Alternating Hemiplegia Foundation

International Foundation For Alternating Hemiplegia Of Childhood

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International Foundation for
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Address Correction Requested

Medical Advisory Board

Letter from the Presidents

In the spirit of uniting with a common goal of curing our children, we have had a coming-together of the minds and want to share some very important and joyous news with our families.

The IFAHC and the AHFof Michigan are proud to announce that when the details are settled and the papers are signed, we will have one united Foundation called "The Alternating Hemiplegia of Childhood Foundation". We are so very excited and are looking forward to working together and now, we are a stronger organization. We will no longer be duplicating any of our efforts.

This newsletter is a joint effort between both Foundations and bears the logos of both the IFAHC and the AHF of Michigan. When the new Foundation is up and operating, we will distribute only one newsletter, which we hope will be coming out in the Fall of 2001. This will bring one voice to the medical community showing our commitment to a cure!! We will be working together with one Board of Directors, stronger than ever before. Our family lists will be more complete, and we will be able to serve the AHC families more efficiently.

This is a new beginning, and we hope and pray that all the families will now join together with us either by volunteering their time, having a fundraiser, helping with family support helping fund research, or anything else that may arise in the future.

Please be assured that the Foundation leaders will remain in their authoritative positions and that you will be able to speak to the same contact people you have in the past. And remember that now there are additional people on board to help answer any questions or solve any problems that any of you family members may have.

No words could possibly express our excitement and enthusiasm of working together to find a cure for our children!!

Richard George
Lynn Egan

This newsletter is sponsored by Lorne and Annette MacDonald
Grandparents of Kathleen Egan
San Carlos, CA, USA

One Step Closer

Medical Update

By Kathy Swoboda, M.D.

As everyone is probably aware from recent news coverage, the human genome project is nearly completed. Regarding AHC specifically, as you probably know by now, we cloned the translocation breakpoint nearly a year ago, and identified a bacterial artificial chromosome (BAC) spanning the breakpoint between chromosomes 3 and 9. Within the last three months, we have been able to completely assemble the genetic sequence in the region of the translocation on chromosome 9, and we now know all the genes in the region.

We also have the entire sequence in the region of interest on chromosome 3.

With the help of a fabulous technician in the laboratory who recently relocated from Brigham and Women's Hospital in Boston, we have been "sequencing" or decoding genes using a panel of a dozen of the sporadic patients from the database. Unfortunately, it has been a bit more difficult to identify the precise translocation breakpoint due to technical issues. Therefore, with the help of Dr. Liharska, a mother of one of the patients with AHC in the database, we have established a collaborative effort with a group in the Netherlands under the direction of Dr. van den Maagdenberg. Congratulations are in order to Dr. Liharska for this excellent suggestion. Their group is helping to do cosmid FISH (fluorescent in situ hybridization) to help us narrow down even further the exact translocation breakpoint. Because cosmids are much smaller than BACs, they contain a much tinier piece of DNA, thus narrowing down the region to a piece of DNA much smaller than a BAC. The bottom line is, we've got to be close!

Regarding the clinical part of the database, we need to do some more work, but we are making great progress. Catherine McKenna has been working hard to help get all the corresponding medical records and completed questionnaires back on each child, but it has been challenging. Regarding these questionnaires, We are particularly interested in getting people to answer the questions regarding prior benefits and side effects of medications which may have been tried along the way. We have some preliminary data that another category of medications besides flunarizine may sometimes be helpful in controlling certain symptoms. We realize that it is difficult for families to remember all the details, which is why obtaining the medical records are so vital. I am still hoping to get as much detail regarding the prior metabolic workup in these kids - they went through all that testing, so we may as well try to make some sense of it. Sometimes what doesn't appear significant in a single child can show up as a pattern when all the data is reviewed. We also hope to establish a photograph database to analyze the children for subtle features that might share in common. We plan to digitize those photos and use computer software to help in our analysis. For this, we would like families to take two photos, one straight on of the head and face, and one lateral view of the face and head only. Send us the copies and we'll take it from there. These photos will only be used for this purpose, and we have a separate consent form we'd be happy to forward to families.

