Neurogenic origin of articular hyperemia in early degenerative joint disease

Jason J. McDougall, William R. Ferrell, and Robert C. Bray

Ligaments are crucial for maintaining diarthroidal joint stability and preventing abnormal displacements during motion. Ligament injury often results in joint laxity, and consequent changes in joint mechanics are associated with articular cartilage degradation; osteoarthritis often ensues (17, 18, 22, 33). Despite their relative hypovascularity, ligaments have an extensive neurovascular network (5, 27), with the majority of nerves and vessels found in the superficial epiligamentous layer (5, 9, 27) that covers the collagenous bundles. Epiligamentous vessels supply the underlying, relatively poorly vascularized mass of the ligament and are therefore likely to play an important physiological role in maintaining ligament integrity. It is known that deterioration of the mechanical properties of the medial collateral ligament (MCL) in injured rabbit knees is closely correlated with substantial increases in ligament perfusion (4). This is possibly related to the rate of formation or reabsorption of interstitial fluid in the substance of the ligament, inasmuch as changes in the water content of a ligament alter its material properties (8). These observations indicate an important relationship between ligament perfusion and mechanical adaptive responses, but at present little is known about the factors that regulate ligament blood flow.

In an earlier investigation (13) it was demonstrated that epiligamentous blood vessels in the MCL of the rabbit knee joint are potently vasodilated by the sensory neuropeptide calcitonin gene-related peptide (CGRP), which is known to be a powerful vasodilator in many tissues and in many species, including humans (3). CGRP is contained in unmyelinated afferent nerve fibers (16, 27). Under physiological conditions, CGRP is continuously released from the peripheral terminals of knee joint afferents to oppose sympathetic vasoconstrictor tone since local administration of the CGRP receptor antagonist CGRP-(8—37) results in a fall in articular basal perfusion (13, 31).

Surgical transection of the anterior cruciate ligament (ACL) results in an unstable knee joint (15), and ultimately osteoarthritis is a common outcome (22, 24, 33). In a process termed “microtrauma by proxy” (25), loss of joint stability elicits a detrimental effect on the mechanical integrity of other ligaments of that joint. Although the underlying mechanism of this phenomenon is obscure, one possibility could be the excessive secretion of CGRP. The ligament hyperemia this would cause would increase vascular hydrostatic pressure, altering the delicate balance of tissue Starling forces and culminating in interstitial fluid accumulation. As mentioned earlier, the elevated water content would increase ligament viscoelasticity (8), aggravating the instability of the joint. It is also known that patients with posttraumatic synovitis demonstrate increased levels of substance P in their synovial fluid (23), giving a credible basis for the hypothesis that injury may result in increased release of sensory neuropeptides.

The purpose of the present investigation was to test the hypothesis that the neurovascular control of ligament perfusion may be altered in the unstable joint. A preliminary account of these findings has been published in abstract form (12, 28).

MATERIALS AND METHODS

A total of 22 adult female New Zealand White rabbits (4.2–5.3 kg) were used in the present study, of which 10...
underwent unilateral surgical transection of the ACL, and 5 underwent saphenous nerve resection followed by ipsilateral ACL transection. The remaining seven animals formed the normal control group, of which four were used in the neuropeptide study and three in the nerve stimulation experiments. An overview of animal assignment to the various treatments is illustrated in Fig. 1. All experimental interventions had prior approval from the University of Calgary Animal Care Committee and were in complete accordance with the Canadian Council for Animal Care guidelines.

