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総説

脳神経内科疾患研究の歩み

下濱　俊
札幌医科大学医学部神経内科学講座

Research activities on neurological disorders up to the present

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ABSTRACT

To offer the best quality of life for patients suffering from various kinds of neurological disorders, I have been conducting numerous matters of clinical and basic research. My main interests include neurobiology and treatment of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis. I also conduct research on demyelinating diseases and autoimmune disorders such as myasthenia gravis with our colleagues. We study the molecular mechanisms of AD, and are trying to develop a novel therapy for it. Accumulation of activated microglia in and around senile plaques has been demonstrated in autopsied brains from AD patients, and is believed to modulate amyloid-beta clearance, inflammation and oxidative stress. Findings from our recent research suggest that microglial activation changes with progression of AD expressing several marker molecules. To explore a novel therapy against PD, we evaluated the therapeutic effects of an alpha-7 nicotinic acetylcholine receptor agonist and human bone marrow-derived mesenchymal stem cells. Excitation–contraction (E–C) coupling of skeletal muscles has been a somewhat under-explored field in clinical neurophysiology. We have explored the impaired post-tetanic potentiation of muscle twitch and the effect of local cooling on E-C coupling in myasthenia gravis.

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Key words: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, demyelinating diseases, myasthenia gravis

はじめに

札幌医科大学医学部神経内科学講座は，1992 年 4 月に附属病院診療科の神経内科として開設され，2008 年 4 月に診療科から医学部神経内科学講座へと昇格した．2006 年 10 月に初代松本博之名誉教授の後任として私が京都大学より着任した．2018 年 8 月より診療科名を神経内科から脳神経内科へ変更した．

脳神経内科は，中枢神経（脳・脊髄），末梢神経，神経筋接合部，骨格筋の器質的疾患に対して診断治療を行う診療科である．脳血管障害や神経感染症などの迅速な対応が必要な急性疾患から，多くが難病である神経変性疾患，他疾患に伴う神経障害の診断と治療など全身にわたる広範囲な知識や診療技術が要求される分野である．脳神経内科疾患に対するより精緻な診断法と効果の高い治療法の構築のためには，病態解明や治療法開発のための基礎的研究が大変重要である．

本稿では，札幌医科大学の医学生や若い医師に少しでも参考になればと思い，私の脳神経内科疾患に対する研究の変遷について述べる．

1　大学院時代の研究（1983 年 4 月～ 1987 年 3 月）

私は，1981 年に京都大学医学部を卒業し，亀山正邦教授が主宰されていた神経内科教室に入局した．大学病院で 1 年，東京都養育院付属病院（現在の東京都健康長寿医療センター）で 1 年の研修を行い，1983 年に京都大学大学院医学研究科博士課程に入学した．亀山教授がこれからは痴呆（認知症）の研究が極めて重要になってくるとの助言をいただき，また，東京都養育院付属病院で多くの剖検脳の脳切に立ち会っていたので，認知症疾患である「アルツハイマー病」をテーマに研究することにした．1970 年代後半から 1980 年代

前半にかけて，アルツハイマー病の剖検脳を用いた生化学的研究から，アセチルコリン系の障害が認知機能低下と密接に関連しているとのコリン仮説が誕生していた時期であった．これまでの生化学的研究は神経伝達物質の変動を解析する研究が主体であったので，「アルツハイマー病における神経伝達物質受容体に関する研究」をテーマに研究を行った．神経内科教室で収集した剖検脳を用いて，実質的には京都大学医学部薬理学教室で研究を施行し，論文として発表した[1～5]．特に，ニコチン性受容体のダウンレギュレーションが認知機能の低下と相関することは，世界の研究者において検証された先駆的な研究成果となった．アルツハイマー病におけるニコチン性受容体の病態的意義と新たな予防・治療法開発に関する研究は，現在においても大きな研究テーマとなっている．

2　留学時代の研究（1987 年 4 月～ 1989 年 3 月）

医学博士を取得後，異国の地での留学を希望した．今と違いインターネットの無い時代であり，図書館の文献内容から留学先を検討し，手紙でポストドクトラルフェローとして受入可能であるかを問い合わせた．アルツハイマー病の研究を続けたいと思い，世界的に有名であったアルツハイマー病の臨床神経学者である Robert Katzman 教授と神経病理の大家である Robert Terry 教授がおられ，アルツハイマー病センターを持つ米国カリフォルニア大学サンディエゴ校医学部神経科学部門に留学することができた．直接のボスは Fred Gage 教授（現在，Salk Institute 所長）で，遺伝子導入細胞の脳内移植により神経機能の回復を目指す研究（神経疾患に対する Gene Therapy）（図 1）ならびに神経可塑性の研究に従事した．また，同部門斉藤綱雄教授とアルツハイマー病の発症機構における Protein kinase C の役割などに関する研究に従事した[6～12]．基礎研究と共に米国における脳神経内科診療の実態およびアルツハイマー病センターで認知症診療における医師，心理士，看護師，ケースワーカー等によるチーム医療の大切さについて学ぶことができた．