One final note: We are currently writing an NIH grant for further support on this project.

Best wishes,

Kathy Swoboda M.D.

Pictures Needed

Dr. Swoboda needs pictures of your children. She needs frontal head (from shoulders up) and a profile shot. She has begun to build a data base of this information to compare features of AHC children.

Also needed are any videos you have of your children during an episode.

Please send them to:
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Interim Progress Report on "The Effects of Flunarizine on Neocortical GABAergic and Glutamatergic Function"

Principal Investigator: Johannes F.M. van Brederode, PhD
Co-Investigator: Jong M. Rho, MD; Co-investigator: Paul T. Golumbek, MD, PhD
Submitted: 12/12/00

The following is an update on the Flunarizine research that has been being conducted by Drs. Johannes F.M. van Brederode, PhD, Jong M. Rho, MD and Paul T. Golumbek, MD, PhD. This research is the result of a grant that was awarded to these researchers early last year.

Please note that since this update is being reprinted in it's original form, parts of it may be difficult to understand. And although we did consider trying to condense it, we felt that by doing so we would not be doing justice to the research that was being conducted or the researchers themselves. For further explanations on what is contained in this update, you might consider providing a copy of it to your child's doctor.

Good reading!
Kim Cooper

Introduction:

Alternating hemiplegia of childhood (AHC) is an extremely rare, episodic neurological disorder characterized by recurrent attacks of paralysis affecting all limbs, and is associated with a variety of oculomotor abnormalities, autonomic disturbances, and movement disorders. Patients with this condition are generally expected to experience progressive cognitive impairment , and some develop frank epileptic seizures. Despite numerous clinical studies, there is virtually nothing known about the pathophysiology of this unusual condition. Hemiplegic attacks have usually been treated with anticonvulsant drugs, generally without much success. However, two classes of pharmacological agents appear to demonstrate clinical efficacy in a subset of patients with AHC. Flunarizine, a dihenylpiperazine compound that blocks voltage-dependent calcium channels, is perhaps the most widely cited drug. The second general class of compounds found effective in the treatment of AHC are those that are positive allosteric modulators of the inhibitory GABAA receptor including benzodiazepines, and chloral hydrate. Despite the efficacy of these GABAA receptor modulators, it is not clear whether these drugs abort the hemiplegic attacks through some direct mechanism or indirectly by inducing sleep via general inhibition throughout the central nervous system. Flunarizine (FLU) has been shown to decrease the severity and duration of hemiplegic attacks but does not significantly alter their frequency or improve long-term outcome in AHC patients. The precise mechanisms underlying flunarizine's actions are essentially unknown. Flunarizine exhibits broad efficacy in a variety of neurological disorders, including in stroke, epilepsy, migraine, and cerebrovascular disorders. As such, it is not surprising that flunarizine possesses many nonspecific actions in the CNS, including blockade of voltage-gated sodium channels, modulation of dopamine release, re-uptake and metabolism, reduction in calcium-dependent serotonin release, and inhibition of vascular smooth muscle and endothelial cell contraction. The clinical actions of flunarizine cannot be explained simply on the basis of its effects on calcium channels; there may be as of yet unidentified targets that could explain its relatively unique effects on patients with AHC. Since GABAergic modulators are effective in aborting hemiplegic attacks, a closer examination of the effects of flunarizine on GABA-mediated synaptic inhibition may yield further insights into cellular mechanisms underlying the pathophysiology of AHC. In contrast to GABA, glutamate is the principal excitatory neurotransmitter in the mammalian central nervous system. Flunarizine, as an unselective calcium channel blocker, may affect GABAergic and/or glutamatergic transmission through calcium-dependent processes not associated with direct modulation of GABAA receptors. In support of this, epileptic activity induced by the GABAA receptor antagonists bicuculline (BMI) and picrotoxin have been shown to be blocked by organic calcium antagonists such as flunarizine, and flunarizine blocked re-uptake of GABA in primary rat cortical neurons in culture. Additionally, flunarizine has been shown to inhibit both calcium-dependent and -independent release of glutamate from synaptosomes and cultured cerebellar granule cells. It is conceivable that either enhanced cortical inhibition, and/or diminished excitation may underlie the hemiplegic attacks that have been referred to by some as "negative seizures". Understanding the mechanism of action of flunarizine may impact clinical practices as well as basic neuroscience.