Induction of knee joint instability. Animals were premedicated by intravenous injection of 0.2 ml of Atrovet (acepromazine maleate, 25 mg/ml) and then deeply anesthetized using gaseous anesthesia (2% halothane; 1 l/min O2). Once the flexor withdrawal reflex abated, the rabbit was placed in a supine position, and the right knee joint was shaved. Under aseptic conditions, the limb of interest was flexed, and a longitudinal incision was made in the subpatellar region of the lateral aspect of the knee. A similar incision was then made in the joint capsule, and the skin and patellar ligament were retracted. The infrapatellar fat pad was externalized and retracted medially so as to allow visualization of the cruciate ligaments. The ACL was then isolated and surgically transected with a no. 12 scalpel blade. Finally, the fat pad was replaced, and the wound was closed with silk sutures. Postoperative care was given to the animals, which were caged and allowed to recover for 4 wk before being used in terminal experiments. Before these experiments, the joint was assessed to ensure that the ACL remained sectioned by examining the extent of laxity of the knee joint in the anteroposterior plane.

Nerve resection. Five animals underwent simultaneous ACL transection and articular denervation. After surgical division of the ACL as described above, the saphenous nerve, which innervates the medial aspect of the knee joint, was isolated, and a 5-mm length of nerve was resected. The animals were then allowed to recover for 4 wk before being taken to the terminal experiment. This period of time is more than sufficient for neural degeneration, which is normally established as early as 10 days postresection (11).

Blood flow assessment. Animals were sedated with acepromazine maleate (0.2 ml iv) and then anesthetized with urethan (1 g/kg ip). The right carotid artery was cannulated (PE-90, 0.86-mm internal diameter; Clay Adams, Sparks, MD) and connected to a pressure transducer (Elcomatic EM752, Neilston, UK) for the measurement of systemic blood pressure, which was monitored by a computerized recording system using CODAS software (Dataq Instruments, Akron, OH). Body temperature was maintained at 37°C by means of a homeothermic blanket (American Pharmaseal, Valencia, CA). With the animal placed in dorsal recumbency and the hip externally rotated with the knee in the rest position, the diameter of the right joint was measured with a digital micrometer (Mitutoyo, Tokyo, Japan). This was achieved by orienting the calipers across the joint line in a mediolateral plane distal to the femoral condyles and proximal to the tibial plateau. A longitudinal incision was then made medially, and the overlying skin was reflected to expose the underlying joint tissues. All covering aponeurotic and fascial tissues were carefully excised to allow unobstructed assessment of the MCL and medial gutter capsule (synovium and overlying fibrous tissues). To prevent the exposed joint from drying out, warmed (37°C) physiological saline (0.9% NaCl) was applied intermittently to the joint surface throughout the experiment. Tissue perfusion was measured using a laser-Doppler perfusion imager (LDI; Moor Instruments, Axminster, UK), which uses methodology similar to that in previous studies of the rabbit knee joint (13, 29) and which has been validated for both ligament (6) and joint capsule (21) blood flow determinations. Briefly, a low-power (1 mW) laser beam (633 nm) scans the exposed medial aspect of the knee joint. The backscattered Doppler-shifted photons are collected by a photodetector in the scanner head and are processed to generate two-dimensional color-coded images of joint tissue perfusion. These images represent spatial maps of the perfused tissue, and, unlike laser-Doppler flowometry, in which measurements are obtained only at a single point, they consist of hundreds of measurement points that yield a more accurate assessment of overall tissue perfusion. Images were processed using customized software (Moor Instruments) to generate measurements of perfusion, which were expressed as arbitrary perfusion units. With the scanner head placed 19 cm above the exposed joint, a scan region was chosen that included the MCL and medial gutter capsule. Typically, scan times lasted ~30 s. Measurements were taken during various experimental interventions (test) and related to control scans, which were performed before the test scan. The hemodynamic changes effected by the experimental manipulations were of much longer duration than the scan time, and thus the possibility of missing any response was minimized. Warmed (37°C) saline was applied to these exposed tissues, which in some experiments were then covered with cling film to prevent desiccation. This was removed to allow topical administration of drugs in 100-μl bolus applications and then replaced. At the end of the experiment, the animal was killed by an overdose of pentobarbital sodium (360 mg ic), and a final perfusion measurement (the "biological zero") was obtained. In each image, two distinct sites were identified, corresponding to the mid substance of the MCL and a portion of the medial gutter synovium (Fig. 2). The dimensions and position of the analysis regions were kept constant between control and test images, and the mean flux values for both regions were obtained. To compensate for the effects of tissue noise, the corresponding biological zeroes were subtracted from each image before any calculations were carried out. To account for any changes in basal perfusion between different animal groups, experimental responses were normalized by expressing them as a percent change in perfusion from control.

