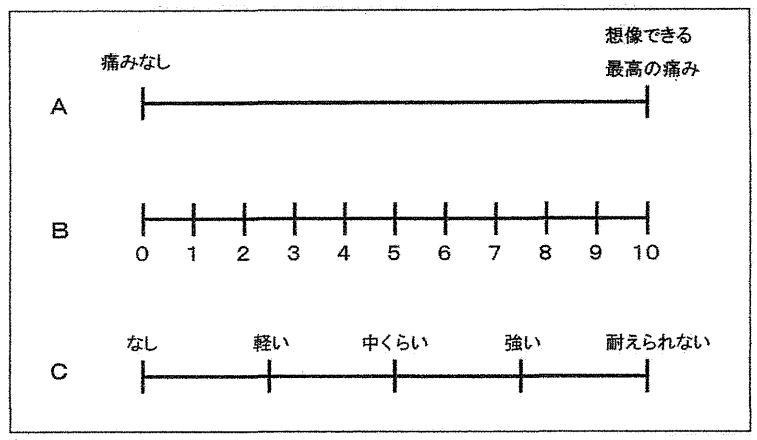

図1 痛みのスケール
A：VAS，B：NRS，C：VRS

最もよく用いられるスケールであるVASにつき述べるが，これは100mmの線分の片方の端に痛みのない状態として0(ゼロ)の数字を与え，もう片方には想像できる最強の痛みとして100の数字を与えておき，患者の痛みが0から100の方向にどの程度向かっているかを示してもらい，0からその点までの長さ(mm)をもってその患者の痛みの強さとする方法である．本法は非常に感度が高いことが報告されている[2]．この方法では治療前後の痛みの程度の変化や，経時的な痛みの程度の変化を評価できる．また，非常に直感的に痛みを評価でき，かつ簡便であることから頻用されている．この方法で注意すべき点は，ほかの患者との比較ができないことである．言い換えると1人の同一患者における痛みの程度とその変化を見るときに意味を成すことである．

2. 痛みの程度を人間の表情で評価しようとする方法

Face Scaleが用いられている．痛みのない状態を笑顔で表わし，最も痛みの強い状態を泣きはらした表情で示し，その間に4つの表情を段階的に示したWong-Baker Face Scaleが最もよく用いられている[3]．

3. 質問紙法による評価法

痛みの強さのほか，性質，場所，時間的変化などを分析する方法であり，McGill Pain Questionnaire (MPQ；マギルあるいはマクギル疼痛質問表)が最も代表的なものである[4]．この方法は痛みを表現する感覚・情動を表わす102の言語を示しておき，その中から患者が選択した言語を総ランク数，選択した言語の数，痛みの程度につき評価するものである．信頼性，妥当性とも適切であることが知られている．質問への回答に時間がかかる(約20分)ので，質問事項を減らした簡易法も用いられている．

4. 行動から評価する方法

Prince Henry Pain Scaleは術後の患者の行動から疼痛を評価しようとする方法である[5]．0点から4点の5段階に分け，0は咳をしても痛まない，以下，1：咳をすると痛むが，深呼吸では痛まない，2：深呼吸をすると痛むが，安静にしていれば痛まない，3：多少安静時痛はあるが，鎮痛薬は必要ない，4：安静時痛があり，鎮痛薬が必要である，としたものである．

そのほかBehavioral Pain Scale(BPS)は人工呼吸中の患者の痛みに関する評価法で，表情，上肢の動き，人工呼吸器との同調性の3項目につき評価する方法である[6]．

Ⅲ 機器を用いた方法

1. 電流知覚閾値検査

電流知覚閾値とは皮膚に与えた電流によって知覚を感じる最小電流値のことである．この値が小さい

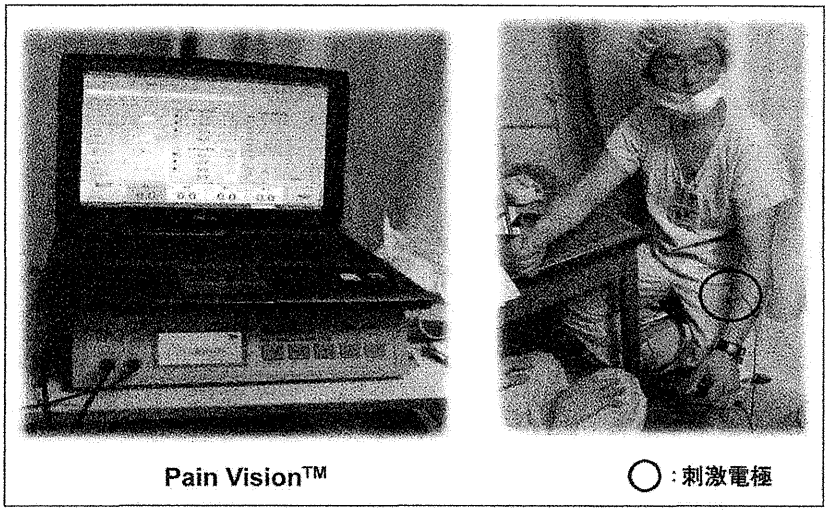

図2　Pain Vision™

ということは，低い刺激で知覚が起こることになるので知覚過敏の存在を示す．大きい場合は知覚鈍麻となる．

2. Neurometer™[7]

電流知覚閾値と疼痛耐性閾値を測定できる装置である．疼痛耐性閾値とは，電気刺激を徐々に強めていき，疼痛に耐えられなくなったときの電流値をいう．電気刺激の頻度によりAβ，Aδ，およびC線維の感受性を別々に区別して評価できる．

3. Pain Vision™[8] (図2)

痛みの強さを，痛みを伴わない異種感覚に置き換えて定量的に測定する機器である．人間は同時に2つの部位の痛みを区別して評価できないことを利用している．すなわち痛みのない部分に電気刺激を与え，その刺激が現在実際に存在する痛みより大きく感じる時点での電気刺激の大きさを「痛み度」として定量するものである[9]．

「痛み度」の求め方は以下のとおりである．

①電流知覚閾値の測定

左前腕の電極から徐々に強くなる電流刺激を与え，違和感を感じた時点で左手のスイッチを押してもらい，そのときの電流値を測定する．この測定を3回行い，平均の電流値を電流知覚閾値とする．

②痛み対応電流値の測定

患者の持っている痛みよりも左手の電流刺激が強く感じられた時点でスイッチを押してもらう．そのときの電流値を痛み対応電流値とする．

③痛みの定量

感じた痛みの強さを「痛み度」として，電流知覚閾値と痛み対応電流値から下記の式で算出する．

痛み度＝100×(痛み対応電流値−電流知覚閾値)
／電流知覚閾値

Ⅳ　そのほかの方法

1. 脳画像診断[10]

fMRI，PET，MRSなどが用いられている．fMRIは，神経活動に伴う局所脳血流量の変化と血中ヘモグロビンの酸素化の度合いの変化をMRIの信号強度に反映させて測定するものである[11]．痛み刺激などの刺激時に脳のどの部分の活動が亢進するかなどにつき評価できる．

2. 薬理学的疼痛機序判別試験(Drug-challenge Test：DCT)[12),13)]

鎮痛に関与する薬物を少量ずつ静脈内投与して痛みの程度の推移を観察し，痛みの発生機序を策定しようとする方法である．特に神経障害性疼痛の発生機序の推測に用いられている．用いられる薬物とし

てはモルヒネ，リドカイン，ケタミン，フェントラミン，ATP，抗うつ薬，バルビツレートなどであり，それぞれ反応する薬物に則ってその後の治療薬や治療法の選定に役立っている．例えば，フェントラミンテストで一時的にも痛みの程度が減少すれば，その後，交感神経(節)ブロックを行おうとするものである．

おわりに

痛みという感覚はあくまで主観的なものであることから，これを評価，定量化することが困難である．しかし，臨床の場面では痛みを理解し，適切な治療法を選択するために可能な限り適切に評価する必要があり，さまざまな方法を利用・併用して評価している．本稿では疼痛スケール，機器による評価，脳画像を用いる方法，および薬物を用いる方法について紹介，解説した．今後，より客観的な評価法の開発が求められる．

参考文献

1) 平川奈緒美："痛み"のスケール．ペインクリニック 29：1580-1588，2008
2) Scott J, Huskisson EC：Graphic representation of pain. Pain 2：175-184, 1976
3) Wong DL, Baker CM：Pain in children：comparison of assessment scales. Pediatr Nurs 14：9-17, 1988
4) Melzack R, Katz J：Pain measurement in persons in pain. Textbook of Pain, 4th ed. Edited by Wall PD, Melzack R. Churchill Livingstone, Edinburgh, 1999, 409-426
5) Torda TA, Hann P, Mills G, et al.：Comparison of extradural fentanyl, bupivacaine and two fentanyl-bupivacaine mixtures of pain relief after abdominal surgery. Br J Anaesth 74：35-40, 1995
6) Payen JF, Bru O, Bosson JL, et al.：Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 29：2258-2263, 2001
7) Katims JJ(光畑裕正，宮崎東洋訳)：疼痛患者での知覚神経機能の電気生理学的診断法による評価：神経選択的電流知覚閾値(CPT)と疼痛耐性閾値(PTT)．ペインクリニック 19：535-549，1998
8) 嶋津秀昭，瀬野晋一郎，加藤幸子ほか：電気刺激を利用した痛み定量計測法の開発と実験的痛みによる評価．生体医工学 43：117-123，2005
9) 加藤実，後閑大，小林あずさ：Pain Vision．ペインクリニック 30：23-27，2009
10) 福井弥己郎(聖)，岩下成人：機能的脳画像診断機器(fMRI，PET，MRS)．ペインクリニック 30：15-22，2009
11) Poznanski RR, Riera JJ：fMRI models of dendritic and astrocytic networks. J Integr Neurosci 5：273-326, 2006
12) 小川節郎：ドラッグチャレンジテストの意義と方法．ペインクリニック 17：587-595，1996
13) 加藤実：ドラッグチャレンジテスト．ペインクリニック 24：323-329，2003

Evaluation and Monitoring of Pain

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International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional tissue damage, or described in terms of such damage". This means that pain is a completely subjective sensation. Therefore, it is very difficult to evaluate this sensation quantitatively. We must, however, try to evaluate pain in the clinical field because the evaluation of pain is indispensable for the diagnosis of diseases and the selection of treatments. Some methods to evaluate pain such as pain scales, pain questionnaire, devices for the measurement of the degree of pain, and drug-challenge test with pharmacological analysis of pain are described in this article.