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Elementary Student Helps Peers Understand Rare Disorder

Throughout the 1999-2000 school year, Nick Riley, a third grader at Delano Elementary School, has been sharing his special needs with classmates in Naomi Sorenson's room. Nick began the year by sharing a special book he wrote with the assistance of Sue Jude, his speech/ language clinician.

Nick was born with Alternating Hemiplegia of Childhood (AHC), a rare neurological disorder where repeated transient attacks of hemiplegia (paralysis of part of the body) attack one side of his body or the other, or both sides.

The hemiplegia ranges from simple numbness in an arm or leg to full loss of feeling or movement. The attacks may last for minutes, hours or days in some children and are normally relieved by sleep.

Nick began school at Delano Elementary in the fall of 1994 at the age of four years. He has participated in Early Childhood Special Education with Janet Pattee Larsen, and has received intensive services to improve his developmental and speech/language skills. Nick has also worked with the district's physical therapist and occupational therapist. Working together, the team has helped Nick accomplish a variety of skills including riding a bike, communicating in sentences and learning his way around the Delano Elementary building.

Nick's 1st day of school September, 2000

Nick's disorder has always been openly discussed with his peers. Giving students the opportunity to ask questions eliminates fear or misunderstanding of what is happening when he has an episode.

Nick participates in classroom activities but continues to receive individualized instruction in reading, math and written language instruction, adaptive phy. Ed., and speech/language.

Paraprofessionals Andrea Fair and Joni Decker help Nick participate in classroom activities as fully as possible.

Each week Nick and Jude share a lesson with classmates. Their purpose is to help Nick practice a speech or language skill, but it also lets other students develop vocabulary and grammar skills. Each lesson relates to the skills that all third graders are learning.

What is really special about Nick is his desire to be a part of his class. Nick is a well-known and respected part of the Delano Elementary School community.

(Note: Published in the Delano School District Newsletter)

Italian News

By Rosaria Vavssori

A.I.S.EA is the Italian association for AHC. We are now 18 families, the youngest boy is 2 years old, the oldest lady is 37. The severity of the disorder greatly differs from one case to the other.

Last January 27, we had a brief meeting of A.I.S.EA here in my town, in the north of Italy: we were 7 families, four children and a lot of friends and supporters.
We made the point about the activities carried out in the last year and the ones to carry out in this present year; then we passed the final balance for the year 2000 and the budget for the 2001. We raised about 23.000 US $ to fund a grant for a research project to be carried out here in Italy and defined by the doctors of our Scientific Committee. We also go on cooperating with all the foreign AHC associations by sharing information and eventually define new common projects.

On February 24, I was in Rome, where we had another meeting for the families which live in the South and couldn't come to the first assembly. We were 12 families there, three of them were new and I met them for the first time. There was a very smart lady, Stefania, aged 37, who is affected by AHC, with her mother. I was impressed by