Experimental design: neuropeptide studies. Neuropeptide assessment was performed in seven normal, four ACL-deficient, and, in the CGRP experiments, five denervated/ACL-deficient knees as well. After skin removal, the CGRP antagonist CGRP-(8—37) was administered topically (0.1, 1, and 10 nmol), and knee joint perfusion was measured at 1, 5, 10, and 20 min after application. After each dose was administered, the tissues were repeatedly washed with warm saline until basal flux values returned to control values. Subsequently, CGRP (10–11—10–9 mol topical) was applied in a cumulative fashion (10 min between doses) to the surface of the capsule. Scans were obtained 1, 5, and 10 min after each CGRP application. Topical application was used in all of these experiments, because it was found in a previous study that administration of these doses of drugs by this route produced...
local vascular changes without affecting systemic arterial blood pressure (13).

Experimental design: nerve stimulation studies. Nerve stimulation assessments were performed in six normal and five ACL-deficient knees. A small incision was made at midthigh, and a 1-cm segment of the saphenous nerve was isolated. The nerve was resected as proximally as possible, and the distal section was placed over a pair of silver wire bipolar stimulating electrodes and then covered with mineral oil to prevent nerve desiccation. Once a stable knee joint perfusion level was reached, the saphenous nerve was electrically stimulated with a Harvard stimulator (model 6012, Harvard Apparatus, St. Laurent, Quebec, Canada). CGRP was purchased from Rose Scientific (Edmonton, Alberta, Canada). The peptides were dissolved in 0.9% (wt/vol) saline to give the different doses and stored in a freezer at −30°C until used.

Statistical comparisons. Individual data points are presented as means ± SE for n knees. Data sets were tested for normality, and all conformed to a Gaussian distribution with the exception of the frequency-response profile in ACL-deficient joints. Normally distributed data sets were analyzed using parametric statistical tests (i.e., Student's t-test, 1- or 2-way ANOVA, and a general linear model of variance), whereas a nonparametric test (i.e., Mood's median test) was performed on the non-Gaussian data set. All statistical analyses were carried out using either MINITAB (Clecom, Birmingham, UK) or GraphPad Prism (GraphPad Software, San Diego, CA) software. A significance level of P < 0.05 was set for each test.

RESULTS

Effect of ACL transection on joint diameter and basal perfusion. Four weeks after transection of the rabbit knee, joint width showed significant increase compared with normal unoperated controls. ***P < 0.0001; 2-tailed unpaired Student t-test; n = 6 and 10 for normal and ACL-deficient knees, respectively.

Materials. Urethan and CGRP-(8-37) were obtained from Sigma (St. Louis, MO). Atrovet (acepromazine maleate) was acquired through Ayerst Laboratories (Montreal, Quebec, Canada), pentobarbital sodium through MTC Pharmaceuticals (Cambridge, Ontario, Canada), and halothane through Halocarbon Laboratories (River Edge, NJ). Epinephrine hydrochloride was obtained from Epiclor (Calgary, Alberta, Canada). The peptides were dissolved in 0.9% (wt/vol) saline to give the different doses and stored in a freezer at −30°C until used.
ACL, knee joint diameter showed a significant increase compared with normal, rising from (in mm) 21.8 ± 0.1 in control knees to 25.1 ± 0.4 in the unstable joint (Fig. 3).