Key Words : Pain, Evaluation, Pain scale, Questionnaire

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神経障害性疼痛の診断と治療

小川節郎*

［要旨］神経障害性疼痛はペインクリニック診療上，治療が困難な疼痛性疾患の一つである．その理由は疼痛の発生機序が複雑で，機序に見合った鎮痛薬や鎮痛の手段の選択が明確になっていないことがあげられる．本稿では，末梢の神経線維の状態，本症の末梢性疼痛機序に関し，異所性イオンチャネル，神経成長因子の関与，リゾホスファチジン酸の作用，エファプスの発生，アロディニアの発生機序，グリアの関与などにつき解説し，治療においては疼痛機序に見合った鎮痛法を選択することの重要性を強調した．また，近年，本症に対する薬物療法に注目が集まっているので，最近の情報についても解説した．

キーワード：神経障害性疼痛，疼痛機序，神経線維，薬物療法

はじめに

神経障害性疼痛はペインクリニック診療上，治療に困難をきたす疼痛性疾患の一つである．その理由は疼痛の発生機序が複雑で，機序に見合った鎮痛薬や鎮痛の手段の選択が明確になっていないことがあげられる．本稿では本症の疼痛機序に関し解説した後，最近の本症に対する薬物療法について述べたい．また，神経障害性疼痛である特発性三叉神経痛の特徴のある症状と発生機序との関係にふれることにより，本症の神経生理学的な側面についても考察した．

Ⅰ　神経線維について

まず疼痛の発生場所である末梢神経組織の形態を再確認したい．**図1**にはウサギの頚部迷走神経切断面の電子顕微鏡写真を示した．触覚を司る太い有髄線維のAβ神経線維，速痛を司る細い有髄線維のAδ神経線維および遅痛や自律神経機能を司る無髄のC神経線維を見ることができる．この図は正常な状態の末梢神経であり，おのおのの神経線維がお互いに絶縁状態であることがわかる．この神経線維の解剖学的，病理的，機能的な異常により神経障害性疼痛が発生してくる[1]．

神経障害性疼痛は国際疼痛学会(IASP)により次のように定義されている[2]．すなわち，神経障害性疼痛とは「神経系の一次的損傷あるいは機能的障害によって発生する痛み」とされている．このような痛みを起こす疾患としては末梢性と中枢性に分類されて，末梢性の疾患では外傷性神経損傷，神経圧迫や絞扼，多発性ニューロパチー，神経叢損傷，四肢切断後の幻視痛や断端痛，帯状疱疹後神経痛，三叉神経痛，術後瘢痕症候群，がん性ニューロパチーなどが含まれる．一方，中枢性では脳内出血，脳梗塞などの脳卒中，脊髄損傷，脊髄空洞症などがあり，どれも非常に難治性の疼痛となる．

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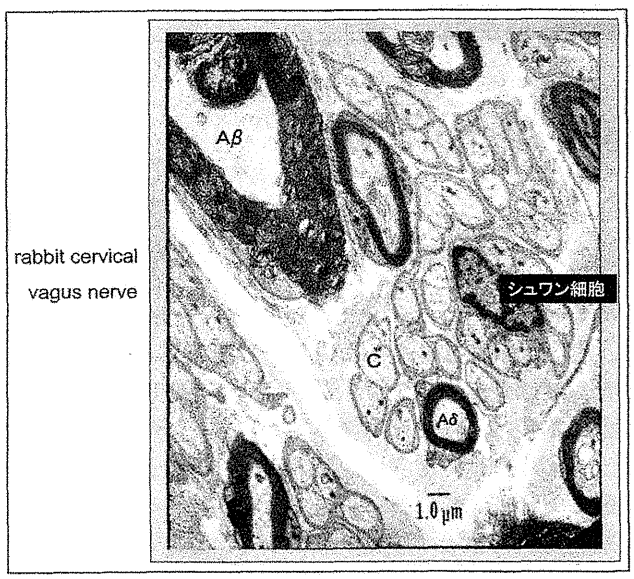

図1　ウサギの頸部迷走神経断面電子顕微鏡写真

Ⅱ　神経障害性疼痛の発生機序[1)]

本症の発生機序については完全には解明されていないが，いくつかの機序が解明されている．まず，末梢で神経組織が損傷されると，その部位に異所性ナトリウムチャネルやαアドレナリン受容体が発現してきて，この受容体に，付近の交感神経から遊離したり循環してきたカテコラミンが結合すると，異常な神経発火が起こって痛みが発生する(**図2**)．また，からしの成分のカプサイシンや熱に反応するカプサイシン受容体(transient receptor potential：TRPスーパーファミリーに属するTRPV1受容体)が炎症により放出されるブラジキニンやアデノシン三リン酸(ATP)の存在下では過敏化し，通常では活性化しない35℃程度の熱で活性化して，神経の異常興奮を起こすようになることも原因の一つである．

ほかにも，損傷された末梢神経内の交感神経線維が，後根神経節に枝を出してきてこれを囲み(basket formation)，これを刺激して自発痛を起こすことも明らかになっている(**図2**)．また，末梢神経が損傷されると，脊髄後角において，触覚を司る有髄神経線維であるAβ線維が芽を伸ばして，疼痛伝達に関与する脊髄2次ニューロンと直接接合することも判明している．このような異常が起こると，触刺激が脊髄で痛みに変換されてしまい，アロディニアの原因となる(**図2**)．

最近，組織損傷に伴って脊髄において産生され発現するリゾホスファチジン酸(LPA)の作用が注目されている[3)]．この物質は，一次求心線維の脊髄後根を取り巻くシュワン細胞に作用して脱髄を誘発し，隣接する神経線維同士の電気的短絡を起こし，異常な神経発火を起こして痛みの発生に至る．また，この物質は神経の発芽を促し，ephapseの発生に関与していることが判明している(**図3**)．

さらに，痛み刺激が繰り返し中枢神経に到達すると，それを受け取った神経細胞が機能的変化を起こし，過敏になることも明らかになっている(中枢性感作)．この機序には脊髄や中枢神経内のNMDA(N-methyl-D-aspartic acid)受容体が関係している．

一方，われわれの体内には，疼痛抑制系の神経系が存在している．これらの神経は中枢神経内から脊髄に降りてきており，下行性疼痛抑制神経系と呼ばれている．これらの神経系の末端からはセロトニンやノルエピネフリンが分泌され，疼痛を抑制することが判明しているが，神経因性疼痛患者ではこの神経系の活動が低下している場合があることも報告されている．

さらに人体にはさまざまな神経反射機構が備わっているが，痛みが繰り返し発生したり，持続的な場合には，この反射機構の活動が亢進する．すなわち，痛み刺激が交感神経や運動神経を興奮させ，局所の循環障害，筋緊張が起こり，それが痛みを発生して，またそれが交感神経や運動神経を興奮させるといった痛みの悪循環が起こる．

また，末梢においても，触覚を司る有髄の太い線維が刺激されると疼痛を抑制することが知られており，これを痛みの門調節機構(gate control mechanism)といっているが，一部の帯状疱疹後神経痛な

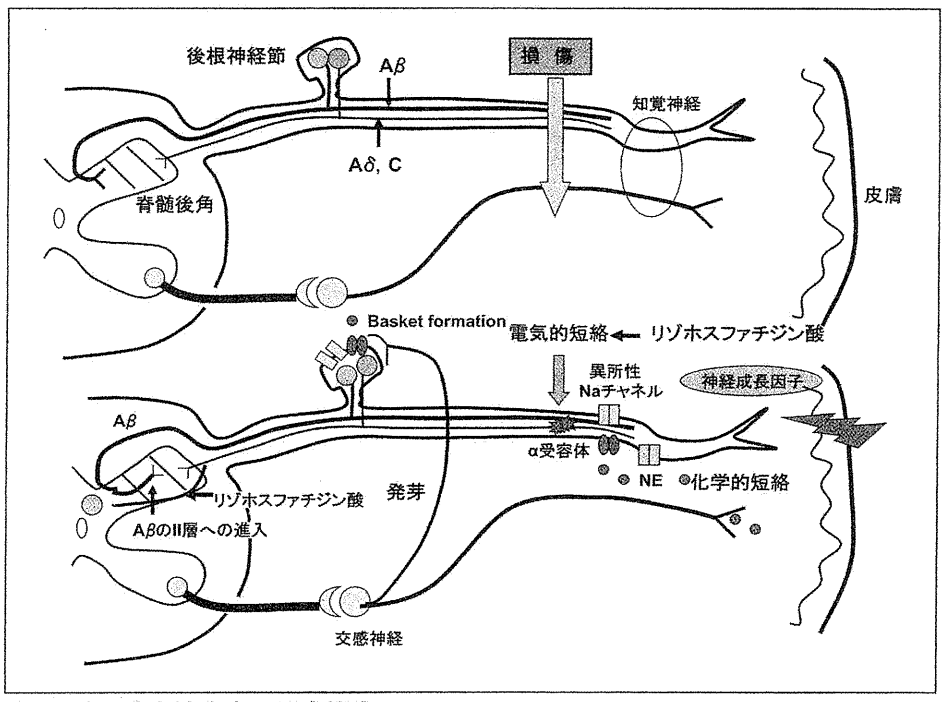

図2　神経障害性疼痛の発生機序
説明は本文参照.

どのようにこの太い有髄線維が選択的に減少するような病態では，門調節機構が破綻して痛みの原因になる可能性がある.

Ⅲ　Gliaと痛み(図4)[4),5)]

従来，脊髄のレベルにおいては，痛みの発生，伝達はニューロンによってのみ行われていると考えられてきた．Astrocyteやmicrocyteなどのgliaは神経組織を物理的に支持するためのみの働きしか持っていないと考えられてきたが，最近の研究からこれらgliaが神経因性疼痛の発生に関与していることが明らかになった.

