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Brain activity in a nonhuman primate model of chymopapain-induced discogenic low back pain

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Introduction

Chymopapain has been used to treat herniated lumbar intervertebral discs (IVDs) and a common adverse effect of chymopapain treatment is low back pain (LBP). (Benoist et al., Spine, 1993) Nonhuman primates are an ideal species to model clinical LBP have IVDs that are anatomically similar to those of humans and undergo comparable to that of human IVDs. In addition, nonhuman processing brain areas similar to those of humans. (Ghitoi et al., study developed a behavioral model of chymopapain- and identified stimulation-evoked brain activation with ance imaging (fMRI).

Material and methods

al treatment procedure and behavioral testing

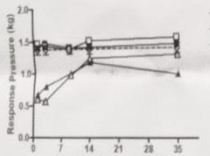
were reviewed and approved by the Hamamatsu University School of he HPR Animal Care and Use Committee. A total of 8 young adult male ques (weight range 3.7-4.3 kg) were used, and divided into 3 groups = 2; chymopapain-treated: n = 2). With the macaque re at the level of L4/L5 vertebrae were eter was pushed until a facial grimace was reported. Under anesthesia and

brain activation

were obtained with a 3.0T MRI of the IVDs were graded at each activation was assessed using a er back was alternately stimulated ressure responses and brain , and 35 days after treatment.

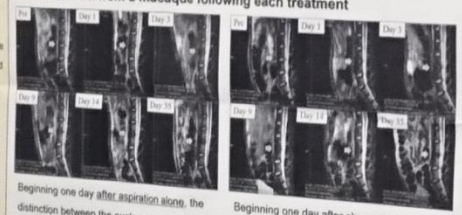
Results

1. Pressure sensitivity of the back following each treatment.



Response pressure thresholds (kg) were measured 1, 3, 9, 14 and 35 days after either chymopapain treatment (n = 2) or aspiration (n = 2) of the IVD. Pressure thresholds of untreated ("control") macaques are expressed as mean ± SD.

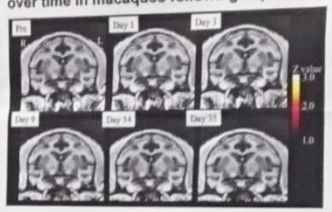
2. Lumbar MRI from a macaque following each treatment



Beginning one day after aspiration alone, the distinction between the nucleus and anulus was unclear (Pfirrmann grade III). The disc pathology appeared stable (grade III from 3 to 35 days after aspiration). Gray arrows show the intervertebral discs between L4/L5.

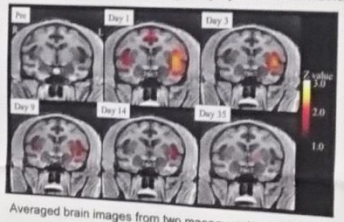
Beginning one day after chymopapain treatment, the distinction between the nucleus and anulus was unclear (Pfirrmann grade III). The disc pathology appeared stable (grade III from 3 to 35 days following treatment). Gray arrows show the intervertebral discs between L4/L5.

3. Lack of low back pressure-induced brain activation over time in macaques following aspiration alone.



Averaged brain images over time from two macaques in which the nucleus pulposus was aspirated. There was a lack of significant pressure-evoked brain activation in these macaques.

4. Low back pressure-induced brain activation over time in macaques following chymopapain treatment.



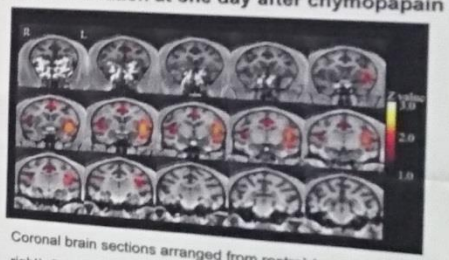
Averaged brain images from two macaques treated with chymopapain. Beginning one day after chymopapain treatment, activation of the secondary somatosensory cortex (SII) and insular cortex (Ins) was observed. There was no significant activation 9, 14 and 35 days after chymopapain injection.

Table. Brain activation during low back pressure stimulation in macaques after chymopapain treatment over time

Area	Hemisphere	Z value	Coordinates (mm) x	y	z
Day 1 after chymopapain					
SII and Ins	Right	0.22	-16	18	4
	Left	0.29	18	18	6
Thalamus	Right	0.15	8	-2	8
	Left	0.17	-6	-4	8
Cingulate cortex		0.24	0	-20	10
Day 1 after chymopapain					
SII and Ins	Right	1.98*	-14	16	4
	Left	2.72*	16	16	6
Thalamus	Right	0.32	4	-4	6
	Left	0.22	-6	-2	4
Cingulate cortex		1.62	0	-22	-6
Day 3 after chymopapain					
SII and Ins	Right	1.32	-16	16	4
	Left	2.41*	14	14	4
Thalamus	Right	0.31	4	-4	6
	Left	0.28	-6	2	2
Cingulate cortex		0.76	2	-20	-4
Day 9 after chymopapain					
SII and Ins	Right	-1.22	-14	14	-6
	Left	1.64	12	10	2
Thalamus	Right	0.34	4	2	4
	Left	0.36	-4	2	2
Cingulate cortex		0.43	2	-22	-6
Day 14 after chymopapain					
SII and Ins	Right	0.78	-10	14	4
	Left	1.38	14	10	4
Thalamus	Right	0.87	6	2	6
	Left	0.56	-6	4	2
Cingulate cortex		0.46	0	-24	-6
Day 35 after chymopapain					
SII and Ins	Right	0.71	-14	8	6
	Left	0.64	16	8	6
Thalamus	Right	1.83	6	4	2
	Left	1.43	-8	4	2
Cingulate cortex		0.38	2	-22	-4

Z values of peak voxels are shown. Stereotaxic coordinates according to Horsley-Clarke's stereotaxic coordinates.
* Peak voxels were considered significant ($P < 0.05$) at Z score > 1.96.

5. Brain activation at one day after chymopapain treatment



Coronal brain sections arranged from rostral (upper left) to caudal (lower right); 2.0 mm separation. One day after treatment, bilateral pressure-induced activation of the SII and Ins was observed.

Conclusions

- Chemonucleolysis of the nucleus pulpous in the macaque leads to low back pressure hypersensitivity and significant brain activation in the SII and Ins.
- Aspiration of the nucleus pulposus alone led to notable pathology of the IVDs, but there was no change in pressure sensitivity or significant brain activation.
- The current macaque model of discogenic LBP parallels clinical LBP and could be used to further elaborate pain mechanisms.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