The normal rabbit knee joint was found to be well perfused with perfusion to the MCL midsubstance being greater than to the capsular region (Fig. 4). Division of the ACL caused a significant increase in knee joint perfusion at 4 wk posttransection, with flow roughly doubling compared with control in the capsule and the MCL (Fig. 4). Denervation before ACL section abolished the injury-induced hyperemia.

Response to CGRP. Normal rabbit knees showed a dose-dependent vasodilatation to CGRP administration, with the maximal response occurring at 10 min. The joint capsule showed a 55.0 ± 13.7% increase in perfusion with the 10−8-mol dose, whereas perfusion to the ligament midsubstance rose by 46.5 ± 21.8% with this dose.

In ACL-lesioned animals there was a virtually complete absence of response to exogenous application of CGRP (Fig. 5), with significant differences (P < 0.002; 2-way ANOVA; n = 4 and 7 treated and control knees, respectively) occurring between normal and ACL-sectioned knees. By contrast, the response to CGRP in ACL-sectioned knees that had previously been denervated was restored to normal at the midsubstance of the ligament, and statistical tests showed that the response to CGRP in normal and denervated ACL-transected knees was not significantly different for this region (P = 0.23; n = 7 and 5 for ACL-transected and denervated ACL-transected knees, respectively). Interestingly, the vasodilator response to CGRP at the capsule was enhanced in denervated ACL-sectioned knees compared with the normal response (P = 0.0001). Not surprisingly, the response to CGRP between ACL-transected knees and denervated ACL-transected knees showed significant (P = 0.0001) differences for both regions.

Response to CGRP-(8—37). The CGRP antagonist CGRP-(8—37) caused a fall in normal articular perfusion that was maximal at 15 min. In animals with ACL section, it was clear that for both the MCL and the synovium the response to CGRP-(8—37) was substantially attenuated compared with animals with the ACL intact (Fig. 6). However, in the unstable knee there was a trend toward reduction in perfusion with increasing dose that proved to be statistically significant (P = 0.038; one-way ANOVA; n = 4), although this level of significance was much less than that of the normal response (P = 0.0001; n = 7).

Effect of increasing constrictor tone on CGRP response in normal and ACL-deficient joints. We previously demonstrated in the normal joint that epinephrine-induced vasoconstriction of ligament blood vessels can be completely reversed and converted into a vasodilatation by coadministration of CGRP (13). In the present study we have confirmed this observation for

![Fig. 4. Comparison of laser-Doppler perfusion imager-derived basal perfusion of medial collateral ligament (MCL) and knee joint capsule. Values are shown for normal (open columns; n = 13) compared with ACL-transected (filled columns; n = 9) and denervated ACL-transected (hatched columns; n = 4) rabbit knees. Joint instability caused articular blood flow to increase significantly; however, effect was ameliorated by denervating joint (P < 0.0001; 1-way ANOVA). Tukey's post hoc multiple comparison test was used to give differences between individual data sets. ***P < 0.001; **P < 0.01; *P < 0.05. NS, not significantly different.](http://ajpregu.physiology.org/content/10/5/594/F4)

---

**ACL, knee joint diameter showed a significant increase compared with normal, rising from (in mm) 21.8 ± 0.1 in control knees to 25.1 ± 0.4 in the unstable joint (Fig. 3).**

**The normal rabbit knee joint was found to be well perfused with perfusion to the MCL midsubstance being greater than to the capsular region (Fig. 4).**

**Division of the ACL caused a significant increase in knee joint perfusion at 4 wk posttransection, with flow roughly doubling compared with control in the capsule and the MCL (Fig. 4). Denervation before ACL section abolished the injury-induced hyperemia.**

**Response to CGRP. Normal rabbit knees showed a dose-dependent vasodilatation to CGRP administration, with the maximal response occurring at 10 min. The joint capsule showed a 55.0 ± 13.7% increase in perfusion with the 10−8-mol dose, whereas perfusion to the ligament midsubstance rose by 46.5 ± 21.8% with this dose.**