Gliaが痛みに関与していると考えられる二つの現象が注目されている．一つは，HIV-1感染症患者の痛みで，これらの患者の多くには明らかな痛みの発生源がないにもかかわらず痛みが発生していることから，神経を好む細菌やウイルスの感染の場であるgliaの存在が注目されてきた．もう一つは組織損傷部位を越えた痛み感覚の広がりが見られるといった現象(extra-territorial pain)を説明する場合，一つのgliaが数本の神経線維を支持している事実から，この現象とgliaとの関係がクローズアップされてきたのである.

これらの現象を起こす原因として，gliaの細胞膜におけるタンパク質の発現が関与していることが明らかになった．すなわち，神経線維が損傷を受けたり，gliaへの病原体の感染が起こると，gliaの細胞上に$P2X_4$というタンパク質が発現するということである．このタンパク質は一つのgliaが支持している他の正常な神経線維にも影響を及ぼし，痛みを発生させたり，損傷された神経線維と隣接する神経線維にも痛みを起こすように働くことが明らかになったのである．すなわち，損傷部位を越えて出現する痛覚過敏帯の発生機序を説明する説の一つとなったことになる.

この現象から，complex regional pain syndrome (CRPS)などの神経障害性疼痛の特徴を説明できる．Complex regional pain syndromeと表現されるこの

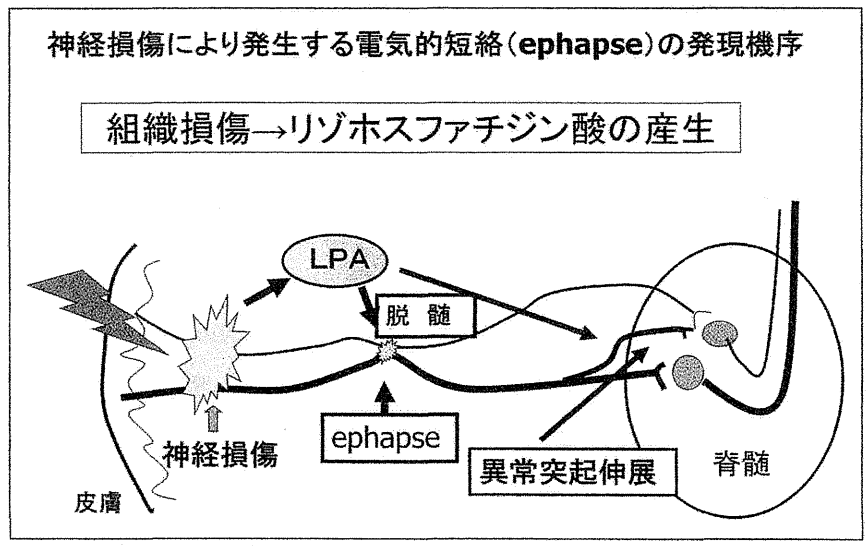

図3　神経障害とリゾホスファチジン酸の作用
説明は本文参照.　〔文献3)より引用・改変〕

病態であるが，このregionalという単語の意味するところは，障害の部位(area)を越えた区域(region)に疼痛が広がるという意味である．このareaを越えて広がる疼痛の発生機序の一つとして，gliaが役割を演じていると考えられる．

これまでも，gliaは一次求心線維の末端から遊離されるP物質やカルシトニン遺伝子関連物質，アデノシン三リン酸などや，一酸化窒素，プロスタグランジンなどに反応して活性化されることが判明している．今回の新しい発見がCRPSなどの難治性慢性疼痛の治療法の確立に寄与するものと期待されている．

Ⅳ　神経障害性疼痛の薬物治療[1),6),7)]

神経障害性疼痛の発生・維持機序がさまざまなので治療法もその機序に見合ったものが必要となる．

神経障害性疼痛の治療法には大きく分けて，①薬物療法，②神経ブロック療法，③神経刺激療法，④手術療法，⑤リハビリテーション，⑥その他があるが，本稿では薬物療法に関しての話題に限った．

基本的な治療薬としては，第1選択薬として三環系抗うつ薬とオピオイド系鎮痛薬があげられ国際的に認められている．第2選択薬としては抗痙攣薬，SSRI，抗不整脈薬，局所麻酔薬，そしてNMDA受容体拮抗薬が入っている(**表1**)[6)]．

最近，薬物の効果を表わす基準として，number needed to treat(NNT)という指標が用いられて来ている．1人の患者に50%以上の痛みの減少を得るのに，何人の患者にその薬物を投与すればよいか，を示した指標である．例えば5名の患者にある薬物を投与して1人にのみ50%以上の鎮痛が得られた場合，その薬物のNNTは5となる．したがってNNTが1という薬物はどの患者に与えてもそのすべてに有効であることを示すことになる．このNNTを指標としてFinnerupら[7)]は2005年，神経障害性疼痛に対するさまざまな薬物のNNTを報告した(**図5**)．これによると，三環系抗うつ薬が最も有効であり，以下，抗痙攣薬のカルバマゼピン，オピオイド，トラマドール，そしてガバペンチンとプレガバリンの順となっており，**表1**と同様な結果となっている．

Ⅴ　中枢神経系の関与[8)]

痛みの認知機能は中枢神経系が司る．中枢神経内においても痛みの認知，修飾に関して複雑な相互関

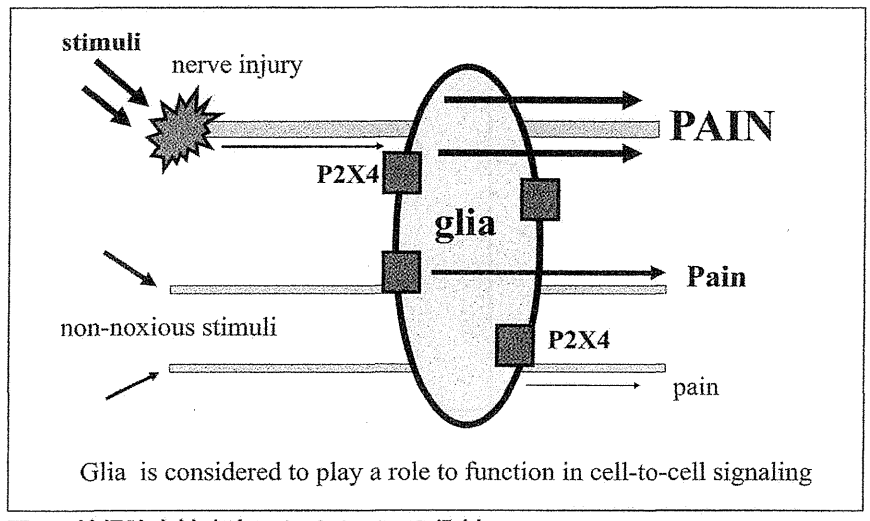

図4　神経障害性疼痛におけるGliaの役割
組織損傷やgliaへの感染によりglia細胞膜上に$P2X_4$タンパクが発現する．その作用により，同一gliaが支持する神経線維の興奮を起こす．
〔文献4)より引用・改変〕

表1　各種神経障害性疼痛に対する治療薬の第1選択薬

Diabetic neuropathy	amitriptyline (Max et al., 1987) dextromethorphan (Nelson et al., 1997) gabapentin (Backonja et al., 1998) oxycodone (Watson et al., 2003) tramadol (Harati et al., 1998)
Post herpetic neuralgia	amitriptyline (Watson et al., 1982) gabapentin (Rowbotham et al., 1998) oxycodone (Watson and Babul, 1998) pregabalin (Dworkin et al., 1998)
Central post stroke pain	amitriptyline (Leijon and Boivie, 1989) lamotrigine (Vestergaard et al., 1982)

〔文献6)より引用〕

係がある．特に視床，帯状回，前頭葉，大脳基底核・帯状核，大脳皮質知覚領野などが深く関与している．これらの機能的関係については最近機能的脳画像診断により徐々に解明されてきている．

中枢神経系を対象とした治療法も行われており，電気痙攣療法，脳深部刺激療法などが臨床的に用いられている．詳細は文献[8]に譲る．

Ⅵ　特発性三叉神経痛の不思議[9]

特発性三叉神経痛は特徴的な臨床症状を持つ神経障害性疼痛である．すなわち，①非侵害性刺激により誘発される，②一過性の増強を見る，③刺激をやめても数十秒間続く，④刺激点を越えてその三叉神経領域全体に痛みが広がる，⑤数十秒で自然と消失する，⑥痛みのある三叉神経領域の知覚障害が見られない，⑦末梢神経や中枢神経障害症状がほとんど見られない，⑧末梢神経ブロックが有効，⑨抗痙攣薬が有効，などの特徴を持つ．

これらの特徴をよく説明する説として，1994年，Rappaportら[9]によるtrigeminal ganglion ignition

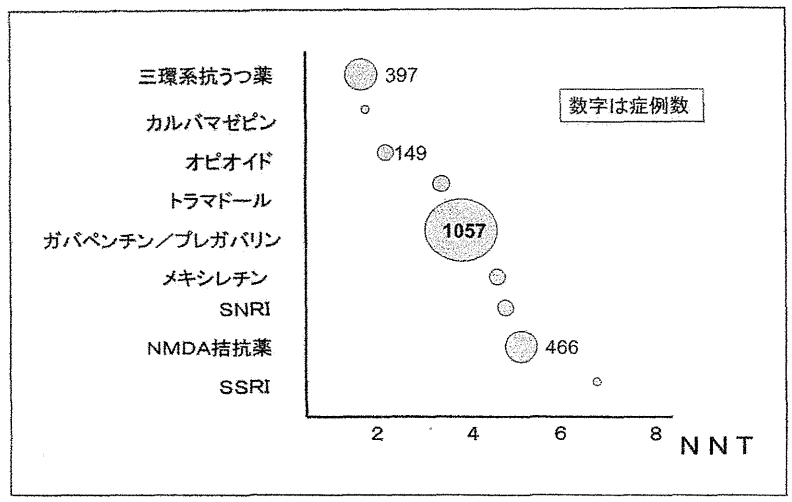

図5　神経障害性疼痛に用いる薬物のNNT

〔文献7)より引用，著者訳〕

hypothesisが出された．彼らは，さまざまな基礎実験から，神経線維の障害が起こると，末梢からの非侵害性刺激によっても隣接する神経線維の自発的発火が起こり，その発火は一次的増強を見た後，頻度依存性抑制機序により自然消滅することを明らかにした．末梢からの刺激を遮断する(神経ブロック)ことにより，痛みの発作が出なくなる理由も説明できる．

