NBQX, An AMPA-Kainate Glutamate Receptor Antagonist, Alleviates Inflammation And Pain Related Behaviour In Two Models Of Osteoarthritis

Cleo S. Bonnet, PhD\(^1\), Sophie J. Gilbert\(^1\), Anwen S. Williams, PhD\(^1\), David A. Walsh, PhD\(^2\), Deborah J. Mason\(^3\).

\(^1\)Cardiff University, Cardiff, United Kingdom, \(^2\)Nottingham University, Nottingham, United Kingdom, \(^3\)Cardiff University, CARDIFF, United Kingdom.


Introduction: Synovial fluid glutamate concentrations increase in various arthritides (1). Activation of kainate (KA) and AMPA glutamate receptors (GluRs) increase interleukin-6 (IL-6) release and cause arthritic pain respectively (2). GluR antagonists represent potential peripheral treatments for inflammatory arthritis and inflammatory mechanisms that contribute to osteoarthritis (OA). We previously found that AMPA and KA GluRs localise to bone, cartilage and synovial tissue from osteoarthritic patients and that the AMPA/KA GluR antagonist, NBQX, reduced knee swelling, gait abnormalities and joint destruction in a rat model of inflammatory arthritis (2). Here, we determined whether NBQX influenced inflammation and pain in a surgical model of OA (medial meniscal transection (MNX)) and a non-invasive model of post traumatic OA (ACL rupture model).

Methods: Right knees of male Sprague-Dawley rats received MNX surgery (n=3 for each group). NBQX (2.5mM, 12.5mM or 25mM) or vehicle control was injected intra-articularly into the right knee immediately after surgery and a second time 7 days later. Over 21 days, knee swelling (digital calliper) and rear limb loading (Linton incapacitance meter) were measured on days 0, 1, 2, 3, 7, 8, 10, 14 and 21. For ACL rupture, custom built cups were used to hold the knee in flexion and a 12N load at 4Hz (ElectroForce® 3200, BOSE) was applied to the right knees of anaesthetised 12-week-old C57Bl6 mice. Ligament rupture occurred on load application, revealed by a continued increase in displacement following release of the applied compressive force during the loading cycle. Left knees served as unloaded controls. NBQX (20mM) or vehicle control was administered into the loaded knee by intra-articular injection immediately following ACL rupture (n=5 for each). Mice moved freely after loading sessions. Over 21 days, knee swelling (digital calliper) was measured on days 0, 1, 2, 3, 7, 16 and 21.

Results: NBQX treatment reduced both inflammation and uneven weight bearing in MNX rats. Vehicle control treated MNX rats had significantly greater knee swelling compared to those treated with 25mM NBQX (P<0.05) on day 8, and those given 12.5mM (P<0.05) and 2.5mM (P<0.01) NBQX on day 14. Incapacitance readings on day 8, immediately after the second NBQX injection, showed that vehicle control treated MNX rats had a significantly greater difference in weight bearing between the left and right leg compared to 12.5mM (P<0.05), 2.5mM (P<0.01) and 25mM (P<0.01) NBQX treated rats. In the ACL model, significantly less knee swelling was found in NBQX treated mice compared to vehicle controls on days 7 (P<0.05) and 21 (P<0.001). In addition, from day 2, NBQX treated mice showed no significant difference in knee swelling compared to day 0 measurements. In sharp contrast, vehicle treated mice had significantly greater knee swelling compared to day 0 at every time point, indicating that knee joint diameter never returned to normal levels in the absence of NBQX.
**Discussion:** This study provides new evidence that NBQX treatment is effective at relieving inflammation and pain in osteoarthritis. Combined with our previous data from an inflammatory model of arthritis (2), NBQX shows promise as a new disease-modifying drug for inflammatory and osteoarthritis.

**Significance:** An estimated 52.5 million adults in the United States are reported to have some form of arthritis, with OA (approximately 27 million) being the most prevalent (statistic from the Centers for Disease Control and Prevention website). There is currently no cure for OA and where pain/disability is intolerable, joint replacement is performed. Surgery is costly, carries significant risks, and up to 20% of knee replacements are unsuccessful (3). Our novel data reveal that NBQX has exciting potential as a new disease modifying drug to tackle the shortfall in OA treatment. Combined with the beneficial effects on inflammatory forms of arthritis (2), NBQX shows great promise as a new disease modifying drug for many forms of arthritis.

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