastal Compounding Pharmacy in Georgia, (866) 354-5188, Email: mail@coastalcompounding.com

Antivirals (Help treat herpes virus family infections known to contribute in microglial activation)

Option 1: Valtrex

Option 2: Famvir

Option 3: Acyclovir

Note: Some children might experience what it is called die-off when antivirals are first introduced.

Antifungals (Help treat herpes virus family infections known to contribute in microglial activation)

Option 1: Nizoral

Rotate to Diflucan after six months

Option 2: Diflucan

Rotate to Nizoral after 1 year

Note: Some children might experience what it is called die-off when antifungals are first introduced.

Diet (Eliminating Food Allergens can help reduce the overstimulation of the immune system)

1. Eliminate Milk Products
2. Eliminate Wheat Products
3. Avoid Sugar
4. Eliminate Fast Foods
5. Limit all fruits other than lemons, limes, dried cranberries, and black currant seed juice.
6. Using a wide variety of protein meats, vegetables, and certain non-gluten (gliadin) grains (quinoa, amaranth, millet and buckwheat).
7. Vegetable juices for increased nutrient bioavailability.

Multivitamins

High quality multivitamins (without dyes and/or artificial flavorings)

Follow up Appointments

Every two weeks the parents should fax/email/mail an update to their child's physician. Every four weeks the parents should bring the child for an office visit, phone or videoconference call.

Use the following form as a template for the patient's update.

Patient Name _____ Date of Birth _____

Patient's Weight _____ Update Date _____

Current Medications	Dosage	Last Dosage Change Date

Current Supplements	Dosage	Last Dosage Change Date

Positives since last update

Negatives since last update

Questions	Yes/No	Describe if needed
Is child bright eyed?		
Is child's skin color good?		
Is child healthy looking?		
Is child more focused?		
Is child on the recommended diet?		
Are child's allergy symptoms improving?		

Other Comments

email: scia@stopcallingitautism.org
web: www.stopcallingitautism.org

Note: The laboratory companies below were used as reference to help doctors identify the lab tests. Physicians or patients may choose a different lab company that offer the lab tests listed below.



Quest Diagnostics Lab Test Codes	
6399	Complete Blood Count (CBC)
10231	Comprehensive Metabolic Panel
7197	Immune Panel (Lymphocyte Subset Panel 1)
34184	Natural Killer Cell Functional Assay
15435	Immune Cell Function (Cell Mediated Immunity Assay)
809	Sedimentation Rate (ESR)
4420	C-Reactive Protein, Quantitative
7083,542	Quantitative Immunoglobulins (IGG, IGA, IGM, IGE)
30666	Herpes Simplex Virus Types 1 & 2, IgG
34282	Human Herpesvirus 6 Antibodies, IgG
403	Cytomegalovirus (CMV) Antibodies, IgG
6421	Epstein-Barr Virus Antibody Panel
964	Measles Antibodies, IgG
8624	Mumps Antibodies, IgG
10268	Rubella Antibodies, IgG
265	Anti-Streptolysin O Antibody (ASO)

LabCorp Lab Test Codes	
005009	CBC With Differential
322000	Comprehensive Metabolic Panel
505370	T- and B-Lymphocyte/NK Cell Profile
910032	Natural Killer Cell Functional Assay
005215	Sedimentation Rate-Westergren
006627	C-Reactive Protein, Quantitative
002295	Immunoglobulins A/E/G/M, Serum
164905	Herpes Simplex Virus Types 1 & 2, IgG
161075	Human Herpesvirus 6 Antibodies, IgG
006494	Cytomegalovirus (CMV) Antibodies, IgG
096230	Epstein-Barr Virus (EBV), IgG
096560	Rubeola Antibodies, IgG
096552	Mumps Antibodies, IgG
006197	Rubella Antibodies, IgG
006031	Antistreptolysin O (ASO) Antibodies

Background and Rational

Evidence of Brain Inflammation in Autism

Recently, Mario Capecchi, a distinguished professor of human genetics at the University of Utah School of Medicine and 2007 Nobel laureate in physiology and medicine showed evidence that there is a direct relationship between psychiatric disorders and the immune system, specifically cells named microglia that are derived from bone marrow. Microglia defends the brain and spinal cord, attacking and engulfing infectious agents. The findings – published in the journal *Cell* – should inspire researchers "to think about potential new immune-based therapies for psychiatric disorders," says Capecchi (e Science News, 2010). Importantly, a study by Johns Hopkins University School of Medicine found evidence of microglial activation in individuals with autism (Pardo et al., 2005).