**In ACL-lesioned animals there was a virtually complete absence of response to exogenous application of CGRP (Fig. 5), with significant differences (P < 0.002; 2-way ANOVA; n = 4 and 7 treated and control knees, respectively) occurring between normal and ACL-sectioned knees. By contrast, the response to CGRP in ACL-sectioned knees that had previously been denervated was restored to normal at the midsubstance of the ligament, and statistical tests showed that the response to CGRP in normal and denervated ACL-transected knees was not significantly different for this region (P = 0.23; n = 7 and 5 for ACL-transected and denervated ACL-transected knees, respectively). Interestingly, the vasodilator response to CGRP at the capsule was enhanced in denervated ACL-sectioned knees compared with the normal response (P = 0.0001). Not surprisingly, the response to CGRP between ACL-transected knees and denervated ACL-transected knees showed significant (P = 0.0001) differences for both regions.**

**Response to CGRP-(8—37). The CGRP antagonist CGRP-(8—37) caused a fall in normal articular perfusion that was maximal at 15 min. In animals with ACL section, it was clear that for both the MCL and the synovium the response to CGRP-(8—37) was substantially attenuated compared with animals with the ACL intact (Fig. 6). However, in the unstable knee there was a trend toward reduction in perfusion with increasing dose that proved to be statistically significant (P = 0.038; one-way ANOVA; n = 4), although this level of significance was much less than that of the normal response (P = 0.0001; n = 7).**

**Effect of increasing constrictor tone on CGRP response in normal and ACL-deficient joints. We previously demonstrated in the normal joint that epinephrine-induced vasoconstriction of ligament blood vessels can be completely reversed and converted into a vasodilatation by coadministration of CGRP (13). In the present study we have confirmed this observation for**

---

**Fig. 4. Comparison of laser-Doppler perfusion imager-derived basal perfusion of medial collateral ligament (MCL) and knee joint capsule. Values are shown for normal (open columns; n = 13) compared with ACL-transected (filled columns; n = 9) and denervated ACL-transected (hatched columns; n = 4) rabbit knees. Joint instability caused articular blood flow to increase significantly; however, effect was ameliorated by denervating joint (P < 0.0001; 1-way ANOVA). Tukey's post hoc multiple comparison test was used to give differences between individual data sets. ***P < 0.001; **P < 0.01; *P < 0.05. NS, not significantly different.**
the intact knee joint, where topical coadministration of epinephrine \((10^{-10} \text{ mol})\) and CGRP \((10^{-9} \text{ mol})\) to the MCL resulted in a dilator response; however, in the ACL-transected knee the same treatment still resulted in vasoconstriction (Fig. 7). Similarly, at the capsule, coadministration of these two agents normally abolishes the vasoconstriction, but in the ACL-transected knee the constrictor response remains (Fig. 7). Thus, despite this increased constrictor tone in the blood vessels of the ACL-transected knee, CGRP remained relatively ineffective as a vasodilator for both the ligament and the capsule.

Effect of nerve stimulation in normal and ACL-deficient joints. In normal joints, a frequency-dependent vasoconstriction \(\text{(<} 0.05; \text{ repeated measures 1-way ANOVA or Mood's median test; } n = 5 \text{ and } 6 \text{ ACL-transected and normal knees, respectively})\) was observed in the ligament and joint capsule after electrical stimulation of the saphenous nerve (Fig. 8). With 30-Hz stimulation, the synovium and MCL midsubstance showed similar falls in blood flow \((18.5 \pm 5.9 \text{ and } 18.2 \pm 5.6\% \text{ for synovium and MCL, respectively})\).

In ACL-sectioned joints, nerve stimulation showed a vasoconstrictor profile similar to control. A general linear model of variance showed that the response in the ligament midsubstance and capsule of injured joints was not significantly different from normal joints \((P = 0.862 \text{ and } 0.110\), respectively\).