おわりに

ペインクリニックにおける慢性難治性疼痛のうち，特に治療に難渋することが多い末梢性神経障害性疼痛に重点をおいてその機序，薬物治療を中心に述べた．本症は末梢性と中枢性に分類されるが，この両者においてもその発生機序には多くの一致した発生機序と同じく，多くの異なった発生機序が存在しているものと考えられる．さまざまな疼痛性疾患の発生機序はいまだ不明な点が多いが，今後それらの機序が明らかになるにつれ，その治療法にも新しい方法が開発されてくることを期待したい．

参考文献

1) 小川節郎：複合性局所疼痛症候群の診断と治療．ペインクリニック 29(別冊)：S95-S108，2008
2) Merskey H, Bogduk N：Classification of Chronic Pain：Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. IASP Press, Seattle, 1994, 40-43
3) 植田弘師，木口倫一，山口明日香：リゾホスファチジン酸誘発性神経因性疼痛．ペインクリニック 26：509-515，2005
4) Watkins LR, Milligan ED, Maier SF：Spinal cord glia：new players in pain. Pain 93：201-205, 2001
5) 津田誠，長谷川茂雄，小泉修一ほか：神経およびグリア細胞培養系を利用した疼痛基礎研究．ペインクリニック 27：1597-1603，2006
6) Hansson PT, Dickenson AH：Pharmacological treatment of peripheral neuropathic pain conditions based on shared commonalities despite multiple etiologies. Pain 113：251-254, 2005
7) Finnerup NB, Otto M, McQuay HJ, et al.：Algorithm for neuropathic pain treatment：an evidence based proposal. Pain 118：289-305, 2005
8) 倉田二郎：疼痛研究と慢性疼痛治療におけるfMRIの役割．ペインクリニック 26：15-23，2005
9) Rappaport ZH, Devor M：Trigeminal neuralgia：the role of self-sustaining discharge in the trigeminal ganglion. Pain 56：127-138, 1994

Diagnosis and Treatment of Neuropathic Pain

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It is recognized that neuropathic pain is very difficult to treat in pain-clinic practice. The reason that it is difficult to treat is considered a complexity of the mechanisms. Therefore, treatment of this condition must be done with adequate treatment strategies and/or pharmacological application.

In this article, the author describes nerve fibers, ectopic ion-channel, the contribution of nerve growth factor and lysophosphatidic acid to the development of ephapse and allodynia, the contribution of Glia to development of neuropathic pain, etc., concerning the mechanisms of neuropathic pain. Pharmacological management is also described.

Key Words : Neuropathic pain, Pain mechanisms, Nerve fiber, Pharmacotherapy

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Review Article

The Animal Model of Spinal Cord Injury as an Experimental Pain Model

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Pain, which remains largely unsolved, is one of the most crucial problems for spinal cord injury patients. Due to sensory problems, as well as motor dysfunctions, spinal cord injury research has proven to be complex and difficult. Furthermore, many types of pain are associated with spinal cord injury, such as neuropathic, visceral, and musculoskeletal pain. Many animal models of spinal cord injury exist to emulate clinical situations, which could help to determine common mechanisms of pathology. However, results can be easily misunderstood and falsely interpreted. Therefore, it is important to fully understand the symptoms of human spinal cord injury, as well as the various spinal cord injury models and the possible pathologies. The present paper summarizes results from animal models of spinal cord injury, as well as the most effective use of these models.

1. Introduction

Spinal cord injury (SCI) often results in severe motor dysfunction, such as complete paralysis. These patients typically cannot only walk, but also lose bowel, bladder, and sexual functions. Pain impact following SCI has been reported as 37% of higher-level SCI patients with pain and 23% of lower-level SCI patients with pain; given the choice, these patients would trade pain relief for loss of bladder, bowel, or sexual functions [1]. Pain management is, therefore, an important health problem and topic of study.

Pain experiments with human subjects have proven to be practically challenging, fundamentally subjective, and ethically self-limiting. For these reasons, there remains a need for the use of laboratory animal models of pain. Pain is subjective in humans, and interpretation of animal model results requires careful attention. In fact, some have called for the abandonment of animal pain studies in favor of more extensive human testing.

A number of animal models of SCI exist and are primarily used to determine mechanisms of motor dysfunctions [2–4]. Recently, these various SCI animal models have been utilized for pain studies [5]. However, when SCI animal models are used for pain research, special attention should be paid to the concomitant conditions. The present paper discussed the various SCI animal models as models for pain, with an emphasis on the complexities and limitations, as well as strategies for improvement and future use.

2. Pain in SCI Patients

2.1. SCI and the Social Impact. SCI occurs in most countries at an annual rate of 20–40 individuals per million. SCI is a devastating event that results in motor dysfunction below the level of lesion, as well as development of chronic pain syndromes. Studies have reported the prevalence of pain in SCI patients. A summary of results from 10 studies indicates that an average of 69% of the patients experienced pain, and nearly one-third of patients in pain rated their pain as severe [6]. The stakes are enormous, given the impact of pain on the economy (pain-related treatment costs 1 trillion US dollars

per year in developed countries) [7]. If SCI pain could be eliminated, the quality of life could be greatly improved in patients; they would no longer suffer from pain and could take part in social aspects of life or earn money.

2.2. Spinal Cord Injury and Chronic Pain. Following mechanical injury to the spinal cord, a wave of secondary pathological changes occurs and amplifies the extent of initial damage. Apoptosis is critical for triggering collateral damage following primary injury to the spinal cord. Spontaneous and evoked pain is frequent in traumatic or ischemic spinal cord injury.

In complete and partial spinal lesions, chronic pain develops within months following injury [8]. Up to 80% of patients experience clinically significant pain, which is described as burning, stabbing, and/or electric-like [9, 10]. Post-SCI pain results in drastically impaired daily routines and quality of life to a greater extent than motor impairment [11]; it is refractory to clinical treatments, despite a variety of neurosurgical, pharmacological, and behavioral therapeutic strategies [12, 13]. The pain so greatly affects quality of life that depression and suicide frequently result [14, 15].

3. Chronic Pain Classification in SCI (Tables 1 and 2)

Siddall and colleagues [16] classified SCI pain from spinal cord injury into two broad types, with three regions of pain.

3.1. Nociceptive Pain. It is crucial for a pain clinician to distinguish between nociceptive or neuropathic pain, because the clinical approach for each is different. The first choice for nociceptive pain treatment following SCI is often a nonsteroidal, anti-inflammatory drug, or opiate, which often results in sufficient pain control.

3.1.1. Musculoskeletal Pain. Musculoskeletal pain is very common in SCI patients. In chronic states, secondary overuse or abnormal use of structures, such as the arm and shoulder, occurs [17]. Muscle spasm pain is a commonly observed type of musculoskeletal pain and is refractory for treatment of common musculoskeletal pain; analgesics are sometimes helpful, but antispasticity treatment may be needed in many cases [18].

3.1.2. Visceral Pain. Pathology in visceral structures, such as urinary tract infection, bowel impaction, and renal calculi, generally results in nociceptive pain. Visceral pain usually exhibits a delayed onset following SCI, which could be due to normal afferent input *via* sympathetic or vagal nerves in paraplegics or *via* the vagus nerve in tetraplegics [19, 20]. Patients with upper thoracic injury or cervical SCI may present with autonomic dysreflexia headache, because of bowel impaction or bladder distension.

3.2. Neuropathic Pain. SCI often results in neuropathic pain, which is difficult to treat and exhibits various patterns due to its pathology.

Table 1: Classification of the Spinal Cord Injury Pain Task Force of the International Association of the Study of Pain.

Broad type	Broad system	Affected structures/Pathologies
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma, or inflammation
		Mechanical instability
		Muscle spasm
		Secondary overuse
	Visceral	Renal calculus (kidney stones)
		Bowel and sphincter dysfunctions
		Headache by autonomic dysreflexia
Neuropathic	Above-level	Compression mononeuropathy
		Complex Regional Pain Syndrome
	At-level	Nerve root compression (cauda equine)
		Syringomyelia
		Spinal cord trauma/ischemia
		Dual-level cord and root trauma (double-lesion syndrome)
	Below-level	Spinal cord trauma/ischemia

Table 2: SCI pain classification by Bryce and Ragnarsson.

Location		Type	Etiologic subtypes
Above-level	nociceptive	1	Mechanical and musculoskeletal
		2	Autonomic dysreflexia headache
		3	Others
	neuropathic	4	Compressive neuropathy
		5	Others
At-level	nociceptive	6	Mechanical and musculoskeletal
		7	Visceral
	neuropathic	8	Central
		9	Radiculopathy
		10	Compressive neuropathy
		11	Complex Regional Pain Syndrome
Below-level	nociceptive	12	Mechanical and musculoskeletal
		13	Visceral
	neuropathic	14	Central
		15	Other

3.2.1. At-Level Pain. At-level pain occurs in dermatomes near the spinal injury and develops shortly after the injury. The pain is often characterized as stabbing or stimulus-independent and is accompanied by allodynia [21, 22].

3.2.2. Below-Level Pain. Below-level pain is localized to dermatomes distal to the injury site and develops more gradually than at level pain; it is often classified as a stimulus-independent, continuous, burning pain [21, 22].

3.2.3. Above-level Pain. Above-level pain occurs at dermatomes cranial to the injury site [21, 22].

3.3. Other Classification of SCI Pain (Table 2). Bryce et al. classified SCI pain by location of the pain [23]. In terms of animal behavior, this classification helps to provide a better understanding of pain pathology. In basic pain research, pain is defined as neuropathic or nociceptive. Similarly, SCI pain is complex and the pathology should be taken into consideration at the same time. It is important to understand the pathologies in each model.

4. The Role of Animal Model

Human self-ratings of pain, using questionnaires and scales, are reliable, accurate, and versatile for measuring experimental and clinical pain [24]. Nonetheless, the subjectivity of these measures has led to a decade-long search for surrogate biomarkers. To date, an objective surrogate with acceptable high sensitivity and specificity has not been identified. However, individual function-imaging scans could provide a reliable and objective measurement of subjective pain perception [25]. In addition, genetic biomarkers could prove to be useful. However, it is likely that too many genes are involved [26]. Moreover, genomic DNA variants could predict trait sensitivity to pain rather than ongoing levels of pain. Only a small percentage of injuries, infections, or others causes that results in chronic pain syndrome actually develop chronic pain. Therefore, in human studies, it will be difficult to determine the correlation between genetic background and pain severity. Furthermore, common clinical pain conditions, such as back pain, are too polygenic to be effectively modeled and genetically understood.