Indeed, several studies now provide evidence that children with autism suffer from an ongoing neuroinflammatory process in different regions of the brain involving microglial activation (Pardo et al., 2005; Vargas et al., 2005; Zimmerman et al., 2005; Enstrom et al. 2005). Evidence of neuroinflammation includes activated microglia and astrocytes found in post-mortem brain tissue (Pardo et al., [2005](#); Vargas et al., 2005; Morgan et al., 2010) and irregular, proinflammatory cytokine profiles in the brain and cerebrospinal fluid of children with ASD (Zimmerman et al., [2005](#); Vargas et al., 2005; Chez et al., 2007). Neuroinflammation, in general, is characterized by the reactivity of microglial cells and astrocytes, activation of inducible NO-synthase (i-NOS), and increased expression and/or release of cytokines and chemokines (Monnet-Tschudi et al., 2011). As Herbert (2005) pointed out in her review of the brain abnormalities in ASD, the autistic brain is not simply wired differently, but neuroinflammation is a part of the pathology in autism from childhood through adulthood. Furthermore, studies have found that activated microglia are more poised to destroy a synapse (connection between neuron). (Majewska et al. 2010; Tremblay et al. 2010) Individuals suffering from neurological disorders caused by microglial activation exhibited significant cortical synapse loss. (Lue LF et al. 1996; Brachova L et al. 1996; Civin WH et al. 1996; Rogers J. et al. 1996)

Also, once activated, microglia release large amounts nitric oxide (NO) and superoxide as a cytotoxic attack mechanism (Colton and Gilbert 1987). Reactive oxygen and nitrogen species (ROS and RNS) derived from NO and superoxide may also cause local cellular damage by reacting with proteins, lipids, and nucleic acids (Valko et al. 2007). These chemicals can directly damage cells and lead to neuronal cell death.

Evidence of Microglial Activation in Autism

Two post-mortem studies have shown microglial activation in ASD. First, Vargas et al. (2005) examined brain tissue and cerebral spinal fluid (CSF) in those with autism. For the morphological studies, brain tissues from the cerebellum, midfrontal, and cingulate gyrus were obtained at autopsy from eleven patients with autism. Fresh-frozen tissues from seven patients and CSF from six living patients with autism were used for cytokine protein profiling. The authors found active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of patients with autism, with marked activation of microglia and astroglia. The authors stated that the CSF showed a unique proinflammatory profile of cytokines. The authors stated that the pattern of cellular and protein findings suggests the brain's own immune system (not immune abnormalities from outside the brain) and that the *neuroinflammatory process appears to be an ongoing and chronic mechanism of CNS dysfunction*.

Later, Morgan et al. (2010) examined the dorsolateral prefrontal cortex of male cases with autism (n = 13) and control cases (n = 9) and found microglial activation and increased microglial density in the dorsolateral prefrontal cortex in those with autism. They also noted process retraction and thickening, and extension of filopodia (small protrusions sent out from a migrating cell in the direction that it wants to move) from the processes. The authors stated that the microglia was markedly activated in 5 of 13 cases with autism, including 2 of 3 under age 6, and marginally activated in an additional 4 of 13 cases. The authors stated that because of its early presence, microglial activation may play a central role in the brain pathogenesis of autism.

Microglia and Their Role in Brain Inflammation

Microglia, a type of glial cell, are the resident tissue macrophage of the central nervous system (CNS). They act as the first and main form of active immune defense in the brain and spinal cord. They are readily detected within the CNS during early prenatal (embryonic) development and are found in all regions of the healthy adult brain and spinal cord. They comprise 10-15% of the total cells in the CNS (Carson et al 2007). Microglia promote inflammation in infected or damaged tissue and are important for maintaining homeostasis in non-infected regions.

