Newsletter
der
Deutschen Gesellschaft für Neurogenetik

January, 2001
DGNG News No. 13

Society News

Der Neurologe und Psychiater as a Forum for the DGNG

The newly established German language journal „Der Neurologe & Psychiater" will serve as a forum for the Society. All Newsletters will be printed in this Journal starting with a German translation of Newsletter 12 (DNP 1: 10-12, 2000).

DGNG a member of the vdbiol

The DGNG has become a member of the Verband Deutscher Biologen und biowissenschaftlicher Fachgesellschaften e.V. (vdbiol).

Neurogenetics in Dresden

The 7th Workshop Neurogenetics in Germany, 6th Annual Meeting of the German Society of Neurogenetics, was held in Dresden from September 14-September 16, 2000. The meeting was organized by Prof. Dr. Heinz Reichmann, Prof. Dr. Peter Seibel, Dr. Janet Schmiedel, and Dr. Friedmar Kreuz. The workshop focussed on mitochondrial disorders but other topics in Neurogenetics were also covered. The conference started with an exciting keynote lecture on Alzheimer disease by Konrad Beyreuther (Heidelberg, Germany). This excellent presentation covered the latest progress in Alzheimer research including the recently reported discovery of Nicastrin (see Research News) which might have important implications for future drug design. The morning sessions of 9/15 were devoted to mitochondrial diseases. Arnold Munnich (Paris, France) gave an overview of mitochondrial disorders and reported on the successful therapy of a patient with ubiquinone deficiency by substitution of this compound. He also presented data on treatment of Friedreich ataxia (FA) with quinone (idebenone). While he observed some improvement of cardiac symptoms, further studies are required to confirm a beneficial effect of this substance in FA. In the following presentation, Eric Shoubridge (Montreal, Canada) introduced chromosomal complementation for the detection of nuclear genes in mitochondriopathies. This was exemplified by his experiments on Leigh syndrome that resulted in the identification of mutations in the gene *SURF 1*. Antonio Torroni (Rome, Italy) talked about the role of mtDNA background in disease expression. He provided evidence that mitochondrial haplogroups might influence the penetrance of two common mutations in Leber´s hereditary optic neuropathy (LHON). Kirsi Huoponen (Turku, Finland) pointed out the extreme heterogeneity of the phenotype in LHON. She presented data, disillusioning for genetic counselors, demonstrating that the percentage of heteroplasmy observed in patients does not permit prediction of the phenotype, i.e. development of blindness. In his contribution Ian Trounce (Fitzroy, Australia) discussed xenomitochondrial mouse cybrids as mtDNA disease models. Bob Lightowlers (Newcastle upon Tyne, UK) completed the morning sessions by outlining the potential usefulness of antigenomic strategies for the treatment of disorders of the mitochondrial genome.

The afternoon sessions were grouped in talks on basic mechanisms of mitochondrial functions by invited speakers and on short presentations of various aspects of mitochondrial function that were selected from submitted abstracts. The first group included talks on the possibility of mitochondrial recombination by Jose Antonio Enriquez (Zaragoza, Spain), the regulation of mitochondrial biogenesis by Rudolf Wiesner (Köln, Germany) and the function of Fe/S proteins in iron homeostasis by Gyula Kispal (Pecs, Hungary). The sessions on 9/16 covered various topics including defects of the respiratory chain during ageing (Joseph Müller-Höcker, München, Germany), genetic factors in Parkinson disease (Olaf Riess, Rostock), genes coding for the nuclear envelope in neuromuscular disease giving Emerin and Laminin A/C mutations as examples (Clemens Müller-Reible, Würzburg, Germany), and genes in hereditary motor and sensory neuropathies (HMSN) (Clemens Hanemann, Ulm, Germany). The final four contributions covered spino-cerebellar ataxias (Thomas Klockgether, Bonn, Germany), the restless-legs syndrome (Thomas Gasser, München, Germany), aspects of research into multiple sclerosis in animal models (Ralf Gold, Würzburg, Germanny) and mutations in the RET protooncogene in Hirschsprung´s disease and in the rare syndrome of Ondine´s curse that can be associated with Hirschsprung´s (Hans-Konrad Schackert, Dresden, Germany). Abstracts of presentations have been published in Med Genet, No 3 Sept. 2000, pp 381-391.

8th Workshop Neurogenetics in Germany, 7th Annual Meeting of the DGNG

The next workshop (8th Workshop Neurogenetics in Germany and the 7th Annual Meeting of the DGNG) will be organized by Prof. P. Wieacker and colleagues and held in Magdeburg from October 25-27, 2001.