Animal models cannot self-report. In response to noxious stimuli, behaviors can be reliably and objectively scored, although these simple reflexes or innate responses (such as licking an inflamed paw) seem to lack clinical validity. Indeed, experiments with behavioral measurements of pain in animal models have become more common. According to studies published in flagship journals, pain studies comprise approximately 25% of total studies, more than any other field of study [27].

The animal model of pain plays a central role in analgesic drug development and the fundamental mechanisms that drive it. Despite the development of human imaging studies, such as functional MRI, the use of animal models of pain is a continuing necessity [5].

5. Spinal Cord Injury Dynamics and Procedures

Several models of neuropathic pain due to spinal cord injury have been simulated in rats. These studies have primarily focused on spinal cord injury caused by contusion or weight dropping, spinal cord compression, excitatory neurotoxins, photochemical-induced ischemia, spinal cord transaction, or crushing of the spinal cord. These models have also been adapted for mice [28–31]. The development of reliable neurotrauma mouse models provides great promise for evaluating overexpression or inactivation of certain genes on lesion pathophysiology and functional outcome. However, more attention should be focused on motor recovery while evaluating pain behavior, because of the delayed motor recovery in mice compared with rats [32, 33]. The utility for each model summarizes in Table 3.

5.1. Contusive or Hemicontusive Models. Spinal contusion is the oldest and most widely used animal model. In addition to motor dysfunction, this injury elicits sensory dysfunction, including neuropathic pain, tactile allodynia, and thermal hyperalgesia [34, 35]. Cervical contusion is rarely reported, because life-threatening adverse effects could occur. Therefore, cervical hemicontusion, following hemilaminectomy, is used to analyze the unilateral spinal cord contusion model. Because motor dysfunction appears in the forelimbs, pain-related behavior is difficult to estimate, and for this reason, cervical contusion is often utilized for motor functional analysis [2, 3]. The thoracic spinal cord contusion model is the most popular pain research model and is induced with impactors, such as the weight-drop impactor [36]. In brief, the exposed spinal cord is injured by dropping a 10.0-g rod from specified heights [37, 38]. After 2 or 3 weeks, motor dysfunction is recovered and pain behavior can be analyzed. The impact of the injury tends to vary. Therefore, especially in short distances from the rod to spinal cord, pain behavior does not always appear. It is difficult to bilaterally drop the rod onto the spinal cord. Following injury, motor function analysis is needed to exclude unilateral paralysis and the possibility of unilateral contusion. Abnormal sensations due to mechanical, thermal, or cold stimuli are observed for several weeks or longer [32, 33, 39–52], and all regions (at-, above-, below-level) of allodynia are analyzed [53–56].

5.2. Transection or Hemisection Models. The complete spinal transection injury model reflects symptoms of complete SCI patients. Following laminectomy, spinal cord transection is performed with spring scissors. Occasionally, to attach the two ends for regeneration, a sterile, gel foam is placed between the two resected spinal cord ends. At-level and below-level neuropathic pains are then analyzed [57, 58]. Many studies have reported muscle spasms in the spinal complete transection model [18, 59, 60], and musculoskeletal pain pathology during spasticity could help to clarify the use of this model.

The partial spinal transection injury model (hemisection) has become popular in neuropathic pain studies [61–78]. Motor dysfunction appears only in the ipsilateral injured side and persists from 5 days to 4 weeks [64, 75]. Mechanical allodynia and thermal hyperalgesia are bilaterally observed in above-level and below-level cases [61, 76–81].

5.3. Photochemical Model. Over the past two decades, the photochemical model of spinal cord injury, developed by Watson et al. [82], has proven to be one of the most reliable and reproducible graded experimental rat models of spinal cord injury [83–94] and has been widely used to study neurotrauma in mice [88]. The biggest advantage of

Table 3: Animal spinal cord injury models and symptoms.

Impact to spinal cord	Laterality and devices	Injury area			Sensory abnormality			Duration	
		Cervical	Thoracic	Lumbar	At-level	Below-level	Above-level	Allodynia	Maximal motor dysfunction
Transection	Bilateral		○	○	○	○	×	Several weeks or more	Less than 4 weeks
	Unilateral	◎	◎	◎		◎	◎	1–5 weeks or more	Ipsilateral to injury: 4 weeks
Compression	Contusion		○		○	○	○	Weeks to months	1-2 weeks
	Hemi-contusion	○							3 weeks
	Clip		○		○	○: severe injury impossible		4 weeks	4 weeks severe injury
	Displacement					◎		4–6 weeks	2 weeks
	Canal stenosis			○		○ or ×		8 days or hypoalgesia	
Photochemically			◎		◎			10–20 days	Various
Excitotoxic			○		○	○	○?	5 weeks or more	
Spinothalamic tract lesions			◎		◎		◎	Several weeks	Less than 1 week

Many spinal cord injury models exist for pain research. Pain behavior should not be measured in injured animals during maximal motor dysfunction.

this method is that the resulting injury does not induce mechanical trauma to the cord, because there is no need for laminectomy. Instead, an intravascular photochemical reaction occurs through the use of a dye that is activated by an argon ion laser to produce single oxygen molecules at the endothelial surface of spinal cord vessels. This results in an intense platelet response, as well as subsequent vessel occlusion and parenchymal tissue infarction [83]; the pathology is of a purely ischemic origin. Motor deficits are related to irradiation duration, as well as mechanical allodynia (cold, not thermal), which lasts for several days [91]. Following application of the von Frey filament to the trunk, behavioral analysis is performed according to vocalization threshold. Antiallodynic effects of analgesics have been determined using this model [84, 85, 90]. However, extent of injury is difficult to control. Therefore, motor deficit scores, such as BBB [95] and CBS [96], have been widely utilized [86, 90].

5.4. Excitotoxic Models. Intraspinal or intrathecally injection of some excitotoxins, such as quisqualic acid or other excitatory amino acids (glutamate, N-methylasparate, and kainic acid), produces long-lasting spontaneous pain, mechanical allodynia, and thermal hyperalgesia in rats and mice [97, 98]. Following excitotoxin injections, neuronal loss, cavity formation, astrocytic scaring, and prominent inflammation occur. The advantage of this model is the ability to correlate specific areas of tissue damage with behavioral changes. Moreover, the percentage of animals that exhibit pain-related behaviors following injury is greater than with other models; induced mechanical allodynia was 67% in the contusion injury model [99], in contrast to 44% chronic allodynia following ischemic injury [86]. In excitotoxic animal models, nearly 100% animals develop varying degrees of hypersensitivity to mechanical and thermal stimuli [98].

5.5. Other Mechanical Spinal Cord Injuries

5.5.1. Clip Compression Injury. Clip compression injury resembles spinal contusion injury at the point of the injury caused by pressure to the spinal cord. Following laminectomy, compression injury is induced with clips calibrated to exert a force of 50 or 35 g. The 50-g clip induces severe injury and the 35-g clip induces moderate injury. Either clip is dorsoventrally closed over the entire cord for 1 min and then subsequently removed [58, 100–102]. A vascular clip is used for this procedure in mice [103]; the spinal cord becomes ischemic and mimics common clinical injuries and outcomes.

5.5.2. Spinal Cord Displacement. The spinal cord displacement model attempts to regulate trauma impact by controlling displacement length of the spinal cord. Through the use of this model, a cutoff for normal sensory function has been determined [104]. In human SCI, trauma severity is not proportional to pain severity, because the method of injury varies. The unique features of controlled displacement and monitoring of biomechanical parameters at the time of impact help to reduce outcome variability [105].

5.5.3. Canal Stenosis. Lumbar canal stenosis is due to entrapment of the cauda equine and/or lumber nerve roots by hypertrophy of osseous and soft tissue structures

surrounding the lumbar spinal canal. A typical pathology is reduced blood flow to the peripheral nerve, resulting in demyelination or axonal degeneration, depending on the magnitude of ischemic injury. Canal stenosis can also be termed a spinal cord injury model, in which square-shaped pieces of silicon are placed into the epidural space in the rat [106, 107]. However, these procedures also induce mechanical hypoalgesia [107]. Nevertheless, this model could help to clarify pathophysiology of chronic, light pressure to the spinal cord.

5.5.4. Spinothalamic Tract Lesions. The spinothalamic tract is the core pain pathway in the spinal cord. This model is designed to lesion only the spinothalamic tract area using a tungsten microelectrode. Although this model injures the unilateral spinothalamic tract, bilateral above- and below-level hyperalgesia, as well as allodynia, is induced and can persist for many weeks. These features resemble allodynia and hyperalgesia experienced by humans suffering from central pain syndromes following spinal cord injury. Therefore, this model could provide useful and novel insights into the underlying biological mechanisms of spinal cord injury [108].

6. Pain-Related Behavior As an Evaluation of Symptoms

Pain-related behavior is recorded using various devices applied to the forelimbs, hindlimbs, trunk, and face. If pain behavior appears in the face, it is considered to reflect the reaction to supraspinal mechanisms, because sensory function in the face is regulated by the trigeminal nerve (a cranial nerve). In thoracic spinal cord injury, trunk allodynia reflects at-level neuropathic pain, and allodynia in the hindlimb reflects below-level neuropathic pain. Forelimb allodynia reflects at-level neuropathic pain in cervical injury and above-level neuropathic pain in other injuries.

Abnormal pain behavior is a result of three different stimulations: mechanical, thermal, and cold.

6.1. Mechanical Allodynia. Mechanical allodynia can be measured in various ways using the von Frey hair. In one of the methods, the "up-down method" [109], each von Frey hair is applied to the test area for 2-3 s, with a 1-2-minute interval between stimuli. The trial begins with application of the 15-mN von Frey probe to the hindpaws. A positive response is defined as a rapid withdrawal and/or licking of the paw immediately upon application of the stimulus. The von Frey hair can also be used to determine vocalization threshold to graded mechanical allodynia as a means to evaluate at-level neuropathic pain in the trunk [92]. When a positive response to stimulus occurs, the next smaller von Frey hair is applied. If a negative response occurs, the next higher force is applied. Testing continues for five or more stimuli after the first change in response, and the pattern of responses is converted to a 50% von Frey threshold using a previously described technique [109]. If the animal shows no response to the highest von Frey hair (160 mN), a von Frey threshold of 260 mN, corresponding to the next log increment in potential von Frey probes, is assigned to the threshold.