Microglia move around, analyzing the CNS for damaged neurons, plaques, foreign bodies, and infectious agents. Microglia are rapidly activated by a wide range of neuropathological insults and changes (Owen & Matthews, 2011). Microglia can be activated by: (1) changes in extracellular potassium levels (even small changes), (2) pathogens/infection (e.g., bacteria, viruses), (3) injury (e.g., damaged neurons), (4) ischemia, (5) inflammation, (6) lipopolysaccharide (LPS) (the major component of the outer membrane of a gram-negative bacteria cell wall), (7) beta amyloid (found in brains of patients with Alzheimer's disease and ASD), and (8) various toxins (Lull & Block, 2010; Wood, 2003; Smith et al., 2011; Sokol et al., 2006; Ding et al., 1997; Sankarapandi et al., 1998; Possel et al., 2000).

It is important to note that microglial can be activated by brain infection and inflammation, as well as, systemic infection and inflammation (Teeling & Perry, 2009). As described by Jang and Johnson (2010), cells associated with the peripheral innate immune system (e.g., macrophages and monocytes) produce inflammatory cytokines such as interleukin (IL)-1b, IL-6, and tumor necrosis factor-a (TNF-a) that facilitate communication

between periphery and brain during infection. They stated that even though there is clear evidence that inflammatory cytokines can be actively transported from blood into the brain, (Gutierrez et al., 1993; Banks & Kastin, 1991; Banks et al., 1994, 1995) peripheral cytokines need not enter the brain to elicit behavioral changes. This is because inflammatory stimuli in the periphery (e.g., LPS and inflammatory cytokines) induce transcripts for IL-1b, IL-6, and TNF-a in discrete brain areas (Ban et al., 1992; Laye et al., 1994).

Microglia act as key cellular mediators of the neuroinflammatory processes and are associated with the pathogenesis of many neurodegenerative and brain inflammatory diseases and disorders, such as Alzheimer's disease, Parkinson's disease, stroke, spinal cord injury, encephalitis and multiple sclerosis (Ginhoux et al. 2010; Carson et al 2007). Microglia are involved in the onset and progression of the inflammatory process, as well as the protection and regeneration of injured neurons (Carson et al., 2008, 2007; Melchior et al., 2006; Butovsky et al., 2006). Their role is critical in both acute and chronic neuroinflammation (Streit and Xue 2009; Streit et al. 2004). According to Carson et al. (2007), in vitro assays of microglial function have demonstrated that they can acquire either neurotoxic or neuroprotective functions.

The neurotoxic effects of microglia are produced in different ways. One, microglia can release a variety of cytotoxic substances, such as proteases, which when secreted by microglia catabolise specific proteins causing direct cellular damage. Microglia can also injure neurons through NMDA receptor-mediated processes by secreting glutamate and aspartate. Cytotoxic secretion is aimed at destroying infected neurons, virus, and bacteria, however, cytotoxic secretion can also cause large amounts of collateral neural damage (Gehrmann et al., 1995).

Also, once activated, microglia release large amounts nitric oxide (NO) and superoxide as a cytotoxic attack mechanism (Colton and Gilbert 1987). Reactive oxygen and nitrogen species (ROS and RNS) derived from NO and superoxide may also cause local cellular damage by reacting with proteins, lipids, and nucleic acids (Valko et al. 2007). These chemicals can directly damage cells and lead to neuronal cell death.

Evidence of Astrocytic Activation in the Brain in Autism

Inflammatory responses in brain are primarily mediated by microglia, but growing evidence suggests a crucial importance of astrocytes (Guerra et al., 2011). Evidence shows that along with microglial activation, there is also astrocytic activation in autism. First, activated astrocytes are found in post-mortem brain tissue in ASD (Pardo et al., [2005](#)). Astrocytic activation is also evidenced by elevated glial fibrillary acidic protein (GFAP) in the brain and spinal cord of patients with ASD. When astrocytes become hypertrophic and proliferative, they upregulate the expression of GFAP (Stichel & Muller, 1998). Thus, GFAP is a biomarker of astrocytic activation.

Numerous studies have shown that GFAP levels are increased in autism. An autopsy report by Bailey et al. (1998), for example, found that the Purkinje cell loss in ASD was sometimes accompanied by gliosis and an increase in GFAP.

A study by Ahlsen et al. (1993) examined the levels of GFAP in the CSF of children with autism, and found their average GFAP was three times higher than it was in the control group. The authors stated that the results could implicate gliosis and unspecified brain damage in children with autism. Laurence and Fatemi (2005) examined levels of GFAP in the **frontal, parietal, and cerebellar cortices** using age-matched **autistic** and control

post-mortem specimens. GFAP was significantly elevated in all three brain areas. The authors stated that the elevated GFAP confirms microglial and astroglial activation in **autism and** indicates gliosis, reactive injury, and perturbed neuronal migration processes.