Research News

Nicastrin, a new player in Alzheimer disease (AD). Mutations in the genes coding for presenilin 1 and 2 (PS1 and PS2) underlie autosomal dominant forms of AD [see DGNG News No.3]. The physiological roles of the presenilins include cleavage of amyloid precursor protein (APP) at an extramembranous (ß secretase activity) and at an intramembranous site (γ-secretase activity) thus generating $A\beta_{40}$ and to a lesser extent $A\beta_{42}$. Mutant presenilins appear to increase the percentage of the highly amyloidogenic $A\beta_{42}$. Presenilins are physiologically also involved in cleavage of the transmembrane protein notch. Cleavage of notch produces intracellular fragments required for mediation of notch-function, i.e. activation of genes involved in the determination of cell-fate. The secretase activities, however, are not exerted by the presenilins alone but additional proteins are necessary. Yu et al. (2000) have now isolated the crucial additional protein required for proper γ-secretase function. This protein is tightly associated with presenilins and was isolated from a PS1 secreting cell line. It was christened nicastrin after the Italian village of Nicastro from which an autosomal dominant family relevant to the identification of PS-associated forms of AD originated. Nicastrin is a transmembrane protein and interacts with both presenilins and the carboxy-terminal fragment of APP that is generated by β secretase function. In vitro experiments showed that mutations of nicastrin can result in alteration of γ-secretase activity thus proving its important function in APP processing. In concert with PS nicastrin is also crucial for normal notch processing and the generation of the intracellular fragments required for notch function. The authors suggest that nicastrin

and presenilins form a multimeric complex for the intramembranous proteolysis of APP and notch. Interestingly, the gene coding for nicastrin was assigned to a region on chromosome 1 that is thought to harbor an AD susceptibility locus. So far, however, mutations in the nicastrin gene have not been detected in patients with AD.

Yu, G.; Nishimura, M.; Arawaka, S.; Levitan, D.; Zhang, L.; Tandon, A.; Song, Y.-Q.; Rogaeva, E.; Chen, F.; Kawarai, T.; Supala, A.; Levesque, L.; and 18 others : Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and beta-APP processing. Nature 407: 48-54, 2000

Treatment of Alzheimer disease in sight? Alzheimer disease (AD) is the most common neurodegenerative disorder in humans and is characterized by progressive cognitive decline and behavioural problems. Since the prevalence of AD increases with age, increased longevity and growing numbers of the elderly stress the need for effective treatment even further.

Recently, the American based company Elan Pharmaceuticals developed an immunization approach to treat mice transgenic for the mutant human amyloid precurser protein (APP). These mice develop amyloid plaques similar to those seen in the brain of AD patients. The Elan group investigated the effects of immunization against APP (Schenk et al. 1999). After receiving 11 immunizations over an 11 month period the mice had serum antibody titres against $A\beta_{42}$ of greater than 1:10,000. Most importantly, however, was the observation that amyloid β deposition in the brain was almost completely prevented. Astrocytosis, another hallmark of plaque-associated pathology in both AD and PAPP mice, was dramatically reduced. Finally, amyloid β immunization significantly retarded the progression of pathology and reduced reactive astrocytosis in affected animals. This suggests that $A\beta_{42}$ immunization has the potential to be further developed for both the treatment and prevention of AD.

A recent paper by the same group demonstrated that peripherally administered antibodies against amyloid β peptide enter the central nervous system and reduce pathologic changes using the same animal model (Bard et al. 2000). The authors started with 10 month old mice using intraperitoneal injection of antibodies which reduced plaque burden by up to 93%. Unlike actively immunized mice, mice receiving exogenous antibodies against Aβ did not demonstrate a T-cell proliferative response to Aβ. These results indicate that in the absence of T-cell immunity, antibodies against Aβ peptide are sufficient to decrease amyloid deposition. Similar results were obtained by administering Aβ antibodies peripherally. Although in these experiments there was no obvious change in the number of large plaques after 35 days of treatment, nearly 60% of the small plaques and diffuse amyloid had been eliminated. Weiner et al. (2000) confirmed the results by nasal administration of amyloid β peptide. They also found significantly reduced Aβ plaque burden and decreased microglial and astrocytic activation, suggesting a novel mucosal immunological approach for the treatment and prevention of AD.

It is likely that Aβ antibodies cross the blood-brain barrier. This is supported by the finding of serum proteins in the CSF at levels of approximately 0.3% of those in the blood. Aβ antibodies might be captured by the plaques and might induce proteolysis or phagocytosis. This needs to be investigated in more detail. Also, behavioural studies on these mouse models have not been published yet and it is questionable whether Aβ immunization is equally effective in mice and humans without a mutation in the APP gene. For

clinical implications, trials will have to be of sufficient duration to detect meaningful changes in the rate of disease progression. For the first time there is legitimate hope for an effective treatment of patients with AD and their relatives.