Touch-evoked agitation is another evaluation of mechanical allodynia [110] and can be used to test the animal response to tactile stimulation. The animal skin is briskly stroked with a pencil point in a rostral to caudal direction. The animal response is graded with a score of 0: no response, 1: moderate efforts to avoid the probe, transient vocalization, and 2: vigorous efforts to escape the stimulus, frequent and sustained vocalization in response to the probe.

Pathological reactions between the von Frey probe and pencil point vary due to reactions to the von Frey hair (caused by A-delta-fiber and C-fiber) or the pencil (A-beta fiber).

6.2. Thermal Hyperalgesia. Thermal hyperalgesia can be measured by latency of paw withdrawal in response to a radiant heat source [111]. Briefly, animals are placed in Plexiglas boxes on an elevated glass plate heated by a radiant heat source directed by a beam of light to the planter surface of each paw through the glass plate (47°C). The light beam is automatically turned off by a photocell upon limb-lift, allowing for measurement of time between stimulus start and paw withdrawal (paw withdrawal latency). Three to five minutes are allowed between each trial, and three trials are averaged for each limb.

6.3. Cold Allodynia. Cold sensitivity to acetone can be quantified by foot withdrawal frequency [112]. A total of 100 μL acetone is applied to the paw planter surface using a plastic tubule connected to a 1 ml syringe. Acetone is applied 5 times to each paw at an interval of at least 5 minutes. The number of brisk foot withdrawals is recorded.

7. Evaluation of Motor Functions in the Spinal Cord Injury Model

Locomotor function is observed and recorded using the Basso, Beattie, and Bresnahan (BBB) Locomotor Rating Scale [95]. Briefly, the BBB is a 22-point ordinal scale ranging from 0 (no discernable hindlimb movement) to 21 (consistent and coordinated gait with parallel paw placement of the hindlimb and consistent trunk stability). Scores from 0 to 7 rank early phase of recovery, with return of isolated movements from three joints (hip, knee, and ankle); scores from 8 to 13 describe the intermediate recovery phase with, return of paw placement, stepping, and forelimb-hindlimb coordination; and scores from 14 to 21 represent late phase of recovery, with return of toe clearance during the step phase, predominant paw position, trunk stability, and tail position. Scores are tabulated and considered to be an indicator of motor recovery.

The Basso Mouse Scale (BMS), a 9-point rating scale, has been specially developed for mouse models [113]. An additional scoring systems, described by Gale et al. [96] and termed the Combined Behavioral Score (CBS) (Table 4), has been used to measure locomotor function.

Following cervical spinal cord injury, recovery of forelimb function can be measured [114] by indicators such as the grooming test and forelimb asymmetry test [115]. Forelimb grooming function has been assessed using a scoring system originally developed to examine recovery in a rat brachial plexus reconstruction model [116]. The forelimb asymmetry, or paw preference test, is sensitive to asymmetries produced by a variety of CNS insults [117]. In addition, forelimb motor function recovery and pain behavior should be coanalyzed, because behavior is a result of motor functions [118].

8. Future Direction and Conclusions

8.1. Spinal Cord Injury As a Musculoskeletal Pain Model. Spinal cord injury leads to immediate impaired motor and sensory functions, which are also manifested over time. Following an initial period of spinal shock, reflexes become reduced and a disturbing hyperreflexia develops, which is often referred to as spasticity [119].

Spasticity is a disabling complication that affects individuals with spinal cord injury [18, 120]. Approximately 75% of individuals with SCI exhibit spasticity 1 year after injury and half undergo antispasticity treatment [121]. Significant scientific interest has been devoted to spasticity over the past 10–15 years as an example of plastic changes occurring distal to a central lesion.

The primary mechanisms hypothesized to be responsible for spasticity are increased motoneuron excitability [122, 123] and increased synaptic input, as a result of muscle stretch and reduced inhibitory mechanisms (presynaptic [124] and reciprocal inhibitions [125]). The mechanisms underlying decreased inhibition below the lesion remain poorly understood [59].

The most commonly proposed mechanisms to account for decreased inhibition following spinal cord injury include disruptions of facilitatory supraspinal input to inhibitory interneurons [59, 126]. Motoneuron and sensory neurons are often regulated by common mechanisms [127], and common molecular mechanisms could be responsible for below-level neuropathic pain and spasticity [18, 37].

The spinal cord injury model, in particular the spinal transaction model, is considered useful for spasticity research. Because spasticity results in musculoskeletal pain, the spinal cord injury model could be considered a musculoskeletal pain model.

8.2. Spinal Cord Injury As a Visceral Pain Model. Visceral pain in spinal cord injury commonly triggers autonomic dysreflexia, a potentially life-threatening hypertensive syndrome due to high thoracic spinal cord injury. Pathology correlates with increased sprouting of primary afferent c-fibers into the spinal cord. During motor dysfunction, visceral pain-related behavior is difficult to analyze. However, based on the above-described mechanisms, a morphological approach to spinal complete transection injury has been utilized [128].

Table 4: Combined Behavioral Score (CBS), as reported by Gale et al. [96].

General description		Points
Motor score		
0	Normal walking	0
1	Walks with mild deficit	5
2	Hindlimb can support weight	15
3	Frequent movement of hindlimb, no weight support	25
4	Minor movement in hindlimb, no weight bearing	40
5	No movement in hindlimb, no weight bearing	45
Toe spread		
0	Normal, full, toe spread	0
1	Partial spreading of toes	2.5
2	No spreading of toes	5
Righting		
0	Normal righting, counter to direction of roll	0
1	Weakened attempt to right	5
2	Delayed attempt to right	10
3	Delayed attempt to right itself	15
Extension withdrawal		
0	Normal	0
1	Weak and slow reflex to withdraw hindlimb	2.5
2	No withdrawal reflex	5
Placing		
0	Normal placing	0
1	Weak attempt to place foot	2.5
2	No attempt to place foot	5
Inclined plate		
0	65~70/deg	0
1	55~60	5
2	40~50	10
3	<40	15

8.3. Limitations of Animal Models of Chronic Pain. Limited success in the pain field during the past few decades has resulted in a plethora of basic scientific data. The use of animal models has increased our knowledge of novel, effective, and safe clinical analgesics. Experimental failures with novel drugs are associated with adverse side effects and the lack of efficacy in humans. In addition, psychosocial aspects of chronic pain due to spinal cord injury have been completely omitted, despite a large body of knowledge emphasizing the importance of these factors in chronic pain. Future studies should extend the scope of inquiry to include the psychosocial aspects of chronic pain and spinal cord injury.

8.4. Conclusion. By widening the number of animal models of spinal cord injury, new challenges have emerged. Although experimental methods of spinal cord injury pain lead to various behavioral outcomes, it is clear that some models respond similarly to pharmacological agents. This suggests that common mechanisms could underlie specific symptoms derived from various injury conditions. Etiologies of spinal cord injury pain could vary. However, by focusing on various symptoms of spinal cord injury pain, treatment possibilities for pathologies of spinal cord injury pain could emerge.

Continuous basic and clinical studies focused on different aspects of spinal cord injury pain are needed to better understand the mechanisms involved.

References

[1] C. Nepomuceno, P. R. Fine, J. S. Richards et al., "Pain in patients with spinal cord injury," *Archives of Physical Medicine and Rehabilitation*, vol. 60, no. 12, pp. 605–609, 1979.

[2] J. C. Gensel, C. A. Tovar, F. P. T. Hamers, R. J. Deibert, M. S. Beattie, and J. C. Bresnahan, "Behavioral and histological characterization of unilateral cervical spinal cord contusion injury in rats," *Journal of Neurotrauma*, vol. 23, no. 1, pp. 36–54, 2006.

[3] V. J. Tom, H. R. Sandrow-Feinberg, K. Miller et al., "Combining peripheral nerve grafts and chondroitinase promotes functional axonal regeneration in the chronically injured spinal cord," *The Journal of Neuroscience*, vol. 29, no. 47, pp. 14881–14890, 2009.

[4] K. Sadlaoud, S. Tazerart, C. Brocard et al., "Differential plasticity of the GABAergic and glycinergic synaptic transmission to rat lumbar motoneurons after spinal cord injury," *The Journal of Neuroscience*, vol. 30, no. 9, pp. 3358–3369, 2010.

[5] J. S. Mogil, K. D. Davis, and S. W. Derbyshire, "The necessity of animal models in pain research," *Pain*, vol. 151, no. 1, pp. 12–17, 2010.

[6] J. J. Bonica, "Introduction: semantic, epidemiologic, and educational issues," in *Pain and Central Nervous System Disease: The Central Pain Syndromes*, pp. 13–29, Raven Press, New York, NY, USA, 1991.

[7] W. F. Stewart, J. A. Ricci, E. Chee, D. Morganstein, and R. Lipton, "Lost productive time and cost due to common pain conditions in the US workforce," *Journal of the American Medical Association*, vol. 290, no. 18, pp. 2443–2454, 2003.

[8] J. S. Richards, R. L. Meredith, C. Nepomuceno, P. R. Fine, and G. Bennett, "Psycho-social aspects of chronic pain in spinal cord injury," *Pain*, vol. 8, no. 3, pp. 355–366, 1980.

[9] N. B. Finnerup, I. L. Johannesen, S. H. Sindrup, F. W. Bach, and T. S. Jensen, "Pain and dysesthesia in patients with spinal cord injury: a postal survey," *Spinal Cord*, vol. 39, no. 5, pp. 256–262, 2001.

[10] P. J. Siddall, J. M. McClelland, S. B. Rutkowski, and M. J. Cousins, "A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury," *Pain*, vol. 103, no. 3, pp. 249–257, 2003.

[11] D. H. Rintala, P. G. Loubser, J. Castro, K. A. Hart, and M. J. Fuhrer, "Chronic pain in a community-based sample of men with spinal cord injury: prevalence, severity, and relationship with impairment, disability, handicap, and subjective well-being," *Archives of Physical Medicine and Rehabilitation*, vol. 79, no. 6, pp. 604–614, 1998.