Rosengren et al. (1992) also found GFAP levels in CSF in children with autism were higher than those in normal control children of the same age range. The authors stated that the high levels of GFAP in combination with normal S-100 protein concentrations in CSF indicate reactive astrogliosis in the CNS.

And, Fatemi et al. (2008) investigated whether two astrocytic markers, aquaporin 4 and connexin 43, are altered in Brodmann's Area 40 (BA40, parietal cortex), Brodmann's Area 9 (BA9, superior frontal cortex), and the cerebella of brains of subjects with autism and matched controls. The authors reported that the findings demonstrated significant changes in the two astrocytic markers in the brains from individuals with autism.

Results of Extended Microglial and Astrocytic Activation

When microglia remain activated for an extended period, the production of mediators is sustained longer than usual. This increase in mediators contributes to loss of synaptic connections and neuronal death (Wood, 2003). Streit et al. (2004) state that in the case of chronic neuroinflammation, the cumulative ill effects of microglial and astrocytic activation can contribute to and expand the initial neurodestruction, thus maintaining and worsening the disease process through their actions. Neuroinflammation generally refers to more chronic, sustained injury when the responses of microglial cells contribute to and expand the neurodestructive effects, worsening the disease process (Streita, 2006). As a result, chronic inflammatory response can result in large scale neural damage as the microglia ravage the brain in an attempt to destroy the invading infection (Streita 2006). Smith et al. (2011) stated that mounting evidence indicates that chronic microglial activation contributes to the development and progression neurodegenerative disorders.

Evidence suggests that the collateral neural damage **can involve loss of connections in the brain** (Gehrmann et al., 1995). This topic is discussed further in a following sections.

Microglial Activation and Astrogliosis and Its Effect on Connectivity in the Brain

In a recent review by Colangelo et al. (2011), they explained the relationship between microglial activation and loss of connections in the brain. According to Colangelo et al. (2011) because glial cells play an irreplaceable part in brain homeostasis and synaptic plasticity, changes of astrocytes and microglial cells after traumatic or toxic insults to the central nervous system (namely, reactive gliosis) disrupt the complex neuro-glial networks underlying homeostasis and connectivity within brain circuits. The involvement of glia in neurodegenerative diseases can disrupt connectivity within brain circuits by affecting neuronal-neuronal, neuronal-glial and glial-glial contacts (Heneka et al., 2010). In addition, activated microglia play a major role in inhibiting axon regeneration after injury (Kitayama et al., 2011).

Barger and Basile (2001) found in their research that activated microglia caused synaptic degeneration and neuronal death, ultimately affecting connectivity. Underconnectivity found in autism will be discussed in a later section.