Bard F, Cannon C, Barbour R, et al. (2000) Peripherally administered antibodies against amyloid β-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. Nature Med 6: 916-919

Schenk D, Barbour R, Dunn W, et al. (1999) Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 400: 173-177

Weiner HL, Lemere CA, Maron R, et al. (2000) Nasal administration of amyloid-β peptide decreases cerebral amyloid burden in a mouse model of Alzheimer's disease. Ann Neurol 48:567-579

Genes coding for mitochondrial complex 2 function as tumor suppressors in autosomal dominant paragangliomas.

Nonchromaffin paragangliomas (PGLs, glomus tumors, chemodectomas) are usually benign, neural-crest-derived tumors of parasympathetic ganglia. Most common locations include the carotid bifurcation, the vagal nerve and the middle ear. PGLs usually arise during adulthood with a wide range of patients' age at disease onset. Between 10% and 50% of cases are familial and are transmitted as autosomal-dominant traits with incomplete and age-dependent penetrance. Autosomal dominant PGLs are genetically heterogeneous, and disease loci have been assigned to 11q23 (*PGL1*) and 11q13 (*PGL2*). Both *PGL1*, and *2* are maternally imprinted (inactivated). A third, non-maternally imprinted locus (*PGL3*) was demonstrated by exclusion of chromosome 11 loci in a large family. The genes mutated in PGL1 and 3 have now been identified. PGL1 is caused by mutations in the gene *SDHD* that codes for the small subunit of cytochrome b (cytbS) of the succinate-ubiquinone oxidoreductase (Baysal et al., 2000), and a mutation in *SDHC* coding for the large subunit of cytb was discovered in a family with PGL3 (Niemann and Müller, 2000). SDHD and SDHC are part of mitochondrial complex II and anchor the catalytic subunits SDHB (iron-sulfur protein subunit) and SDHA (flavoprotein subunit) in the inner mitochondrial membrane. While one copy of *SDHD* and *SDHC* is mutated in constitutive DNA of patients with PGL1 and PGL3, the second allele is deleted in tumors resulting in loss of heterozygosity (LoH). These findings suggest that *SDHD* and *SDHC* function as tumor suppressor genes in PGL1 and 3. Presently, the role if any of maternal imprinting in PGL1 in tumor formation is not known.

Baysal, B. E.; Ferrell, R. E.; Willett-Brozick, J. E.; Lawrence, E. C.; Myssiorek, D.; Bosch, A.; van der May, A.; Taschner, P. E. M.; Rubinstein, W. S.; Myers, E. N.; Richard, C. W., III; Cornelisse, C. J.; Devilee, P. Devlin, B. : Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science 287: 848-851, 2000.

Niemann, S.; Müller, U. : Mutations in SDHC cause autosomal dominant paraganglioma, type 3. Nature Genet. 26: 268-270, 2000.

With the best wishes for a successful New Year.

Sincerely yours,

Ulrich Müller
Olaf Riess
G. B. Landwehrmeyer

Protokoll der Mitgliederversammlung 2000

der

Deutschen Gesellschaft für Neurogenetik

Ort: Hörsaal im Medizin-Theoretischen Zentrum (MTZ)

Fiedlerstrasse 42, 01307 Dresden

Zeit: Donnerstag, 14. 09. 2000

Beginn: 18:15 Uhr

Ende: 18:45 Uhr

Anwesend: 8 Mitglieder (Schriftführer Prof. Dr. Manuel Graeber fehlt entschuldigt)

TOP 1: Bericht des Präsidenten

Da Herr Prof. Dr. Graeber nach Übernahme einer Professur für Neuropathologie in London als Sekretär der Gesellschaft zurückgetreten ist und sein Nachfolger noch nicht gewählt war, wurde er als Protokollant dieser Mitgliederversammlung von Frau Dr. Köhler vertreten.

1. Mitglieder

Prof Müller berichtet über die Entwicklung der Mitgliederzahl. Trotz einiger weniger Austritte, meist im Zusammenhang mit Pensionierung/ Berentung, ist die Zahl der Mitglieder der DGNG in diesem Jahr (bis 31. 08. 2000) auf 165 gestiegen. Es wird angeregt, weitere Mitglieder zu werben. Herr Prof Reichmann schlägt vor, die Chefs von Kliniken für Neurologie und Psychiatrie sowie von Instituten für Neuropathologie, Humangenetik etc. in diesem Sinne persönlich anzuschreiben und Beitrittsformulare sowie das präliminäre Programm der nächsten DGNG-Tagung beizulegen. Alle Mitglieder begrüßen diesen Vorschlag. Wegen der geringen Beteiligung an den Mitgliederversammlungen wird angeregt, diese wichtigen Treffen bei zukünftigen Tagungen so zu legen, dass mehr Mitglieder teilnehmen können, etwa direkt nach einer Vormittagssitzung.

