Max-Delbrück-Centrum für Molekulare Medizin, Berlin

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Die Rolle des SorLA-Rezeptors in der Genese der Alzheimer-Krankheit sowie seine Funktion in der Niere

Inaugural-Dissertation

zur Erlangung des Grades Doctor rerum medicarum

(Dr. rer. medic.)

vorgelegt der

Charité – Universitätsmedizin Berlin

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Gedruckt mit Genehmigung der Charité - Universitätsmedizin Berlin

Campus Benjamin Franklin

Promoviert am: 10. Oktober 2006

Inhaltsverzeichnis

5 ZUSAMMENFASSUNG

Die Genfamilie der Vps10p-Rezeptoren umfaßt eine neuartige Gruppe von Proteinen im Säugerorganismus, welche strukturelle Homologie mit Endozytose- und Sortingrezeptoren aufweist. Hohe Expressionsraten für SorLA, einem Mitglied der Vps10p-Rezeptorgenfamilie, findet man unter anderem im Gehirn, im Rückenmark, in der Lunge und in der Niere, dennoch ist dessen physiologische Funktion bisher weitgehend unbekannt.

Zur näheren Aufklärung der Rolle von SorLA im Gehirn und in der Niere wurde einerseits die Interaktion mit dem „Amyloid Precursor Protein“ (APP) im Gehirn näher untersucht, anderseits erfolgte eine phänotypische Analyse der Nierenfunktion SorLA-defizienter Mäuse im Vergleich zu Wildtypmäusen.

APP spielt eine zentrale Rolle bei der Pathogenese von Morbus Alzheimer. Hier erfolgt nach enzymatischer Proteolyse von APP durch die β- und γ-Sekretase die Freisetzung des Spaltprodukts β-Amyloid, welches bei übermäßiger Produktion bzw. bei verminderter Abbaurate extrazellulär aggregieren und akkumulieren kann (amyloidogener Weg). In Folge dessen kommt es zur Apoptose der umliegenden Neuronen was schließlich zum Ausfall der betroffenen Gehirnbereiche führt. Diese Prozesse kennzeichnen die Alzheimer-Krankheit. Von elementarer Bedeutung für die Proteolyse des APP ist der intrazelluläre Transport des Proteins, da APP bei veränderter zellulärer Lokalisation einer alternativen Prozessierungskaskade unterliegt. Dieser Weg, auch bezeichnet als nicht-amyloidogener Weg, wird durch die Proteolyse mit der α-Sekretase eröffnet und führt nicht zur Bildung und Ablagerung des Amyloidpeptids. Er verhindert so die Ausbildung der Alzheimer-Krankheit.

Anhand von Zellkulturstudien und mit Hilfe eines SorLA-gendefizienten Mausmodells konnte gezeigt werden, daß SorLA wesentlich am zellulären Transport von APP beteiligt ist. Die Untersuchungen belegten, daß SorLA direkt an APP bindet und dessen Lokalisation derart beeinflußt, daß es sowohl einer geringeren amyloidogenen als auch nicht-amyloidogenen Prozessierung unterliegt. In Gegenwart von SorLA konnte im Zellkulturmodell die Menge an β-Amyloid$_{40}$ sowie die an sAPPα/β (Spaltprodukte nach Proteolyse durch die α- oder β-Sekretase) drastisch reduziert werden. In Abwesenheit von SorLA (im gendefizientes Mausmodell) ließ sich eine deutliche Zunahme an sAPPα und β-Amyloid$_{40/42}$, im Vergleich zu Kontrolltieren, verzeichnen.

Die Analyse des Nierenphänotyps SorLA-defizienter Mäuse wies Defekte der Salzrückresorption, der Aldosteronhomöostase und der Blutdruckregulation auf. Nähere Untersuchungen verschiedener Ionentransporter lassen einen Fehlregulation des Natrium-Kalium-Chlorid-Cotransporters-2 (NKCC2) vermuten. Darüberhinaus führt eventuell die fehlende Expression von SorLA in der Nebenniere zur Beeinträchtigung der Aldosteronausschüttung, was eine Hypokaliämie und Hypertonie zur Folge hat. Der hier beobachtete Phänotyp ist vergleichbar mit Symptomen des primären Hyperaldosteronismus.