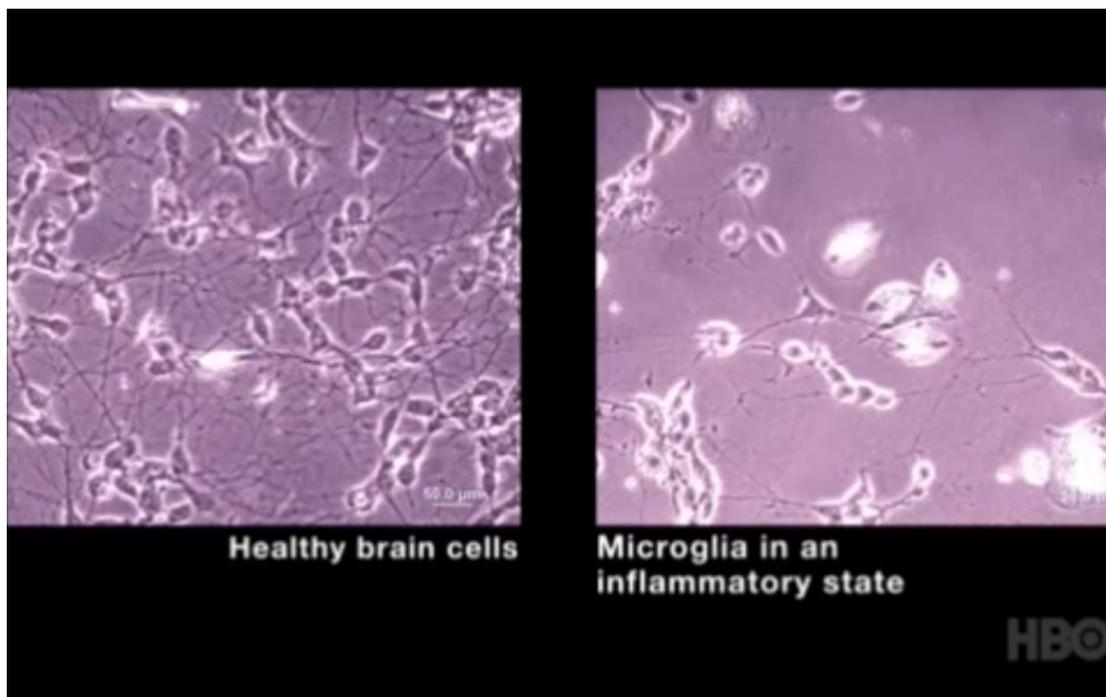


Figure 1: This figure shows loss of connectivity in the brain as a result of microglial activation.

Courtesy of Dr. Joseph Rogers, Sun Banner Health Research Institute

Evidence of increased Nitric Oxide production and related medical symptoms in autism

Once activated, microglia release large amounts nitric oxide (NO) and superoxide as a cytotoxic attack mechanism (Colton and Gilbert 1987). Reactive oxygen and nitrogen species (ROS and RNS) derived from NO and superoxide may also cause local cellular damage by reacting with proteins, lipids, and nucleic acids (Valko et al. 2007). These chemicals can directly damage cells and lead to neuronal cell death.

D Janigro, GA West, TS Nguyen and HR Winn (1994) suggested a role for NO in the regulation of blood-brain-barrier function. They also stated that NO has also been shown to modulate ion channels in excitable cells, thus affecting neuronal firing.

Recent studies on brain circulation have provided evidence that cerebral blood flow is impaired by decreased formation of NO from endothelial cells, autonomic nitrergic nerves, or brain neurons and also by increased production of reactive oxygen species (ROS). The NO-ROS interaction is an important topic in discussing blood flow and cell viability in the brain (Toda N et al. 2009, Ayajiki K et al. 2009, Okamura T. et al. 2009). There is evidence that a statistically significant global reduction of cerebral blood flow (CBF) is found in autistic children (Burroni et al., 2008).

In a review by Ashutosh (et al. 2000) an increase in the exhaled NO has been shown to accompany eosinophilic inflammation and to correlate with other indices of inflammation in asthma. Exhaled NO increases during exacerbation and decreases with recovery in patients with asthma. Yates et al. 2001 also reported that Asthma is characterized by chronic airway inflammation and increased synthesis of NO and other highly reactive and toxic substances (reactive oxygen species). Pro- inflammatory cytokines such as TNFalpha and IL-1beta are

secreted in asthma and result in inflammatory cell recruitment, but also induce calcium- and calmodulin-independent nitric oxide synthases (iNOS) and perpetuate the inflammatory response within the airways. Nitric oxide is released by several pulmonary cells including epithelial cells, eosinophils and macrophages, and NO has been shown to be increased in conditions associated with airway inflammation, such as asthma and viral infections.

It has been suggested that nitric oxide (NO) is an important player in eczema, food allergy and intestinal inflammation. Eczema is characterized by inflammation of the skin and is commonly associated with food allergy. The results of a study by (Devenney et al., 2010; Norrman et al., 2010; Forslund et al., 2010; Fälth-Magnusson et al., 2010 and Sundqvist et al., 2010) was able to support previous studies indicating that the homeostasis of nitrogen radicals is disturbed in childhood eczema.

Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) are chronic diseases that cause inflammation of the intestines. The most common symptoms of IBS are abdominal pain or discomfort often reported as cramping, bloating, gas, diarrhea, and/or constipation. Calatayud et al., 2001; Barrachina et al., 2001 and Esplugues et al., 2001) explained that exaggerated or uncontrolled expression of iNOS itself becomes detrimental to the gastrointestinal tract. In a review by (Dijkstra et al., 2004; van Goor et al., 2004; Jansen et al., 2004 and Moshage et al., 2004), they explained that large amounts of NO can increase gut permeability and induce apoptosis. A study by Reinders et al., 2005 found that NO was low in healthy control subjects (median, 45; 25th-75th percentile, 34-64 parts per billion [ppb]), and variations over time were small. In IBS patients NO was slightly increased (150, 53-200 ppb; $P < .001$), whereas patients with active IBD or collagenous colitis had greatly increased NO levels. Rectal NO correlated with disease activity in IBD and collagenous colitis and decreased markedly in IBD patients responding to anti-inflammatory treatment. Adams et al. (2011) found that there is a strong correlation of gastrointestinal symptoms with autism severity indicates that children with more severe autism are likely to have more severe gastrointestinal symptoms and vice versa. It is possible that autism symptoms are exacerbated or even partially due to the underlying gastrointestinal problems.

A study by Heales et al. (1996) examined brain glutathione and nitric oxide synthase activity. They found that loss of glutathione was accompanied by a significant increase in brain nitric oxide synthase activity by up to 55%. Depletion of glutathione in cultured neurones, by approximately 90%, led to a significant 67% increase in nitric oxide synthase activity, as judged by nitrite formation, and cell death. It is concluded that depletion of neuronal glutathione results in increased nitric oxide synthase activity. Many studies show low plasma GSH levels in ASD (Geier et al., 2009) and reduced glutathione regenerating enzymes (Al-Yafee et al., 2011).

Evidence has also been provided that mitochondrial dysfunction can be induced by elevated levels of nitric oxide (Stewart et al., 2003 and Heales et al., 2003). Excessive generation of nitric oxide (NO) has been implicated in the pathogenesis of several neurodegenerative disorders. Damage to the mitochondrial electron transport chain has also been implicated in these disorders. NO and its toxic metabolite peroxynitrite (ONOO(-)) can inhibit the mitochondrial respiratory chain, leading to energy failure and ultimately cell death. . In recent study, Giulivi et al. (2010) found that children with autism were more likely to have mitochondrial dysfunction than typically developing children.

A team of researchers at the University of Florence, Italy, provided evidence on the possible actions of nitric oxide in the etiology of eating disorders (Vannacci et al. 2006). In this study, plasma nitrite and cGMP levels were significantly higher in eating disorder patients than in healthy controls. Eating Disorder Examination scores were also significantly higher in eating disorder patients than in controls. Furthermore, in a research study by

Coombs et al. (2010) it was concluded that those registering higher levels of Eating Disorders (ED) symptomatology also reported higher levels of attention to detail and communication difficulties associated with ASD.

In a study by Kovács et al. (2009) the researchers proposes that NO-dependent enhancement of synaptic transmission is a key promoting factor for the initiation of seizures. Additionally, NO might exert long-term effects in epilepsy. NO-dependent inhibition of mitochondrial electron transport chain activity (Brown, 2001), disruption of the mitochondrial networks (Yuan et al., 2007), and blockade of mitochondrial trafficking (Rintoul et al., 2006) might contribute to the metabolic impairment as described for the epileptic hippocampus (Kunz et al., 2000; Kann et al., 2005). In the presence of superoxide, NO gives rise to highly toxic peroxynitrite, thus contributing to free radical-mediated damage after long-lasting epileptic activity (Kovács et al., 2002; Patel, 2004).

Evidence of Abnormal Brain Connectivity in ASD

It is apparent from many studies that ASD involves the loss of critically important neuronal connections and networks (Di Martino et al., 2011; Wass, 2011). Abnormal connectivity, limited connections, and a limited capacity of cortical networks to coordinate information processing have been suggested to be critical in ASD, and posits a deficit in integration of information at the neural and cognitive levels. Furthermore, connectivity constraints are suggested to include issues akin to a limitation in bandwidth (Minshew and Keller, 2010; Just et al., 2007; Kana et al., 2009) which can decrease in the speed of neuronal communication (D'Agati et al., 2010).

There are many studies that suggest problems with connectivity in those with an ASD diagnosis. In a recent review of connectivity in ASD, Wass (2011) stated that there is “considerable convergent evidence suggesting that connectivity is disrupted in ASD.” From his review of the literature, he states that the evidence indicates both local over-connectivity and long-distance under-connectivity, and that disruptions appear more severe in the later-developing cortical regions.