3．留学帰国後の京都大学臨床神経学教室時代（1989 年 4 月～ 2006 年 9 月）

留学帰国後は米国のアイオワ大学医学部神経内科教授から京都大学医学部神経内科教授に異動された木村淳先生のもとで神経内科医員となり，臨床と共に研究を継続した．木村　淳教授の専門分野は臨床電気生理学を基盤とした末梢・筋疾患であったが，自由にこれまでの研究を続けることを許可してくれた．1990 年に神経化学研究室の責任者であった中村重信先生が広島大学医学部神経内科教授で異動されたために，34 歳の医員の立場で神経化学研究室の責任者となった．その後，助教，講師，助教授と昇任したが，多くの若者に声をかけて大学院生として研究室に入ってもらい，最終的に 25 名に医学博士の称号を取得させることができた．また，8 名が学位取得後海外留学を経験した．研究テーマは神経変性疾患を対象としたが，大学院生にそれまでの臨床研修で興味をもった疾患研究を自由に決めさせた．アルツハイマー病，パーキンソン病，および筋萎縮性側索硬化症（ALS）が研究対象となった．私がこれまで共同研究してきた京都大学薬学部や京都薬科大学の教室の教授と連携してその教室の若い大学院生やスタッフの方たちの力も借りて研究を進め