2. DGNG-Tagungen 2001 und 2002

Die nächste DGNG-Tagung wird vom 20.09.-22.09.2001 in Magdeburg stattfinden (Organisation Prof. Wieacker und Mitarbeiter). Im Herbst 2002 wird Ulm Tagungsort sein (Organisation Prof. Landwehrmeyer und Mitarbeiter).

3. Neuroreport

Prof. Müller teilt mit, dass der Gesellschaft vom Herausgeber der neuen Zeitschrift „Der Neurologe & Psychiater“ (DNP) angeboten worden ist, dieses Journal als Forum zu verwenden. Dieser Vorschlag wurde begrüßt. Newsletter 12 und alle weiteren Newsletters sowie sonstige Nachrichten der Gesellschaft werden in Zukunft in dieser Zeitschrift in deutscher Sprache publiziert werden. Es soll versucht werden zu erreichen, dass die Zeitschrift, die sich in erster Linie an Praktiker und an Kliniker der Neurologie und Psychiatrie richtet, Mitgliedern der DGNG zu günstigen Konditionen angeboten werden kann.

4. Aufnahme in den VdBiol

Prof. Müller schlägt vor, als Gesellschaft dem Verband Deutscher Biologen beizutreten. Sein Vorschlag wird von allen Anwesenden begrüßt. Auch die Aufnahme in andere biowissenschaftliche Fachgesellschaften sollte eruiert werden.

5. Verschiedenes

Wegen der stabilen positiven Kassensituation der DGNG wird angeregt, bereits auf dieser Tagung und auch in Zukunft Posterpreise zu vergeben. Dies sollen drei gleichrangige Preise sein, die eine Kommision an den Erstautor/in der drei besten Poster der Tagung vergeben soll. Für diese Tagung wird ein Gremium gebildet, dem Prof. Riess (Humangenetik), Priv. Doz. Dr. Egensperger (Neuropathologie) und Priv. Doz. Dr. Bandmann (Neurologie) angehören. Prof. Reichmann schlägt vor, den Preisträgern die nächste Tagung zu finanzieren (Fahrt, Unterkunft, Tagungsgebühr). Alle anwesenden Mitglieder begrüßen diesen Vorschlag sehr.

TOP 2: Bericht der Schatzmeisterin, Kassenprüfung

Dr. Egensperger vertritt die abwesenden Kassenprüfer. Frau Dr. Köhler erläutert die Einnahmen und Ausgaben der Gesellschaft für den Zeitraum 01.09.1999-30.08.2000. Wegen der weiterhin guten Entwicklung des Kassenstandes wurde am 24. 02. 2000 nach Beratung durch die Sparkasse Giessen ein „Zins und Cash“-Konto eröffnet, das einen guten Zinsertrag sichert, der sich am Dreimonats-EURIBOR-Satz orientiert. Frau Dr. Köhler bittet die Mitglieder der Gesellschaft, ihr umgehend mitzuteilen, wenn sich deren Kontonummern ändern. Auch in diesem Abrechnungszeitraum mussten wieder Rückbuchungen vorgenommen werden, weil Konten von Mitgliedern erloschen waren. Die damit verbundenen Kosten würden wir gerne einsparen. Nach Prüfung der Kasse stellt Dr. Egensperger den Antrag auf Entlastung der Schatzmeisterin. Dieser wird mit einer Enthaltung, ohne Gegenstimme angenommen.

TOP 3: Vorstandswahl

Die Wahl des Vorstands wird auf Freitag, 15.09.00, 12:30 verschoben, um einer größeren Zahl von Mitgliedern die Teilnahme an den Wahlen zu ermöglichen.

Beginn: Freitag, 15.09.00, 12:45 Uhr

Ende: 13:15 Uhr

Anwesend: 18 Mitglieder

Prof. Müller wird als Präsident im Amt bestätigt (17 Ja-Stimmen, 1 Enthaltung)

Prof. Riess wird als Vizepräsident im Amt bestätigt (17 Ja-Stimmen, 1 Enthaltung). Das Amt des Schriftführers wird neu besetzt, Prof. Graeber steht nicht mehr zur Verfügung. Prof. Landwehrmeyer wird als einziger Kandidat vorgeschlagen. Er stellt sich für das Amt zur Verfügung und wird einstimmig gewählt (17 Ja-Stimmen, 1 Enthaltung). Frau Dr. Köhler wird als Schatzmeisterin im Amt bestätigt (17 Ja-Stimmen, 1 Enthaltung). Alle Gewählten nehmen die Wahl an.

Dr. A. Köhler
(Vertreterin des Schriftführers)

Prof. Dr. B. Landwehrmeyer
(Schriftführer ab 15.09.00)

Prof. Dr. U. Müller
(Präsident)