As a result, the functional connectivity among regions of autistic brains is diminished (Herbert et al. 2004, 2005, Herbert 2005). For example, Damarla et al. (2010) investigated the cortical underconnectivity theory in autism by examining the neural bases of the visuospatial processing in high-functioning autism. Using a combination of behavioral, functional magnetic resonance imaging, functional connectivity, and corpus callosum morphometric methodological tools, they found that the autism group had lower functional connectivity between the higher-order working memory/executive areas and the visuospatial regions (between frontal and parietal-occipital).

Ebisch et al. (2010), using functional magnetic resonance imaging (fMRI), found reduced functional connectivity in ASD, compared with controls, between anterior and posterior insula and specific brain regions involved in emotional and sensory processing. Di Martino et al. (2011) found that children with ASD have abnormal functional connectivity between nearly all striatal subregions and heteromodal associative and limbic cortex previously implicated in the physiopathology of ASD (e.g., insular and right superior temporal gyrus).

Shukla et al. (2010) found fiber tract abnormalities in the corpus callosum (indicating impaired interhemispheric transfer), internal capsule and middle cerebellar peduncle, and all three segments of the internal capsule in ASD. Boger-Megiddo et al. (2006) also found the corpus callosums were disproportionately small adjusted for increased ASD cerebral volume. The ASD clinical subgroup analysis revealed greater

proportional callosum reduction in the more severely affected autistic disorder (AD). Just et al. (2007) found that relevant parts of the corpus callosum, through which many of the bilaterally activated cortical areas communicate, were smaller in cross-sectional area in the autistic participants and that the size of the genu of the corpus callosum was correlated with frontal-parietal functional connectivity.

Particularly implicated in deficits of long-range connectivity is the cerebellum, one of the most common sites of anatomic abnormality in autism (Belmonte et al, 2004; Courchesne, 1997; Courchesne and Pierce, 2002). The Purkinje cell is the main output cell in the cerebellum and it is diminished in number in ASD (Palmen et al., 2004).

NSAIDs, Microglial Activation and Nitric Oxide

One way to control neuroinflammation is to reduce or inhibit microglial activation (Wood, 2003). The main cellular target for non-steroidal anti-inflammatory drugs (NSAIDs) is thought to be microglia. This is supported by the evidence that number of activated microglia is decreased by 65 % in patients taking NSAIDs (Wood, 2003).

Non-steroidal anti-inflammatory drugs (NSAIDs) have proven to be effective in reducing the risk of Alzheimer's Disorder (AD), a disease that presents itself with microglial activation (Mrak, 2005). Sustained treatment with NSAIDs lowers the risk of Alzheimer's Disorder by 55%, delays disease onset, attenuates symptomatic severity and slows the loss of cognitive abilities.

According to Bendlin et al. (2010), the use of non-steroidal anti-inflammatory drugs (NSAIDs) in humans is associated with brain differences including decreased number of activated microglia. In animals, NSAIDs are associated with reduced microglia, decreased amyloid burden, and neuronal preservation.

In the Wistar rat, for example, Jin et al. (2008), reported that peripheral administration of the NSAID dexibuprofen (S(+)-isomer ibuprofen), which causes less gastric damage and has better anti-inflammatory effects than ibuprofen, reduces the microglial activation in the cortex and hippocampus, and reduces the phosphorylation of extracellular signal-regulated kinases in the hippocampus, which has been induced by chronic infusion of lipopolysaccharide (LPS) into the fourth ventricle of Wistar rats. In addition, they measured the effects of dexibuprofen on impairments of spatial working memory induced by LPS infusions were measured with a trial-unique matching-to-place task in a water maze which assessed memory for place information over varying delays. According to the authors, when performing the water maze task, the rats with the LPS infusions showed spatial working memory impairments relative to the rats with the artificial cerebrospinal fluid. Daily administrations of dexibuprofen reduced the spatial working memory impairment induced by the chronic LPS infusion. The authors stated that the results indicate that NSAID treatments using dexibuprofen significantly attenuate the processes that drive the pathology associated with AD and that this process may involve the suppression of microglial activation.