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My name is Stefania Rinaldi

By Stefania Rinaldi, Original Letter

My name's Stefania Rinaldi. I'm almost 37 and I live in Naples (Italy). When I was 4 and very young I began to be sick and to feel very odd. At the beginning I couldn't explain what was happening to me. I just saw that my parents and my relatives were extremely worried.
Now I have grown up and I can better explain what happens to me when I have an episode. I, Stefania, thought that I wasn't a normal girl, but eventually it turned out that it wasn't like that:
I mean, I'm living a normal life, full of interests and hobbies.
This is the reason why I'd like to help other families that have to face the same problem.
The attacks come without warnings: I begin to feel giddy and I have a terrible headache at the forehead, I feel very weak when I walk and therefore I need a strong person to help me move, otherwise I risk falling. I feel that a side of my body gets stiff and so my arm and leg become very hard. I often can't end a word I'm saying and find it hard to pronounce a letter or a whole sentence. I, Stefania, am aware of what is happening to me, but the only way to recover is to go to bed and sleep for a couple of hours at least. The headache is so strong that makes me cry for hours on account of all the bad thoughts I have during this ordeal. I think that God has punished me but I don't know why; I think it is deeply unfair; I think I wish to die because only in this way will the others stop suffering and I feel better when I think about it. When you are having these terrible attacks you think you can't have a normal life because people have to help you whenever you feel bad. I suggest that the families tell teachers and friends about the disorder, sport trainers too if their children play sports. Only in this way will they be able to go out in the world without having to worry too much about their attacks, as I did for many years.
After so much searching and so many bad moments, my family and I found a drug which is effective for me: thanks to TOAMAX, which I call my friend, I overcame the awful attacks that during Spring 2000 harassed me almost
every week. Both the drugs and the willing people help to relieve my grief.

Only when I feel that I am wholly accepted as a normal girl, do I feel happy.

Italian News

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her naturalness and peace of mind when speaking of her disease.

She wrote a letter describing what she feels when she's having an attack and she read it at the meeting, we parents were all astonished.

At the two meetings a student of the Psychology University of Padova spoke to us parents about her work. These last two months she visited all our children at their homes in order to have some tests done on them and to collect also some medical and clinical data. She traveled all around Italy and spent two days with each family, our association paid for the hotels and the trips. She is preparing a thesis on AHC for her graduation, in order to find out if there are general psychologic, intellective and behavioural features in all our children and determine if they are someway related to the severity of the disorder rather than to the rehabilition methods adopted. Her work will then be published by the university and I hope also on some international magazines. The University of Padova will then put one of its specialists at disposal of our association in order to go on studying the disorder, define better and better teaching and educational methods and help all the needing families.

Rosaria Vavssori, Alberto's (8)

We Need You to Join The Fundraising Team!!

By Richard George

The new millenium holds the answer for the cure for our precious children, and the cure is not beyond our lifetime. The Alternating Hemiplegia of Childhood Foundation (AHCF) has been working closely with the doctors to find a cure. And guess what everybody, the #1 ingredient is funding of the critical research being done right now.

Here are some of the fundraisers planned for 2001 and the people who are doing them:

Here in Michigan, we are doing our annual golf outing this September, which raises between $15 and $20 thousand each year. Also, on Friday September 21, 2001, there is a Tribute to Michael George for his many accomplishments in our community, and he has graciously offered to make the AHCF one of the beneficiaries; thank you Mike!! On a daily basis, we work with Charity Motors in which people donate their cars and we benefit from the proceed of the vehicles donated.

Cindy and Dave Ryan of Illinois are going hog-wild with fundraising there. They hosted the Country Opry, which was both fun and successful. They are planning a Gospel Show in June and on June 23rd, they
are involved in a Outing called "Golf 2001", which includes golf, of course, and an auction all to benefit our Foundation. Thanks for the great work, guys!!

How about our family members in New Jersey, Mark and Mindy Jonkoski, who had a healthy baby boy late last year -- congratulations!! Mindy is working on a 50/50 Raffle right now and she will be getting out her annual Holiday appeal letter. In addition to taking care of 2 kids, she has been putting money canisters at different retail locations. They never slow down....

WE NEED EVERYONE'S HELP... YOUR HELP..... NOT JUST THE HELP OF A FEW, DEDICATED FAMILIES AS IN THE PAST. The answer to a cure is now closer than ever before and the key ingredient is fundraising. Please search your hearts and try to find the time to work with a Foundation member who will walk you through all details to host a fundraiser. It's fun, it's easy and oh how satisfying to know that you are helping the children. Host anything from a bake sale bike-a-thon, bowl-a-thon, walk-a-thon; bottle drive; Pampered Chef party, wine tasting event ...there are thousands of ideas...too many to list. Call Richard George at (888)557-5757; fax (734)525-9905 or Laura Cooper (888) 263-2454 or Greg Wisyanski (814) 234-4460; fax (814) 234-3880 to get started.