[12] T. E. Balazy, "Clinical management of chronic pain in spinal cord injury," *Clinical Journal of Pain*, vol. 8, no. 2, pp. 102–110, 1992.

[13] J. A. Turner, D. D. Cardenas, C. A. Warms, and C. B. McClellan, "Chronic pain associated with spinal cord injuries: a community survey," *Archives of Physical Medicine and Rehabilitation*, vol. 82, no. 4, pp. 501–508, 2001.

[14] D. M. Cairns, R. H. Adkins, and M. D. Scott, "Pain and depression in acute traumatic spinal cord injury: origins of chronic problematic pain?" *Archives of Physical Medicine and Rehabilitation*, vol. 77, no. 4, pp. 329–335, 1996.

[15] M. Segatore, "Understanding chronic pain after spinal cord injury," *The Journal of Neuroscience Nursing*, vol. 26, no. 4, pp. 230–236, 1994.

[16] P. J. Siddall, R. P. Yezierski, and J. D. Loeser, "Pain following spinal cord injury: clinical features, prevalence, and taxonomy," *IASP Newsletter*, vol. 3, pp. 3–7, 2000.

[17] M. Dalyan, D. D. Cardenas, and B. Gerard, "Upper extremity pain after spinal cord injury," *Spinal Cord*, vol. 37, no. 3, pp. 191–195, 1999.

[18] K. C. Murray, A. Nakae, M. J. Stephens et al., "Recovery of motoneuron and locomotor function after spinal cord injury depends on constitutive activity in 5-HT receptors," *Nature Medicine*, vol. 16, no. 6, pp. 694–700, 2010.

[19] B. R. Komisaruk, C. A. Gerdes, and B. Whipple, "'Complete' spinal cord injury does not block perceptual responses to genital self-stimulation in women," *Archives of Neurology*, vol. 54, no. 12, pp. 1513–1520, 1997.

[20] R. A. Kuhn, "Functional capacity of the isolated human spinal cord," *Brain*, vol. 73, no. 1, pp. 1–51, 1950.

[21] P. J. Siddall, R. P. Yezierski, and J. D. Loeser, "Taxonomy and epidemiology of spinal cord injury pain," in *Spinal Cord Injury Pain: Assessment, Mechanism, Management, Progress in Pain Research Management*, R. P. Yesierski and K. J. Burchiel, Eds., vol. 23, pp. 9–24, IASP Press, Seattle, Wash, USA, 2002.

[22] C. J. Vierck Jr. and A. R. Light, "Allodynia and hyperalgesia within dermatomes caudal to a spinal cord injury in primates and rodents," in *Nervous System Plasticity and Chronic Pain*, J. Sandkuhler, B. Bromm, and G. Gebhart, Eds., vol. 129, pp. 411–428, Elsevier, Amsterdam, The Netherlands, 2000.

[23] T. N. Bryce, M. P. J. M. Dijkers, K. T. Ragnarsson, A. B. Stein, and B. Chen, "Reliability of the Bryce/Ragnarsson spinal cord injury pain taxonomy," *The Journal of Spinal Cord Medicine*, vol. 29, no. 2, pp. 118–132, 2006.

[24] D. D. Price, P. A. McGrath, A. Rafii, and B. Buckingham, "The validation of visual analogue scales as ratio scale measures for chronic and experimental pain," *Pain*, vol. 17, no. 1, pp. 45–56, 1983.

[25] D. Borsook and L. Becerra, "Phenotyping central nervous system circuitry in chronic pain using functional MRI: considerations and potential implications in the clinic," *Current Pain and Headache Reports*, vol. 11, no. 3, pp. 201–207, 2007.

[26] M. L. Lacroix-Fralish and J. S. Mogi, "Progress in genetic studies of pain and analgesia," *Annual Review of Pharmacology and Toxicology*, vol. 49, pp. 97–121, 2009.

[27] J. S. Mogil, K. Simmonds, and M. J. Simmonds, "Pain research from 1975 to 2007: a categorical and bibliometric meta-trend analysis of every research paper published in the journal, pin," *Pain*, vol. 142, no. 1-2, pp. 48–58, 2009.

[28] M. L. Starkey, M. Davies, P. K. Yip et al., "Expression of the regeneration-associated protein SPRR1A in primary sensory

neurons and spinal cord of the adult mouse following peripheral and central injury," *Journal of Comparative Neurology*, vol. 513, no. 1, pp. 51–68, 2009.

[29] S. A. Marques, V. F. Garcez, E. A. Del Bel, and A. M. B. Martinez, "A simple, inexpensive and easily reproducible model of spinal cord injury in mice: morphological and functional assessment," *Journal of Neuroscience Methods*, vol. 177, no. 1, pp. 183–193, 2009.

[30] H. Kanno, H. Ozawa, A. Sekiguchi, and E. Itoi, "Spinal cord injury induces upregulation of Beclin 1 and promotes autophagic cell death," *Neurobiology of Disease*, vol. 33, no. 2, pp. 143–148, 2009.

[31] R. V. Ung, E. S. Landry, P. Rouleau, N. P. Lapointe, C. Rouillard, and P. A. Guertin, "Role of spinal 5-HT receptor subtypes in quipazine-induced hindlimb movements after a low-thoracic spinal cord transection," *European Journal of Neuroscience*, vol. 28, no. 11, pp. 2231–2242, 2008.

[32] E. L. Hoschouer, F. Q. Yin, and L. B. Jakeman, "L1 cell adhesion molecule is essential for the maintenance of hyperalgesia after spinal cord injury," *Experimental Neurology*, vol. 216, no. 1, pp. 22–34, 2009.

[33] B. J. Kerr and S. David, "Pain behaviors after spinal cord contusion injury in two commonly used mouse strains," *Experimental Neurology*, vol. 206, no. 2, pp. 240–247, 2007.

[34] M. Tanabe, K. Ono, M. Honda, and H. Ono, "Gabapentin and pregabalin ameliorate mechanical hypersensitivity after spinal cord injury in mice," *European Journal of Pharmacology*, vol. 609, no. 1-3, pp. 65–68, 2009.

[35] E. L. Hoschouer, F. Q. Yin, and L. B. Jakeman, "L1 cell adhesion molecule is essential for the maintenance of hyperalgesia after spinal cord injury," *Experimental Neurology*, vol. 216, no. 1, pp. 22–34, 2009.

[36] J. A. Gruner, "A monitored contusion model of spinal cord injury in the rat," *Journal of Neurotrauma*, vol. 9, no. 2, pp. 123–128, 1992.

[37] A. Nakae, K. Nakai, T. Tanaka et al., "Serotonin2C receptor mRNA editing in neuropathic pain model," *Neuroscience Research*, vol. 60, no. 2, pp. 228–231, 2008.

[38] E. D. Crown, Z. Ye, K. M. Johnson, G. Y. Xu, D. J. McAdoo, and C. E. Hulsebosch, "Increases in the activated forms of ERK 1/2, p38 MAPK, and CREB are correlated with the expression of at-level mechanical allodynia following spinal cord injury," *Experimental Neurology*, vol. 199, no. 2, pp. 397–407, 2006.

[39] J. G. Meisner, A. D. Marsh, and D. R. Marsh, "Loss of GABAergic interneurons in laminae I-III of the spinal cord dorsal horn contributes to reduced GABAergic tone and neuropathic pain after spinal cord injury," *Journal of Neurotrauma*, vol. 27, no. 4, pp. 729–737, 2010.

[40] E. L. Hoschouer, D. M. Basso, and L. B. Jakeman, "Aberrant sensory responses are dependent on lesion severity after spinal cord contusion injury in mice," *Pain*, vol. 148, no. 2, pp. 328–342, 2010.

[41] C. M. Mann, J. H. T. Lee, J. Hillyer, A. M. T. Stammers, W. Tetzlaff, and B. K. Kwon, "Lack of robust neurologic benefits with simvastatin or atorvastatin treatment after acute thoracic spinal cord contusion injury," *Experimental Neurology*, vol. 221, no. 2, pp. 285–295, 2010.

[42] S. M. Carlton, J. Du, H. Y. Tan et al., "Peripheral and central sensitization in remote spinal cord regions contribute to central neuropathic pain after spinal cord injury," *Pain*, vol. 147, no. 1-3, pp. 265–276, 2009.

[43] T. Furuya, M. Hashimoto, M. Koda et al., "Treatment of rat spinal cord injury with a Rho-kinase inhibitor and bone marrow stromal cell transplantation," *Brain Research*, vol. 1295, pp. 192–202, 2009.

[44] I. D. Hentall and S. B. Burns, "Restorative effects of stimulating medullary raphe after spinal cord injury," *Journal of Rehabilitation Research & Development*, vol. 46, no. 1, pp. 109–122, 2009.

[45] M. A. Hook, G. Moreno, S. Woller et al., "Intrathecal morphine attenuates recovery of function after a spinal cord injury," *Journal of Neurotrauma*, vol. 26, no. 5, pp. 741–752, 2009.

[46] S. Lord-Fontaine, F. Yang, Q. Diep et al., "Local inhibition of Rho signaling by cell-permeable recombinant protein BA-210 prevents secondary damage and promotes functional recovery following acute spinal cord injury," *Journal of Neurotrauma*, vol. 25, no. 11, pp. 1309–1322, 2008.

[47] A. M. Tan, S. Stamboulian, Y. W. Chang et al., "Neuropathic pain memory is maintained by Rac1-regulated dendritic spine remodeling after spinal cord injury," *The Journal of Neuroscience*, vol. 28, no. 49, pp. 13173–13183, 2008.

[48] F. Knerlich-Lukoschus, M. Juraschek, U. Blömer, R. Lucius, H. M. Mehdorn, and J. Held-Feindt, "Force-dependent development of neuropathic central pain and time-related CCL2/CCR2 expression after graded spinal cord contusion injuries of the rat," *Journal of Neurotrauma*, vol. 25, no. 5, pp. 427–448, 2008.

[49] Y. Berrocal, D. D. Pearse, A. Singh et al., "Social and environmental enrichment improves sensory and motor recovery after severe contusive spinal cord injury in the rat," *Journal of Neurotrauma*, vol. 24, no. 11, pp. 1761–1772, 2007.