Wilkinson et al. (2010) examined the effects of ibuprofen in aged R1.40 mice. After 9-months of treatment, the researchers saw a 90% decrease in plaque burden and a similar reduction in microglial activation. In addition, ibuprofen treatment reduced levels of lipid peroxidation, tyrosine nitration, and protein oxidation, demonstrating a dramatic effect on oxidative damage in vivo. According to the authors, fibrillar beta-amyloid

(Abeta) stimulation has previously been demonstrated to induce the assembly and activation of the microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase leading to superoxide production through a tyrosine kinase-based signaling cascade. Ibuprofen treatment of microglia or monocytes with racemic or S-ibuprofen inhibited Abeta-stimulated Vav tyrosine phosphorylation, NADPH oxidase assembly, and superoxide production. Interestingly, they found that ibuprofen acts independently of cyclooxygenase COX inhibition to disrupt signaling cascades leading to microglial NADPH oxidase (NOX2) activation, preventing oxidative damage and enhancing plaque clearance in the brain.

Immunostimulated microglia mediates neurotoxicity by nitric oxide (NO), reactive nitrogen oxides, superoxide anion and NMDA-like substances. This suggest a novel role for microglial-produced NO and reactive nitrogen oxides as a neurotoxic agent in neurodegenerative disease states. (Boje et al., 1992)

Ibuprofen has been shown in vitro to modulate production of nitric oxide (NO) (Vandivier et al. 1999) Treatment with ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) has been reported to decrease the incidence as well as slow down the progression of Alzheimer's disease. Understanding the mechanism of this therapeutic effect would provide a target for development of drugs which may be devoid of side effects observed with NSAIDs. In addition to inhibiting cyclooxygenase (COX), the NSAIDs have recently been shown to decrease inducible nitric oxide synthase (iNOS) activity.

Effects of a Probiotic Mixture on Non-steroidal Anti-inflammatory Drug Enteropathy

NSAIDs have side effects on the gut and other organs, and some of these side effects can be serious (Hirschowitz, 1994; Montalto et al., 2010). No NSAID has been shown to be without side-effect potential and the most serious side effects are perforation of peptic and gut ulcers and gastrointestinal (GI) bleeding, which NSAIDs may promote from both ulcer and nonulcer lesions of both the upper and lower GI tract (i.e., both acid- and nonacid-dependent) (Hirschowitz, 1994).

However, research shows that probiotic use can prevent any serious GI side effects from NSAIDs. Montalto et al. (2010) for example, hypothesized in their study that because intestinal micro-organisms are necessary for the development of NSAID-induced small bowel lesions, then probiotics could protect against NSAID enteropathy. Understanding that faecal calprotectin assay represents a simple and practical method for diagnosis of NSAID enteropathy, the authors evaluated the effect of a probiotic mixture in comparison with placebo on faecal calprotectin concentrations (FCCs) in healthy volunteers receiving indomethacin. Montalto et al. (2010) conducted a double-blind, cross-over trial, of 20 healthy volunteers ingested a daily dose of probiotic mixture (VSL#3) or placebo for 21 days. From day 16 to day 19, all subjects were also administered 50 mg/day of indomethacin. FCCs were measured the day before starting probiotic/placebo ingestion (T0), and every day from day 15 to day 21. During dosing with probiotic, median FCCs were significantly increased only at day 17 with respect to T0 values, whereas during dosing with placebo, they were significantly increased at every day from day 17 to day 21 with respect to T0 values. Montalto et al. (2010) concluded that treatment with VSL#3 before and during indomethacin therapy significantly reduces FCCs in healthy subjects with respect to placebo, suggesting that this approach could be useful in decreasing indomethacin-induced intestinal inflammation.

Senol et al. (2011) examined the effects of a probiotic mixture, including 13 different bacteria, in the prevention of aspirin-induced gastric mucosal injury (aspirin is another type of NSAID). They reported that aspirin Pretreatment with probiotic mixture reduced aspirin-induced gastric damage scores and exerted tendency of downregulation of proinflammatory cytokines elicited by aspirin. They also found that the probiotic mixture increased sIgA production approximately 7.5-fold in the stomach, and significantly reduced the malondialdehyde

(MDA) increase in the gastric mucosa elicited by aspirin. Additionally, pretreatment with the probiotic mixture alleviated aspirin-induced reduction of mast cell count in the gastric mucosa.

These findings on the protective effects of probiotics in NSAID use have been corroborated by several other studies (Tursi et al., 2010; Watanabe et al., 2009; Gotteland et al., 2001). This may be because NSAID ingestion may disrupt the homeostasis of the intestinal flora and induce overgrowth of some bacterial species which exacerbate NSAID-induced mucosal injury (Reuter et al., 1997; Satoh et al., 1983).

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