Neurotransmitter Glutamate is a Novel Neurogenic Initiator in Arthritic Inflammation  (3-Dec-2002)

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Over 90% of the population will suffer from arthritis during their lifetime but present treatment regimens cannot completely abrogate chronic episodes of inflammation, pain, or disability. This costs an estimated 60 billion dollars/year in total costs of medicines, disability and lost wages (Arthritis Foundation, 2002). It is firmly accepted that neurogenic factors play a role in peripheral inflammation. There are 18 published case reports of stroke and nerve injury victims demonstrating a sparing of arthritic inflammation and subsequent disease progression on the patient’s paralyzed side [1]. One case described partial reversal of previous arthritic damage in the paralyzed joint when followed for three years. One case report showed elevated IL-1 levels on both paralyzed and normal sides, but the active arthritic side also had elevated substance P levels and the paralyzed, non-arthritic side did not. To better understand the underlying initiators and arthritic chronicity, studies have been performed to test the hypothesis that neurotransmitter excitatory amino acids (EAA), such as glutamate (GLU), released into the spinal cord and the joint by sensory nerve fiber endings, play a critical role in initiation and persistence of arthritis. Further, GLU contributes directly to inflammatory cascades and the "vicious cycle of inflammation and pain" of arthritis.

The studies thus far characterize GLU receptor mediated events in both animal and cell culture models of arthritis to more fully address the novel concept that release of neurotransmitter GLU in the joint acts as a primary neurogenic initiator and maintenance factor of inflammation and increased nociception. An experimental arthritis model using kaolin/carrageenan (K/C) as an irritant was developed in awake behaving rats to determine the central changes in the nervous system leading to the neuronal sensitization and increased nociception that develops with inflammation in the hindlimb joint. The K/C model is a transient arthritis model with ipsilateral effects in which return to normal GLU levels and nociceptive behavior patterns occur by 12 hours, paralleling effects that might be seen in transient joint insults. The complete Freund’s adjuvant (CFA) model takes longer to see inflammatory effects and nociception, but is bilateral and chronic. From these models, it is hoped that therapeutic interventions can be devised to interrupt these events, possibly preventing development and/or persistence of inflammation and pain.

The animal models have been used to study increased concentrations of glutamate released in the spinal cord during inflammation monitored with the help of an indwelling spinal microdialysis fiber. Behavioral hyperalgesia was monitored in the hindpaw before and after spinal administration of pharmacological agents through the microdialysis fiber. Agents that have successfully reversed the behavioral hyperalgesia include glutamate and GABA, antagonists, as well as gabapentin. A neural circuit was proposed for sensory transmission of nociceptive information through the spinal cord dorsal horn. The animal models were extended for study of neuronal events occurring at the terminal endings of the primary afferent fibers in the periphery. The animal models allowed us to study the generation of dorsal root action potentials in the dorsal horn that propagate back out to the periphery which likely serve as the neurogenic drive contributing to inflammatory and nociceptive events in the periphery in a feed-forward manner. Dependence of the peripheral inflammation on neural input is supported by the finding that half of the inflammatory response in the hindlimb is abrogated by cutting the dorsal roots.

Intra-articular K/C injection also results in increased concentrations of GLU peripherally in the ipsilateral rat joint that can be abrogated by lidocaine on the dorsal root or administration of GLU antagonists to the hindlimb joint [4]. Induction of the arthritis model or administration of GLU to the joint produces a marked increase in electrophysiologically recorded activity in the medial articular nerve [5] and pain related behavioral responses, including thermal hyperalgesia and mechanical allodynia [6]. In addition, ipsilateral dorsal root section or lidocaine also markedly abrogated the neuronal activity and inflammatory response of K/C arthritis. Preliminary studies indicate that intra-articular CFA injection in rats results in a
significant increase in synovial fluid GLU levels by day 7 that persists through day 21 and is abrogated by intra-articular neurotoxin capsaicin. Preliminary data also indicates that the GLU and GLU receptors are upregulated in the joint on type I and type II synoviocytes and the spinal cord after intra-articular CFA injection. Increased articular nerve activity can be evoked bilaterally in the persistent CFA model as well as upon addition of EAA to the joint in the rat.

A clonal synoviocyte culture model (HTB-93), mimicking the inflammatory arthritis models, is also being used (1) to study GLU receptor mediated signal transduction events under controlled conditions and (2) to more carefully assess efficacy and safety of the inhibitory agents prior to animal testing. Furthermore, the glutamate-activated events can be studied in vitro in the absence of blood-borne mediators, demonstrating the ability of GLU to directly evoke inflammatory cascades.

Taken together, these data present compelling evidence that GLU receptor activation centrally in the spinal cord and peripheral (endogenous) GLU sources in the joint contribute the initiation and persistence of arthritis. Activation and upregulation of NMDA NR1 can be demonstrated as early as four hours in the culture models and in animals, before development of clinical signs.

While GLU mediated events have been an intense focus of study in neurosciences, there is little appreciation of GLU’s role in evoking a peripheral immunological response. Little is known about the events precipitating initiation and persistence of arthritic inflammation. The causes are no doubt multifactorial but in some diseases, such as rheumatoid arthritis and viral arthropathies, there may be common end points in which arthritic persistence can continue, presumably long after the initial insult has abated. Characterization of this novel neurogenic pathway and design of therapeutic modalities will require understanding of both neurosciences and immunology. Our future strategic approach will be to molecularly characterize glutamate receptor activation and initiation of the events leading to inflammation of the synovial tissue, using relevant tissue culture and animal models to assist us toward our major goal of identifying mechanisms and delivery systems to abrogate the arthritic process that can be applied to humans conditions.

References

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2. Western Blot Measurement of GLU Receptor Protein

3. EAA is Human Synovial Fluid


4. Increased GLU in Spinal Cord and Joint

A. Rat


B. Human


5. Articular Nerve Activity


6. Nociceptive Behavior and Inflammatory Measures

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