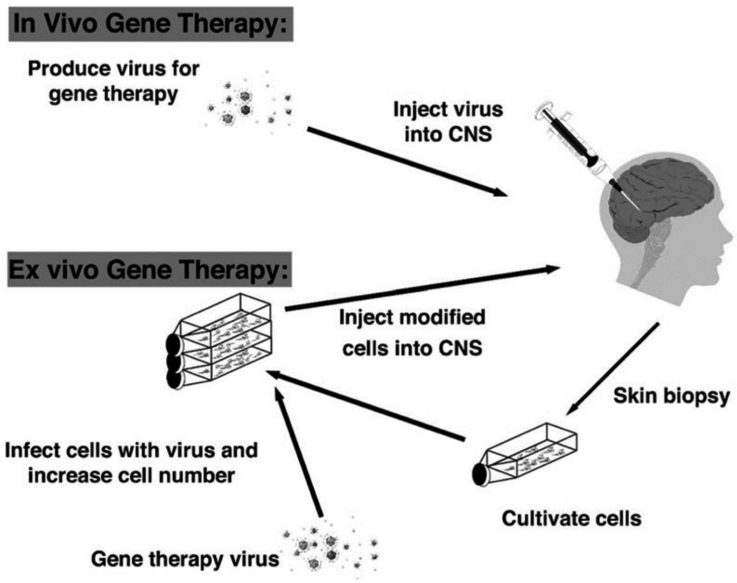

図 1. 神経疾患に対する Gene Therapy

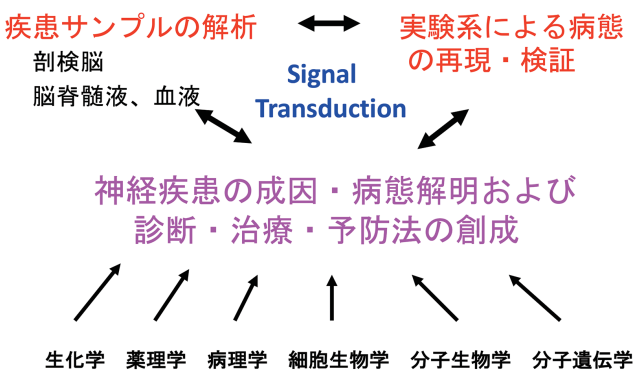

図 2. アルツハイマー病に対する治療戦略

た．研究室の主催者として，科学研究費補助金などのグラントを獲得することに尽力した．

アルツハイマー病に関しては，アルツハイマー病脳で出現する老人斑や神経原線維変化の分子生物学的研究，家族性アルツハイマー病の原因遺伝子の発見，弧発性アルツハイマー病の危険因子としてのアポリポ蛋白 E-ε4 の同定などからアミロイドカスケード仮説が提唱されるようになっていた．そこで，研究戦略（図2）を構築し，治療に向けた研究を進めた．1）剖検脳を用いた病態生化学的研究として，①細胞の恒常性維持に重要な情報伝達分子の解析，②ニューロン変性過程への酸化ストレス，ミトコンドリア機能障害の関与，③ニューロン死へのアポトーシス機構の関与，④プロテオミクス研究，などを展開した[13~69]．2）神経保護治療候補物質の探索およびその作用機序の解明研究として，①ニコチン性受容体を介する神経保護治療の創生，②神経栄養因子やエストロゲンなどの神経保護作用の解明および新たな神経保護治療候補物質として牛血清中からセロフェンド酸を発見し，その作用機序について解明した[70~89]．3）ニューロン・グリア相関の研究として，グリア制御によるニューロン死の抑制・神経保護治療の創成研究を進めた[90~99]．4）家族性アルツハイマー病原因遺伝子の機能解析研究として，家族性アルツハイマー病の原因遺伝子蛋白であるアミロイド前駆体蛋白質やプレセニリン蛋白質の機能解析を行った[100~109]．5）発症因子の研究として，遺伝因子の解析を進めた[110~116]．剖検脳に関しては海外のケースウェスタンリザーブ大学医学部の Peter Whitehouse 教授と George Perry 教授の協力を得て，提供していただいた．以上の成果を基に，「アルツハイマー病のタンパク質分子レベルにおける研究」および「脳アミロイドーシス予防・治療薬のスクリーニング方法」で特許出願した．

パーキンソン病に関しては，1）パーキンソン病における選択的中脳ドーパミンニューロン死および封入体形成機序の解明，2）ドーパミン代謝に関する研究，3）パーキンソン病モデル作製による神経保護治療候補物質の探索及びその作用機序の解明，4）パーキンソン病に対する再生医療研究を進めた[117~152]．一方，点眼薬を用いた瞳孔散大筋機能評価におけるパーキンソン病と他類似疾患の鑑別に関する臨床試験を行い[153]，「パーキンソン病診断キットおよびパーキンソン病診断方法」で特許出願した．

筋萎縮性側索硬化症（ALS）に関しては，1）ALS における選択的脊髄運動ニューロン死の発症機序の解明，2）ALS モデル作製による神経保護治療候補物質の探索およびその作用機序の解明，3）ALS に対する臨床的ヒト遺伝子解析研究などを進めた[154~167]．

研究を遂行するためには，研究資金が必要となる．研究成果を論文として発表し，科学研究費補助金などの研究グラントの獲得に尽力した．この期間に，科学研究費補助金の研究代表者として，基盤研究 A　1 件，基盤研究 B　3 件，基盤研究 C　1 件，萌芽研究　5 件，重点領域研究　3 件，特定領域研究 A　3 件，特定領域研究 C　5 件を獲得した．研究分担者として，基盤研究 A　2 件，基盤研究 B　1 件，重点領域研究　2 件，特定領域研究 A　1 件，基盤研究 C　5 件を獲得した．

4. 札幌医科大学へ異動後（2006 年 10 月～現在）

2006 年 10 月に初代松本博之名誉教授の後任として私が京都大学より着任した．教室には分子生物学・細胞生物学的研究に必要な機器がなかったので，京都大学から貸借の形で研究機器を移動させて，研究を進めることにした．

1）分子神経科学的研究

アルツハイマー病やパーキンソン病のモデル動物を作製し，その分子病態解明やその制御法の確立を目指し，国内外の最先端の研究室との共同研究を推進させている．最近は，ミクログリアの病態における役割に着目し，ミクログリア制御による神経変性疾患治療の開発を目指している．また，骨髄間葉系幹細胞などを