6 ABKÜRZUNGSVERZEICHNIS

(v/v) Volumen pro Volumen

(w/v) Gewicht pro Volumen

ADAM a disintegrin and metalloprotease

AK Alzheimer-Krankheit

Ang-I/II Angiotensin-I/II

Aogen Angiotensinogen

APLP Amyloid precursor like protein

ApoE Apolipoprotein-E

APP Amyloid precursor protein

Aß Amyloid-ß

BACE β-site cleaving enzyme

BSA bovines Serumalbumin

CHO Chinese hamster ovary

c-terminal carboxyterminal

CTF carboxyterminales Fragment

DAB diaminobenzidin

dDAVP desamino-D-arginin-vasopressin

DMEM Dulbecco's modified eagle medium

EDTA Ethylendiamintetraacetat

ER endoplasmatisches Retikulum

JIP1 JNK-interacting protein 1

JNK c-Jun N-terminal kinase

Mena Mammalian enabled

mDab1 Mammalian disabled 1

NCC Na^+-Cl^--cotransporter

NGF nerve growth factor

NKCC2 Na^+-K^+-Cl^--cotransporter

n-terminal aminoterminal

PAGE Polyacrylamid Gelelektrophorese

PBS Phosphate-buffered saline

PS Presenilin

Rab5 (rat sarkomer) associated protein 5

ROMK rat outer-medulla K^+ channel

RT Raumtemperatur

SDS Sodium-dodecyl-sulfat

SLC12A Solute carrier family 12

SPR Surface Plasmon Resonance

TAU Mikrotubule associated protein

TGN *trans*-Golgi Netzwerk

Tip60 Tat interacting protein (60 kDa)

z.Bsp. zum Beispiel

7 LITERATURVERZEICHNIS

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8 DANKSAGUNG

Die vorliegende Arbeit wurde im Labor von Prof. Thomas Willnow am Max-Delbrück-Centrum für Medizin (Berlin) in der Zeit vom September 2001 bis März 2005 erstellt.

Thomas, ich danke Dir herzlichst für das Ermöglichen dieser Arbeit, für Deine exzellente Betreuung, die enthusiastische Unterstützung und für die vielen kleinen Dinge, die ich von Dir lernen konnte.

Ebenso möchte ich Olav Andersen für die Zusammenarbeit, die großartige Geduld, die Sinnhaftigkeit von Positiv/Negativkontrollen und die allzeit wichtigen Fußballergebnisse von Brøndby IF danken. Darüberhinaus danke ich Susanne Schütz für die Unterstützung im Tierstall. Ohne ihre tierpflegerische Hilfe wäre die Arbeit wahrscheinlich nie zustande gekommen. Schon lange vermißt aber nie vergessen ist die wunderbare Zeit mit Helle Heibroch-Petersen. Undenkbar wäre die Zeit in Berlin, in der Mecklenburger Seenplatte, im Labor und auf Konzerten ohne Helle!

Ganz besonderer Dank geht an Hannelore Schulz, Charlotte Räder, Donathe Vetter, Michael Obst, Irene Strauß, Birgit Nernheim sowie an Pernille Jensen für die technische Assistenz. Ebenso danke ich R. Cappai, A. Nykjaer, J. Gliemann, K. Beyreuther, C. Pietrzik und M. Knepper für die Bereitstellung von Proteinfragmenten und Antikörpern sowie M. Gotthardt für die Bereitstellung der SorLA-gendefizienten Maus.

Besonders danken möchte ich aber vor allem den Mitarbeitern der AG Willnow. Sie trugen wesentlich zum Gelingen der Arbeit bei, sei es durch bereits angesetzte Tris-Puffer in allen pH- und molaren Variationen oder durch die vielen angenehm ablenkenden allabendlichen Umtrunksaktivitäten.

Kerstin Bergel und den Volleyball-Damen verdanke ich den wunderbaren Ausgleich auf sportlicher Ebene und hoffe ihnen eine Antwort auf die Frage “Was machst Du eigentlich mit den Mäusen?“ nicht schuldig geblieben zu sein.

Wenn auch zu guter Letzt, gilt nichtdestotrotz ein ganz besonderer Dank meinen Eltern, meinem Bruder und Jan. Sie alle haben mich außerordentlich unterstützt, mir Trondheim schmackhaft gemacht und mein Leben „neben“ der Dissertation unwahrscheinlich bereichert. Dies gilt ebenso für meinen kleinen Karl Fridolin.

9 LEBENSLAUF

Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht.

Publikation:

Andersen OM., Reiche J., Schmidt V., Gotthardt M., Spoelgen R., Behlke J., von Arnim Ch.AF., Breiderhoff T., Jansen P., Wu X., Bales KR., Cappai R., Masters CL., Gliemann J., Mufson EJ., Hyman BT., Pauls SM., Nykjaer A., Willnow TE., Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein; *PNAS Sept. 20; 102 (38):13461-6*

ERKLÄRUNG

„Ich, Juliane Reiche, erkläre, daß ich die vorgelegte Dissertationsschrift mit dem Thema: „Die Rolle des SorLA-Rezeptors in der Genese der Alzheimer-Krankheit sowie seine Funktion in der Niere“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Berlin, den 15. Juni 2006 Juliane Reiche