Remember....our kids have no one else to turn to but us, so join the team and help us raise the funds needed to continue our important research!!

How Can You Help Our Kids?

By Carol Presunka

There has been a lot of work by a few to put together and run a foundation and to raise funds to find a cure for AHC and help our kids. However to be truly effective it takes the volunteer work of many, especially in a group as small as ours. If you are like me, you are wondering how you can help. Well, see the insert for a list of openings in the foundation that need at least two people or more. If you don't feel your abilities lie in that area, we can provide a list of fund raising ideas our families have used. Our families are happy to share their expertise. We are also asking for ideas for our new foundation.

Please choose something where you feel you can contribute and help our kids. Remember, everyone is a volunteer and the majority of money raised goes to finding a cure for AHC. Thank you.

A Word to the Siblings of AHC Kids

By Stephanie Egan

Many people think of a disabled family member as a burden or a setback, and I agree at times it can be annoying or scary. Your parents have to be with your sibling because she or he is sick or having an "attack" (referring to AHC), and they can't spend time with you. Yet, I believe our families are blessed with these special children for a reason. I feel very blessed to have grown up with a sister with Alternating Hemiplegia of childhood (AHC). The way I see it, God gave my family Kathleen because he knew that our loving family would be able to handle it, take care of her and help her. I believe I am a better person because Kathleen has AHC and the disorder has made me more aware of disabled children.

A couple years ago, Kathleen made a wish to go to Disney World. In October 1999, with the help of Make a Wish Foundation and Give Kids the World, my family went to Disney World. Give Kids the World, who works hand in hand with Make a Wish, was such as amazing place. I remember all the wish children with big smiles on their faces. At Give Kids the World, they weren't titled; they were just normal kids having fun. I remember playing air hockey in the Castle of Miracles with this little boy, he had leukemia. The little boy was so excited to play with a big kid, he bet me. It finally hit me, how lucky I was that my sister only had AHC. I know each child suffering from AHC is different, in that each child has different degrees of "attacks", others have complications such as seizures or other things, yet when it all comes down to life, I feel that AHC itself is not a life threatening disease. Our siblings are normal kids, they just need a little help from us, so feel blessed that you get the chance to help someone special in your life, and love them with all your heart.

Executive Functions

Submitted by Marcia Perkins

Marcia Perkins decided to have her daughter Jenny, age 13, seen by a pediatric neuro psychologist because Jenny was having a real hard time making "good" choices and did not think of the consequences of making those choices. The following was given to her by the psycologist and she found that it really hit home.

"Executive functions" are those abilities which allow an individual to anticipate, plan, set goals, carry out goal-directed plans, and monitor/adjust one's behavior to changing demands.

"Executive function" impairment does not directly affect specific cognitive functions. Rather, it affects the regulation and use of all areas of cognition, including attention, memory, problem solving, language, impulse control, motor skills, and planning/ sequencing/monitoring multi-step tasks.

Problems with these functions are common after brain injuries and may be especially apparent in new or novel situations. The nature and extent of these problems vary from person to person, however. The organizational deficits associated with executive impairment can have particularly profound effects on a student's ability to independently manage schoolwork, and some level of support is often necessary to help the student work to his/her potential. In general, executive deficits may be seen in different areas:

Cognitive

* inattentiveness, distractibility
* absence of a plan to solve problems
* difficulty with sequenced, multi-step tasks
* problems anticipating what needs to happen
* difficulty adjusting/changing a problem-solving style when it is not working
* difficulty using feedback from others to modify their behavior
* inefficient memory processed (e.g., interference, difficulty organizing information for easy storage/retrieval); while the information may be stored, the individual with executive problems often "forgets to remember"
* impaired organizational processed; difficulty "multi-tasking"
* effortful or labored problem solving - even those problems within a child's skill level - performing cognitive tasks can be sort of like trying to swim through mud
* inconsistencies in performance across time and setting - one day the person can demonstrate a skill, the next day he/she can't