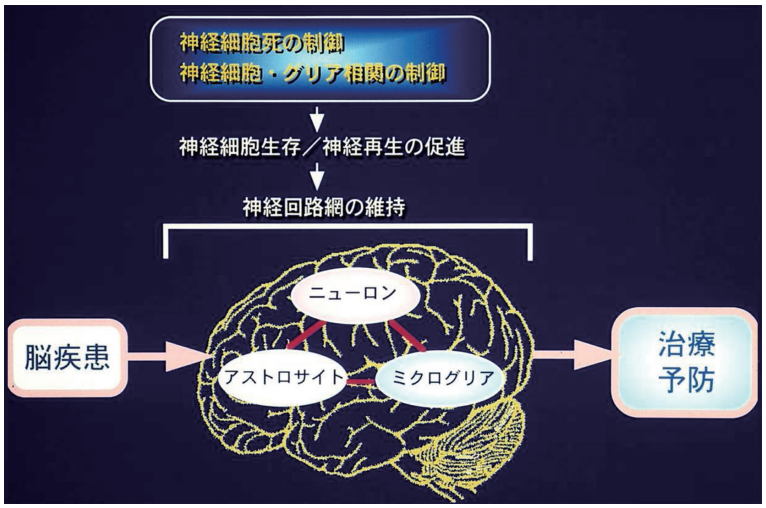

図 3. 神経変性疾患に対する予防・治療法の方向性

用いた神経再生治療法の開発に取組んでいる．ヒストン脱アセチル化酵素 SIRT1 が神経幹細胞に発現が強く神経細胞への分化を正に制御しうる重要な知見を見出しており，細胞の生存にも大きな役割を果たしていることを明らかにし，将来的に多発性硬化症や神経変性疾患の治療戦略の応用に寄与する可能性を検討している（図 3）[168~220]．

2）臨床神経生理学的研究

重症筋無力症 (MG) などにみられる筋疲労の発症機序として従来の神経筋接合部のシナプス接続の障害以外に，興奮収縮連関（Excitation-Contraction coupling, EC-coupling）の障害を想定して研究を進め，MG においては EC coupling の障害を明らかにし，同部位の免疫学的治療により MG 症状が改善される機序の解明を進めている[221~229]．

3）臨床研究

脳卒中研究として，神経超音波の臨床研究と頸動脈狭窄症に対する血管内治療研究を行っている．また，過疎の進む地域における脳卒中医療の質の向上を目指して，医療従事者の脳卒中医療と教育の実態調査などを行い，行政に発信するとともに，脳卒中と認知症に加えて，動脈硬化リスク管理を含めた IT を活用した医療連携システム（DASCH システム：Databank of Stroke Care in Hokkaido）の構築を進めている．また，神経変性疾患伴う呼吸障害の緩和に対する研究は伝統的に継続されており，ALS や多系統萎縮症（MSA）の呼吸不全における非侵襲的呼吸療法の検討を行っている．一方，健常高齢者，軽度認知障害，軽症アルツハイマー病の方を対象とした全国規模の追跡研究「J-ADNI (Japanese Alzheimer's Disease Neuroimaging) 臨床研究」に札幌医科大学は北海道では唯一の施設として参加し，アルツハイマー病治療薬の実用化を早めるために尽力した．現在，AMED 関連でアルツハイマー病，多系統萎縮症，筋萎縮性側索硬化症，多発性硬化症などの臨床研究を進めている．

研究を遂行するためには科学研究費補助金などの研究グラントの獲得が重要であることを教室員に教えてきた．科学研究費補助金の研究代表者として，基盤研究 B　2 件，挑戦的萌芽研究　1 件を獲得した．研究分担者として，基盤研究 B　1 件，基盤研究 C　6 件を獲得した．また，若手教室員が，若手研究 B　4 件，挑戦的萌芽研究　2 件を獲得している．

おわりに

脳神経内科が対象とする疾患は，脳・脊髄・末梢神経・筋肉の疾患と広範に及ぶ．近年，人口の高齢化に伴い，介護を必要とする老年者が急増しており，社会問題となっている．その要因として脳卒中やアルツハイマー病などの認知症あるいはパーキンソン病など神経変性疾患の増加が挙げられる．脳神経内科疾患の克服のために，札幌医科大学医学部神経内科学講座が，今後も最先端の研究を幅広く推進させていくことを教室の目標として取組むことを期待する．

謝辞

これまで私と共に楽しく研究活動をしていただいた下記の研究者に心より感謝申しあげます（敬称を略させていただきます）．

京都大学医学研究科臨床神経学：故亀山正邦，中村重信，木村　淳，柴崎　浩，高橋良輔，辻　輝之，松島秀行，澤田秀行，川又　純，河崎洋志，長谷川浩史，井村徹也，木原武士，漆谷　真，景山　卓，大江田知子，山本兼司，本田和弘，北川尚之，河野隆一，中溝知樹，植村健吾，塩崎愛子，神吉理枝，山下博史，葛谷　聡，

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Case Western Reserve University：
Peter J. Whitehouse，George Perry & his laboratory members，故 Mark A. Smith

National Hospital for Neurology and Neurosurgery, Queen Square：
Martin Rossor

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