[50] J. Biernaskie, J. S. Sparling, J. Liu et al., "Skin-derived precursors generate myelinating Schwann cells that promote remyelination and functional recovery after contusion spinal cord injury," *The Journal of Neuroscience*, vol. 27, no. 36, pp. 9545–9559, 2007.

[51] M. G. Dombourian, N. A. Turner, T. A. Gerovac et al., "B1 and TRPV-1 receptor genes and their relationship to hyperalgesia following spinal cord injury," *Spine*, vol. 31, no. 24, pp. 2778–2782, 2006.

[52] C. D. Mills, J. J. Grady, and C. E. Hulsebosch, "Changes in exploratory behavior as a measure of chronic central pain following spinal cord injury," *Journal of Neurotrauma*, vol. 18, no. 10, pp. 1091–1105, 2001.

[53] C. H. Hubscher, J. D. Fell, and D. S. Gupta, "Sex and hormonal variations in the development of at-level allodynia in a rat chronic spinal cord injury model," *Neuroscience Letters*, vol. 477, no. 3, pp. 153–156, 2010.

[54] C. H. Hubscher, E. G. Kaddumi, and R. D. Johnson, "Segmental neuropathic pain does not develop in male rats with complete spinal transections," *Journal of Neurotrauma*, vol. 25, no. 10, pp. 1241–1245, 2008.

[55] J. Voda, A. Hama, and J. Sagen, "FK506 reduces the severity of cutaneous hypersensitivity in rats with a spinal cord contusion," *Neuroscience Research*, vol. 58, no. 1, pp. 95–99, 2007.

[56] B. C. Hains, J. P. Klein, C. Y. Saab, M. J. Craner, J. A. Black, and S. G. Waxman, "Upregulation of sodium channel Na1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury," *The Journal of Neuroscience*, vol. 23, no. 26, pp. 8881–8892, 2003.

[57] C. Scheifer, U. Hoheisel, P. Trudrung, T. Unger, and S. Mense, "Rats with chronic spinal cord transection as a possible model for the at-level pain of paraplegic patients," *Neuroscience Letters*, vol. 323, no. 2, pp. 117–120, 2002.

[58] V. S. Densmore, A. Kalous, J. R. Keast, and P. B. Osborne, "Above-level mechanical hyperalgesia in rats develops after incomplete spinal cord injury but not after cord transection, and is reversed by amitriptyline, morphine and gabapentin," *Pain*, vol. 151, no. 1, pp. 184–193, 2010.

[59] C. Crone, N. T. Petersen, S. Gimenéz-Roldán, B. Lungholt, K. Nyborg, and J. B. Nielsen, "Reduced reciprocal inhibition is seen only in spastic limbs in patients with neurolathyrism," *Experimental Brain Research*, vol. 181, no. 1, pp. 193–197, 2007.

[60] S. A. Edgley and N. C. Aggelopoulos, "Short latency crossed inhibitory reflex actions evoked from cutaneous afferents," *Experimental Brain Research*, vol. 171, no. 4, pp. 541–550, 2006.

[61] A. D. Bennett, A. W. Everhart, and C. E. Hulsebosch, "Intrathecal administration of an NMDA or a non-NMDA receptor antagonist reduces mechanical but not thermal allodynia in a rodent model of chronic central pain after spinal cord injury," *Brain Research*, vol. 859, no. 1, pp. 72–82, 2000.

[62] M. D. Christensen, A. W. Everhart, J. T. Pickelman, and C. E. Hulsebosch, "Mechanical and thermal allodynia in chronic central pain following spinal cord injury," *Pain*, vol. 68, no. 1, pp. 97–107, 1996.

[63] B. C. Hains, K. M. Chastain, A. W. Everhart, D. J. McAdoo, and C. E. Hulsebosch, "Transplants of adrenal medullary chromaffin cells reduce forelimb and hindlimb allodynia in a rodent model of chronic central pain after spinal cord hemisection injury," *Experimental Neurology*, vol. 164, no. 2, pp. 426–437, 2000.

[64] M. F. Coronel, F. Labombarda, M. J. Villar, A. F. De Nicola, and S. L. González, "Progesterone prevents allodynia after experimental spinal cord injury," *The Journal of Pain*, vol. 12, no. 1, pp. 71–83, 2011.

[65] D. H. Roh, S. Y. Yoon, H. S. Seo et al., "Intrathecal injection of carbenoxolone, a gap junction decoupler, attenuates the induction of below-level neuropathic pain after spinal cord injury in rats," *Experimental Neurology*, vol. 224, no. 1, pp. 123–132, 2010.

[66] J. Kim, J. H. Kim, Y. Kim, H. Y. Cho, S. K. Hong, and Y. W. Yoon, "Role of spinal cholecystokinin in neuropathic pain after spinal cord hemisection in rats," *Neuroscience Letters*, vol. 462, no. 3, pp. 303–307, 2009.

[67] Y. S. Gwak and C. E. Hulsebosch, "Remote astrocytic and microglial activation modulates neuronal hyperexcitability and below-level neuropathic pain after spinal injury in rat," *Neuroscience*, vol. 161, no. 3, pp. 895–903, 2009.

[68] F. Marchand, C. Tsantoulas, D. Singh et al., "Effects of Etanercept and Minocycline in a rat model of spinal cord injury," *European Journal of Pain*, vol. 13, no. 7, pp. 673–681, 2009.

[69] Y. Lu, J. Zheng, L. Xiong, M. Zimmermann, and J. Yang, "Spinal cord injury-induced attenuation of GABAergic inhibition in spinal dorsal horn circuits is associated with down-regulation of the chloride transporter KCC2 in rat," *The Journal of Physiology*, vol. 586, no. 23, pp. 5701–5715, 2008.

[70] F. Labombarda, M. F. Coronel, M. J. Villar, A. F. D. Nicola, and S. L. González, "Neuropathic pain and temporal expression of preprodynorphin, protein kinase C and N-methyl-d-aspartate receptor subunits after spinal cord injury," *Neuroscience Letters*, vol. 447, no. 2-3, pp. 115–119, 2008.

[71] W. Liu, Z. Liu, LI. Liu et al., "A novel human foamy virus mediated gene transfer of GAD67 reduces neuropathic pain following spinal cord injury," *Neuroscience Letters*, vol. 432, no. 1, pp. 13–18, 2008.

[72] N. E. Saadé, H. A. Amin, S. Chalouhi, S. A. Baki, S. J. Jabbur, and S. F. Atweh, "Spinal pathways involved in supraspinal modulation of neuropathic manifestations in rats," *Pain*, vol. 126, no. 1-3, pp. 280–293, 2006.

[73] X. M. Peng, Z. G. Zhou, J. C. Glorioso, D. J. Fink, and M. Mata, "Tumor necrosis factor-α contributes to below-level neuropathic pain after spinal cord injury," *Annals of Neurology*, vol. 59, no. 5, pp. 843–851, 2006.

[74] J. Kim, Y. W. Yoon, S. K. Hong, and H. S. Na, "Cold and mechanical allodynia in both hindpaws and tail following thoracic spinal cord hemisection in rats: time courses and their correlates," *Neuroscience Letters*, vol. 343, no. 3, pp. 200–204, 2003.

[75] B. C. Hains, K. M. Johnson, M. J. Eaton, W. D. Willis, and C. E. Hulsebosch, "Serotonergic neural precursor cell grafts attenuate bilateral hyperexcitability of dorsal horn neurons after spinal hemisection in rat," *Neuroscience*, vol. 116, no. 4, pp. 1097–1110, 2003.

[76] B. C. Hains, K. M. Chastain, A. W. Everhart, D. J. McAdoo, and C. E. Hulsebosch, "Transplants of adrenal medullary chromaffin cells reduce forelimb and hindlimb allodynia in a rodent model of chronic central pain after spinal cord hemisection injury," *Experimental Neurology*, vol. 164, no. 2, pp. 426–437, 2000.

[77] Y. S. Gwak, B. C. Hains, K. M. Johnson, and C. E. Hulsebosch, "Effect of age at time of spinal cord injury on behavioral outcomes in rat," *Journal of Neurotrauma*, vol. 21, no. 8, pp. 983–993, 2004.

[78] C. D. Mills, B. C. Hains, K. M. Johnson, and C. E. Hulsebosch, "Strain and model differences in behavioral outcomes after spinal cord injury in rat," *Journal of Neurotrauma*, vol. 18, no. 8, pp. 743–756, 2001.

[79] J. H.T. Lee, S. Tigchelaar, J. Liu et al., "Lack of neuroprotective effects of simvastatin and minocycline in a model of cervical spinal cord injury," *Experimental Neurology*, vol. 225, no. 1, pp. 219–230, 2010.

[80] J. Kim, J. I. Jung, H. S. Na, S. K. Hong, and Y. W. Yoon, "Effects of morphine on mechanical allodynia in a rat model of central neuropathic pain," *NeuroReport*, vol. 14, no. 7, pp. 1017–1020, 2003.

[81] B. C. Hains, K. M. Johnson, D. J. McAdoo, M. J. Eaton, and C. E. Hulsebosch, "Engraftment of serotonergic precursors enhances locomotor function and attenuates chronic central pain behavior following spinal hemisection injury in the rat," *Experimental Neurology*, vol. 171, no. 2, pp. 361–378, 2001.

[82] B. D. Watson, R. Prado, and W. D. Dietrich, "Photochemically induced spinal cord injury in the rat," *Brain Research*, vol. 367, no. 1-2, pp. 296–300, 1986.

[83] J. X. Hao, X. J. Xu, H. Aldskogius, A. Seiger, and Z. Wiesenfeld-Hallin, "The excitatory amino acid receptor antagonist MK-801 prevents the hypersensitivity induced by spinal cord ischemia in the rat," *Experimental Neurology*, vol. 113, no. 2, pp. 182–191, 1991.

[84] J. X. Hao, X. J. Xu, H. Aldskogius, A. Seiger, and Z. Wiesenfeld-Hallin, "Allodynia-like effects in rat after ischaemic spinal cord injury photochemically induced by laser irradiation," *Pain*, vol. 45, no. 2, pp. 175–185, 1991.

[85] H. K. Erichsen, J. X. Hao, X. J. Xu, and G. Blackburn-Munro, "Comparative actions of the opioid analgesics morphine, methadone and codeine in rat models of peripheral and central neuropathic pain," *Pain*, vol. 116, no. 3, pp. 347–358, 2005.