Behavioral

* impulse control problems
* lacking initiative, drive and verve
* tangential (off topic) speech or perseverative behaviors (e.g., repeating the same things over and over, getting "stuck")
* overly talkative or, conversely, lack of spontaneous conversation
* social difficulties due to problems "reading" social cues, problems interpreting complex social situations, learning from social
* feedback, flexibly adjusting behavior to meet changing social demands
* social disinhibition, or a tendency to impulsively say or do inappropriate things (e.g., hug a stranger, ask an embarrassing question)

Emotional

* apathy
* restricted range of affect
* emotional lability (frequent and rapid change in mood)
* impaired self-awareness of difficulties (denial, lack of concern, poor insight)

Please excuse any typing errors, it will be interesting to hear if others see these things in their children.

"The Effects of Flunarizine....."

(Continued from page 4)

Objectives and methods:
The principal aim of these studies is to examine the effects of flunarizine on excitatory and inhibitory local post synaptic currents (PSC's) in the deep layers of the motor cortex from normal juvenile rodents. The major limitation of the proposed study is the absence of an animal model of AHC. It is possible, as has been shown for epileptic brain tissue, that the molecular targets of pharmacological agents may be different than in normal brain, and thus the cellular responses may be unique. Nevertheless, it will be important to initially define the specific actions of flunarizine on synaptic functioning.
We used a well accepted method to characterize the effect of FLU on cortical signaling. Briefly, fresh brain slices from juvenile rodents were prepared. We formed stable whole cell patch clamps to suitable layer 2 pyramidal neurons. We then recorded spontaneous PSCs from these neurons after application/ equilibration of buffer solutions containing drugs of interest. Identical solutions without the drug are used as to determine the relevant baseline.

Results::
We solved a number of experimental problems that complicate studies of FLU. These include: 1. the insolubility of flunarizine at physiologic pH in aqueous solutions, 2. the lack of a standard assay for flunarizine concentration, 3. the effect of DMSO/solvent on the relevant PSC parameters. By addressing these problems first, we are now confident in obtaining well controlled and reproducible 4. FLU effects on PSC's.

1. Solubility:
It became apparent from the first experiment with flunarizine that solubility problems had not been adequately addressed in the existing basic science literature. The published data appears incomplete. In retrospect, one may have been able to anticipate this, if the whole animal literature is considered. Flunarizine is one the least soluble antiepileptic drugs under physiologic conditions. A brief review of the animal literature is presented here. In In vivo, animal studies only 0.8% is present as free drug in blood plasma, the remaining 99.2% being bound to protein (90%) or blood cells (9%). The drug accumulates in adipose tissue and muscle, with very low levels in the brain. Secondary to slow redistribution, FLU has a very long half life of up to 18 days in healthy individuals. Plasma levels between individuals on the same chronic dose can vary by three to ten fold. In vitro protein binding studies at concentrations of 0.5 mcg/ml found flunarizine to be 99.1% bound.
The conditions used in our studies do not include carrier protein, and our goal concentrations range from 1 to 100 micromolar (0.477 to 47.7 mcg/ml). These goals are typical of the ranges and conditions existing in the published in vitro literature. Despite this, we could find no direct reference to solubility problems in the literature. Follow-up phone discussions with authors, indicate that our experience is, in fact, typical. The only reported success generating stable solutions of flunarizine utilize cyclodextran as a carrier. The laboratory that reported these finding was unable to formulate the complex and received it as gift from a pharmaceutical company. The only successful fabrication of the flunarizine/ cyclodextran complex has been achieved by a commercial laboratory and has not been reported in the literature.
We have attempted to form complexes of flunarizine with cyclodextran (CD) without great success. We are continuing our efforts to obtain a more soluble form of FLU from the company that produces it. This form reportedly causes renal damage and thus has limited utility in vivo human treatment but could be helpful in in vitro experiments.
2. Standard Assay:
We have therefore concentrated our efforts on developing reproducible experimental data using the conditions originally proposed. Attempts to develop a stable aqueous solution of FLU were unsuccessful. We varied time, temperature, DMSO concentration, ethanol concentration and counter ion concentrations without any appreciable increase in FLU solubility. Attempts with various pH solutions revealed that FLU is soluble at the required concentrations when the pH is 5.4 or lower. Unfortunately it rapidly precipitates, even with slow adjustment above pH 5.4.
We subsequently concentrated on characterizing the unstable but reproducible conditions of our assay. Addition of concentrated FLU/ DMSO to the aqueous solution results in a microprecipitate (cloudy solution). Rather than a typical flocculate falling to the bottom of the container, this microprecipitate then transitions rapidly to a clear coating on the container wall at the air/ solution interface. This may falsely be interpreted as the drug entering