**DISCUSSION**

Knee joints that lack an intact ACL are known to become unstable and ultimately show signs of tissue degeneration typical of osteoarthritis \((17, 18, 22, 33)\). In experimentally induced osteoarthritis in dogs where the ACL is surgically transected, osteophytes have been detected as early as 1 wk after treatment \((24)\). Because the animals in the present study were ACL deficient for 4 wk, it may reasonably be assumed that their knees were developing incipient osteoarthri-
This investigation strongly indicates, therefore, that joints are hyperemic during the early stages of osteoarthritis. The observed increase in articular blood flow cannot be a result of the surgical procedure but is probably a result of mechanical instability of the joint, because a comparable sham operation has no effect on knee joint perfusion (4). Because denervation ameliorated the hyperemia in the present study, it appears that the vascular changes that arise after ACL transection are neurogenically mediated.

Previous studies have shown that there is tonic release of CGRP in the normal joint, as evidenced by the fall in perfusion in response to administration of CGRP-(8—37) (13, 31). Therefore, one potential mechanism to explain the increased perfusion of the ACL-deficient joint is increased release of CGRP, leading to a profound vasodilatation. Such increased presence of CGRP in the tissues would ultimately result in down-regulation and/or desensitization of CGRP receptors, and this could explain why administration of exogenous CGRP failed to elicit further vasodilatation at the doses used. It could be argued, however, that the articular vessels were maximally dilated in the ACL-deficient joint and that no vasodilator, let alone CGRP, could increase blood flow in these tissues. By coadministering CGRP with the vasoconstrictor epinephrine, it was possible to test the effectiveness of the neuropeptide while the articular vessels were in a state of increased tone. It has previously been shown in normal joints that this maneuver results in a net dilatation, indicating that CGRP is more potent than epinephrine in these tissues (13). The present study confirmed this finding, but when the coadministration of CGRP and epinephrine was carried out in ACL-deficient knees a constrictor response was still apparent, corroborating the concept of reduced CGRP receptor availability/function. A more striking indication of increased CGRP release comes from the fact that the response to exogenous CGRP was restored in the denervated ACL-sectioned knee. In this instance the endogenous source of CGRP would have been removed and thus any ligand-induced downregulation and desensitization would be avoided. Indeed, the enhanced response to topically applied CGRP in the synovium even suggests a degree of denervation hypersensitivity. Further evidence for extensive CGRP release after ACL transection is afforded by the attenuated response to CGRP-(8—37). The minimal effect of the antagonist on basal perfusion even at the highest dose tested implies that CGRP levels were elevated beyond the point at which CGRP-(8—37) could proficiently exert its full antagonistic effect. Administration of higher doses of CGRP or its antagonist, which may have been sufficient to elicit changes in basal perfusion, was not carried out because...
of concerns regarding potential changes in arterial blood pressure. Further experiments, such as radiolabeled CGRP binding studies and tissue CGRP quantification, need to be performed in the ACL-deficient model to confirm that CGRP is released in large quantities posttrauma, causing receptor downregulation.

The present study also found that ACL transection had no effect on nerve-mediated constrictor responses in the joint capsule and MCL midsubstance. This observation shows that instability-induced joint hyperemia cannot be attributed to a fall in sympathetic drive but is entirely due to the actions of proinflammatory factors such as CGRP. The preservation of sympathetic responses here is in contrast to what has previously been found in chronic models of rheumatoid arthritis. Experiments performed at a similar time point found that adjuvant-induced arthritis caused an attenuation of both sympathetic vasoconstrictor and neuropeptidergic vasodilator effects in rat capsule (30). This suggests that the neurovascular mechanisms contributing to immunologic arthritides may be subtly different from those found in degenerative joint disease.

