Ectopic discharge in surgically- and chemotherapeutically-induced neuropathic pain models: an electrophysiological comparison

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1. AIM OF INVESTIGATION:

Neuropathic pain is a common syndrome associated with nerve injury resulting from a variety of causes: trauma, viral infection, metabolic diseases such as diabetes, or as one of the adverse effects of chemotherapy. The treatment of neuropathic pain is difficult and remains an unmet clinical need. However, though great effort has been made to explore new therapies, the basic mechanisms of neuropathic pain are still not fully understood. Ectopic discharge (ED) is a common electrophysiological feature observed in the peripheral nerves of neuropathic pain models. However, few studies have attempted to compare the properties of ED in different neuropathic pain models. To investigate whether differences in ED characterise neuropathic pain models of different aetiologies, we compared the basic properties of ED from rat models of chronic constriction injury (CCI), spinal nerve ligation (Chung) and chemotherapy-induced neuropathy (Chemo).

2. METHODS

Adult Sprague-Dawley rats were used. CCI and Chung models were prepared as described previously. The electrophysiological experiments were carried out 2 weeks after modelling. Chemotherapy-induced neuropathic pain was induced by multiple paclitaxel injections (4 mg/kg, iv, twice a week, 5 times). In all models, the neuropathic pain state was validated behaviourally with von Frey hairs. ED was recorded from sural nerve filaments in CCI models below the nerve ligation area, from L4 dorsal root filaments in the Chung model (with clear receptive fields on the ipsilateral hindpaw) and from peripheral ends of sectioned sural nerve fibres in chemotherapy models.

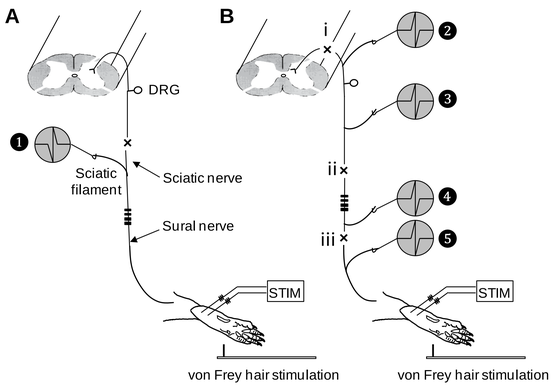


Figure 1. A schematic diagram indicating the sites of recording and nerve sections. Different combinations can be adopted to produce specific preparations to record ectopic discharge from any particularly site. For example, 1 or 4 with section at iii, for recording ED originating from the neuroma area; 2 or 3 with section at i or ii for ED generated from DRG; 5 for ED from more distal areas of axons connected with the receptive field.

3. RESULTS AND DISCUSSION

a. Origins of ectopic discharge

We found that ED in Chung models was mainly generated at the level of the DRG, whilst in CCI models, ED originated at both the level of the neuroma, around the ligation area, and from the DRG. Ectopic activity in chemotherapy-induced neuropathic pain models, had origins more toward the peripheral ends, either at the receptive fields or axons proximal to the receptive fields.

Model	CCI	CCI	Chung	Chung	Chemo	Chemo
Recording site (Ref: Figure 1)	Neuroma (4)	Distal (5)	DRG (2)	Distal (5)	Distal (5)	DRG (3)
Active/ total fibres (%)	247 /756 (32.7%)	30/358 (8.4%)	196/419 (46.8%)	46/425 (10.8%)	168/541 (31.1%)	37/383 (9.7%)

b. Frequency of ectopic discharge

With 'classic' recording setups (blue columns in Table 1), ED in surgically-induced neuropathic pain models (CCI and Chung models) was of higher frequency compared to that in chemotherapy-induced neuropathy. However, using 'less-favoured' set-ups (white columns in Table 1), not only was there less fibres firing ED, but also the frequency of ED was much lower than the in the 'classic' recording set-ups.

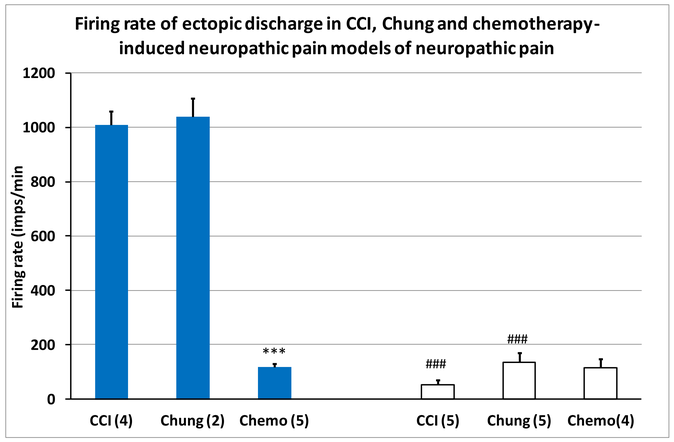


Figure 2. Comparison of firing rate of spontaneous activity in CCI, Chung and chemotherapy models. The numbers in bracket correspond to the set-ups shown in Figure 1. Blue and white columns correspond to the blue and white columns in the Table 1. Blue columns were results from the 'classic' recording set up; the white columns were results from 'less-favoured' set-ups. ***: $P < 0.001$, compared the Chung and CCI models.###: $P < 0.001$, compared to the same models with 'classic ' set-ups on the left.

c. Firing patterns of ectopic discharge

'Burst-like' and 'regular' firing are the predominant patterns of ED in CCI and Chung models using the 'classic' recording set-ups (blue columns in the Table 1). In chemotherapy model the major ED pattern was irregular.

Pattern	Burst-like	Regular	Irregular	Other	Total
Chung	23.0% (45)	46.4% (91)	27.0% (27)	3.6% (7)	100% (196)
CCI	47.8% (118)	8.5% (21)	25.5% (63)	18.2% (45)	100% (247)
Chemo	9.5% (16)	6.5% (11)	82.7% (139)	1.2% (2)	100%(168)



Figure 3. Example of typical firing patterns of ectopic discharge: A: burst-like, B: Regular, and C: irregular

d. Categories of fibres with ectopic discharge

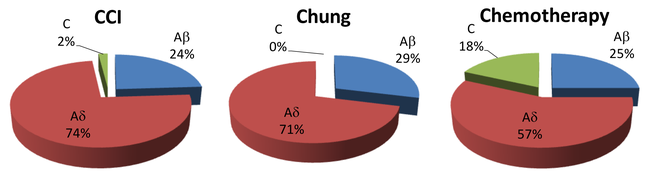


Figure 4. shows the categories of fibres recorded in CCI, Chung and chemo-therapy-induced neuropathy models. In CCI and Chung models, the majority of fibres firing spontaneous activity were Aβ ($CV > 20$ m/s) or Aδ ($CV > 2$ m/s but $\leq$ 20 m/s) fibres and few C-fibres ($CV \leq 2$m/s). However, in the chemotherapy model, there were a significant proportion of 'active' C-fibres.

4. CONCLUSION

Ectopic discharge in surgically- and chemotherapeutically-induced neuropathic pain models are different in their origin, firing frequency and patterns of activity. These differences may be related to the different aetiologies underlying neuropathic pain in these different models and may have significant clinical relevance.