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"The Effects of Flunarizine....."

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solution.
We developed a novel assay for the concentration of FLU from the aqueous solution in order to elucidate these changes. By combining test samples with acidic buffer and we were able to develop a standard spectrophotometric assay for FLU based on its' absorption of light at 250 nanometers (See Figure A1). This allows real time sampling of the unstable FLU solutions.
By analyzing the unstable solution we found that the FLU concentration, though falling continuously, remains in the necessary range for up to 20 minutes (See Figure A2) The loss of the cloudy appearance also corresponds to the completion of the transition to the clear film precipitate. By making the solution immediately before use, we are able to equilibrate the slice and record effects in this time window. As a control we directly sample the solution from the reaction chamber at the recording time so that the highest and lowest exposure concentration can be determined. It is also therefore necessary to completely wash the apparatus after each experiment with flunarizine to avoid cross contamination.
3. DMSO/Solvent and Technical Considerations:
It became apparent that DMSO, while needed for making stock solutions and for generating the test solutions, causes changes in the relevant neuron parameters to be measured. Analysis of ten experiments, revealed that 0.1% DMSO effects the amplitude and frequency of PSC relative to control solutions. Also 0.05% DMSO seems to cause a smaller total change in these parameters from baseline even though the percentage of effected experiments is approximately the same. We therefore are using 0.05% final concentration DMSO in all ongoing experiments. All FLU effects are calculated using DMSO as the baseline. By minimizing the DMSO effects we will maximize sensitivity to FLU effects.
We have also implemented real time analysis of electrode/neuron interface stability, or access resistance. Flunarizine effects on access resistance can lead to spurious results. Cells with unstable access resistance are not included in this analysis and are not included in the 17 experiments detailed below.
4. FLU effects on PSC
We have thus completed the more difficult first phase of these flunarizine studies. Using these improved methodologies we are now able to test with a high degree of certainty the effect of FLU on synaptic transmission. The data reported below concerns the effect of FLU on spontaneous postsynaptic currents (sPSC). Under these conditions both excitatory (EPSC) and inhibitory (IPSC) are recorded. The majority of these currents are IPSCs (VanBrederode et al, Neuroscience in press).
We have recorded from 17 layer 2 pyramidal neurons using the immediate fresh preparation of FLU solutions. In five of these experiments we have analyzed real time FLU concentrations from the slice chamber as discussed above. Those experiments reveal the minimum FLU concentration during recording to range from 35-100 micromolar. The remaining 12 experiments likely are also in this range as they were prepared from the same stock solutions.
We found FLU decreases/has no effect on the amplitude (70/18% of experiments) and frequency (82/12% of experiments) of PSC relative to DMSO alone respectively. FLU increased the amplitude in only 2 of 17 and increased the frequency in only 1 of 17 experiments.
Under the conditions originally proposed, using normal potassium (3mM), the magnitude of the frequency inhibition observed is rather low. Also it was noted that the FLU seemed to preferentially effect the high frequency PSC's whereas DMSO effected low frequency PSC's (See Figs. B1&B2). It is known that at high potassium concentrations the baseline frequency and amplitude of PSC's is increased. At these higher potassium levels one may mimic excessive cortical firing. We therefore repeated all the experiments with higher potassium concentrations (9 and 12 mM). We found greater inhibition of the frequency by the FLU and greater inhibition of amplitude by both DMSO and FLU under these conditions (See Figs.C1&C2). This may duplicate the effect of flunarizine at times of excessive cortical activity.
In addition we were able to get information on washout of the FLU effects in 13 experiments. It is important to document washout to assure oneself that the cell is truly stable and responsive. Exhausted or damaged cells may nonspecifically manifest reduced amplitude/frequency without the ability to recover. We documented during washout partial reversal of FLU effects on amplitude (3 of 13 experiment, 13%) and frequency (8 of 13 experiment, 62%) (See Figs. B1,B2 and C2). There was a trend to longer washout periods