Neurogenic vasodilatation in the unstable knee is probably a protective physiological response to the initial injury insofar as increasing perfusion to the joint would promote soft tissue healing. However, the persistence of these effects at 4 wk postinjury, particularly in the MCL, could ultimately be detrimental to the long-term integrity of the joint. Chronic hyperemia in the MCL would cause a local rise in hydrostatic pressure, which would upset the equilibrium of Starling forces present in the ligamentous microcirculation, culminating in an increase in interstitial fluid formation. Indeed, this concept has been demonstrated in the ACL-deficient joint, where joint instability led to an augmentation of tissue water content in the majority of articular structures, including the MCL (26). Because tissue water content promotes ligament viscoelasticity (8), MCL hyperemia could indirectly cause a loss of ligament stiffness, and the joint would become even more unstable, particularly if other ligaments in the joint are similarly affected. As an aside, it has been suggested that angiogenesis, which is known to occur in the MCL of an ACL-deficient knee (26), may further jeopardize the functional integrity of the MCL by disrupting the homogeneous architecture of the ligament substance. Thus the combination of flow-related viscoelasticity and angiogenesis-related collagen fibril disorganization may conspire to bring about the ultimate demise of the MCL as an articular stabilizer. The additional loss of MCL function means that knee stability will be further compromised in varus and internal-external rotation. This syndrome of multiple plane joint instability would exacerbate joint tissue degeneration and may explain the rapid deterioration of knees after ACL rupture.

The ACL-deficient joint is known to show other signs of inflammation. Histological studies have described synovial hyperplasia along with mononuclear cell infiltration into the subsynovial region of the joint (20, 32). The increase in joint diameter reported here could have been a result of bone remodeling and osteophyte formation but was more likely a consequence of edema formation in the knee, which may also have been mediated by CGRP activity. Although CGRP can by itself increase vascular permeability (19), its contribution to inflammatory edema is primarily produced by synergism with other mediators of extravasation, such as substance P and histamine (1, 2, 7, 10).

In conclusion, this study showed that transection of the ACL led to a neurogenically driven hyperemic response in the medial compartment of the rabbit knee joint. Although alternative mediators cannot at this stage be discounted, the present investigation provides indirect evidence of CGRP involvement in effecting this posttraumatic hyperemia.

Perspective

In light of the putative correlation between changes in ligament blood flow and a decline in soft tissue material properties (4), posttraumatic neurogenic inflammation may contribute to the pathogenesis of instability-induced joint degeneration. The current management of ACL rupture involves either reconstruction or primary repair of the damaged cruciate to help reestablish joint stability. Because the remaining supporting structures are responsible for minimizing any abnormal kinematics of the joint, the homeostasis of these tissues is of paramount importance for articular recovery. With respect to maintaining joint perfusion, a large enough dose of CGRP-(8—37) could provide a useful means of treating chronic posttraumatic synovitis as well as protect the joint from further loss of function. At present only CGRP peptide fragments are available as CGRP receptor antagonists, which limits their scope in terms of routes of administration and duration of action. However, if drug development follows the same pattern as that of tachykinin receptor antagonists, which were initially only peptide fragments but are now available as nonpeptide compounds, then the future possibility exists of orally active nonpeptide CGRP receptor antagonists, which could be used as a short-term therapy after ACL damage to prevent injurious articular hyperemia.

The authors acknowledge the technical assistance of Craig Sutherland.

J. J. McDougall is a recipient of concurrent postdoctoral fellowships from the Alberta Heritage Foundation for Medical Research (AHFMR) and the Medical Research Council of Canada. W. R. Ferrell is a Reader in Clinical Physiology and R. C. Bray is an AHFMR Scholar in Orthopaedic Surgery.

Address for reprint requests and correspondence: J. J. McDougall, McCaig Centre for Joint Injury and Arthritis Research, 3330 Hospital Drive NW, Univ. of Calgary, Calgary, Alberta, Canada T2N 4N1 (E-mail: mc dougaj@ucalgary.ca).

Received 10 June 1998; accepted in final form 2 December 1998.

REFERENCES

2. Brain, S. D., and T. J. Williams. Interactions between the tachykinins and calcitonin gene-related peptide lead to the