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"The Effects of Flunarizine....."

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(>20 MIN) being more likely successful. Given the relative insolubility of FLU, we don't necessarily expect full reversal.
In addition we sought to confirm the trends seen with FLU by comparing our results with those of cadmium, a well known calcium channel blocking agent. Cadmium caused very large and reproducible decrement in amplitude and frequency PSC's regardless of the potassium concentration tested (See Fig D1&D2) This effect could also be washed out.

Conclusions :
We have successfully generated a carefully controlled experimental system to assay the effects of FLU on PSC's. We have been able to minimize background noise effects and have maximized the relevant PSC signal by manipulation of the conditions.
The experiments to date indicate a decrement in amplitude and frequency of total PSC by FLU. These finding are in agreement with results of cadmium, a potent but nonspecific voltage gated calcium channel inhibitor. In addition, there appears to be an important element of use-dependent inhibition as higher frequencies PSC are preferentially effected by FLU. We do not see this use dependence in cadmium effects. It is tantalizing to consider that FLU may therefore suppress excessive inhibition preferentially. Excessive inhibition may play a role in hemiplegic attacks(or so-called "negative seizures"). FLU may likewise suppress excessive excitation, which could account for it's anti-epileptic effect. These hypotheses are shortly to be tested.

Future Plans:
I. We will complete ongoing studies on the effects of FLU on spontaneous Post Synaptic Currents in high and normal potassium.
II. We will complete experiments on the effects of FLU on pharmacologically isolated inhibitory or excitatory spontaneous post synaptic currents in high potassium.
III. We will initiate experiments on the effects of FLU on stimulus-evoked inhibitory or excitatory synaptic currents.
IV. Depending on the above results we may also employ more specific voltage gated calcium channel blocking agents to dissect the presynaptic effects of flunarizine.
When completed we will have a comprehensive view of the effect of FLU on excitatory and inhibitory circuits in the juvenile brain. We are poised to rapidly collect this data having already completed the difficult ground work.

Internet Corner

By Lynn Egan

With the combing of the foundations, the Internet Corner will not be published this issue.

We would like to hear from you. How do you feel about the Internet Corner?

Would you like to see it continue?

Is it informative?

Do you find it redundant?

We have enclosed a questionnaire with many questions about our new foundation and would love to have your input.

Please take a few minutes to fill it in and return it. All of your thoughts, comments and ideas count!

If you would like to be a sponsor of the newsletter, please contact Laura Cooper at 888-263-2454, email: klcoop@gte.net or Lynn Egan at 650-365-5798, email: laegan@aol.com

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Website
We have been making changes to the www.ahckids.org website and will continue to update and change. Please bear with us during this time. Thank you.

AFHA website

The AFHA hosts a bulletin board. Everyone can subscribe. Families post their questions, concerns and ideas regarding AHC and their children.

To subscribe send an email to http:// www.egroups/community/afha and you will be signed up. You can also then view all the previous posting.

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