PHARMACOLOGICAL DIGEST

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Acetaminophen : an Effective Treatment for the Least Disabling Migraines

Acetaminophen is highly effective in treating pain, functional disability, photophobia, and phonophobia in some patients with migraine. The investigators randomized 289 subjects to treatment with oral acetaminophen 1000 mg or placebo for a single acute migraine attack. Excluded from the study were subjects who usually required bed rest with their migraine, or who vomited with more than 20% of their migraine attacks. At 2 hours postdose, 57.8% of patients in the acetaminophen arm and 38.7% in the placebo arm reported response to treatment. This included 22.4% and 11.3%, respectively, who were free of pain. For those reporting severe pain at baseline, response at 2 hours was 50.9% and 27%, respectively. Treatment was rated as good to excellent by 51.7% of subjects who used acetaminophen, compared with 28.2% of those treated with placebo. Similar trends were documented for the proportions of subjects whose functional disability, photophobia, and phonophobia were reduced to zero at 2 hours and 6 hours following treatment. However, the investigators observed no significant difference between groups in the proportion of patients whose nausea was relieved, and suggested that migraine was a symptom complex and that effective treatments that made the pain better also made the associated symptoms better.
[Arch Intern Med 2000; 160: 3486-3492]

Synthetic Helical Peptides Block HIV Infectivity

Synthetic helical peptides derived from the fusion mediating portion of HIV glycoprotein gp41 potently inhibit HIV infection. The extracellular domain of gp41, including two helical regions, is important for oligomerization and virus-induced fusion, the authors explain. Both helical structure and bonding patterns called helix-capping motifs appear to be important in the inhibition of fusion and infectivity seen with so-called C peptides derived from these regions. The investigators tested several synthetic peptides, designed to be highly helical in solution, with and without helix-capping motifs, for their HIV-inhibiting potential. Simply adding capping motifs to a 19 amino acids wild-type (WT) peptide (creating Caps-WT) did not induce the desired helical conformation, the report indicates, but changing eight residues to alanine or lysine (creating MT) did. Moreover, introducing capping motifs to the modified peptide (forming Caps-MT) significantly enhanced its helical conformation. Among the various peptides, WT and MT showed weak affinity to the coiled-coil motif needed for gp41 mediation of fusion, but peptides with capping motifs showed significant association. Caps-MT, with the highest helical propensity, also showed the highest affinity for the coiled-coil motif of gp41. In fact, binding affinity for the coiled-coil motif of gp41 proved to be proportional to the helical content of the peptides, the results indicate. The inhibition of cell fusion by the peptides paralleled their binding affinity for the coiled-coil motif of gp41, the investigators observe. Again, Caps-MT was the most effective inhibitor among the peptides tested. These observations indicated that the designed peptides were able to prevent the membrane fusion process mediated by gp41 by binding specifically to the coiled-coil motif of gp41. These results implied that such modification was enough to change a short peptide derived from gp41 into a potent inhibitor against the infection of HIV.
[AIDS Res Hum Retroviruses 2000; 16: 1797-1804]

Experimental Drug Reverses Cognitive Impairment in Rats

The investigational drug GT 715 may restore lost brain function, results of an animal study suggest. The drug increases brain activity of guanylyl cyclase (sGC). GT 715 acts on the

same cell-signaling pathway as nitroglycerin, but the drug's action is targeted more to the brain than to the cardiovascular system. When GT 715 was administered to healthy rats before they entered a water maze, it did not affect their navigational abilities, even when given at very high doses. But when GT 715 was given to the animals after they had received another drug that reduced their mental abilities, the rats' performance improved, and higher doses of the drug led to greater improvement. This study provides the first evidence that activating sGC may improve mental performance. The results of this study therefore suggest that stimulation of cerebral sGC activity may be an effective strategy to improve learning and memory performance in individuals in whom cognitive abilities are impaired by injury, disease or aging. The researchers' goal is to develop a drug that not only relieves symptoms of neurological diseases but also prevents further impairment. Depending on funding for the research, a safety study of GT 715 may begin within the next year or so.
[NeuroReport 2000; 11: 3883-3886]

Sexual Behavior Abolished in Male Mice Lacking Estrogen Receptors

Male mice engineered to lack both the alpha and beta estrogen receptors show no sexual behavior toward receptive female mice and greatly reduce their aggressive behavior toward other male mice. The investigators found that these mice exhibited no sexual behavior, including simple mounting. In addition, ultrasonic vocalization, a normal male mating behavior, did not occur in the presence of a receptive female mouse. Aggressive behaviors such as lunge and bite aggression were also reduced and they rarely demonstrated offensive attacks. It appears that either one of the estrogen receptors is sufficient for the expression of simple mounting in male mice, indicating a redundancy in function. Offensive attacks, on the other hand, depend specifically on the estrogen receptor-alpha gene. In other studies, it has been shown that all components of sexual behavior are intact when estrogen receptor-beta is missing, and that decreased intermissions and no ejaculations occur when estrogen receptor-alpha is lacking.
[Proc Natl Acad Sci USA 2000; 97: 14737-14741]

Lotronex Withdrawn from US Market

At the request of the US Food and Drug Administration (FDA), Glaxo Wellcome announced that it would voluntarily withdraw alosetron (Lotronex), a prescription medication for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS) and planned to cease distribution of Lotronex immediately. Glaxo Wellcome took this step after in-depth discussions with the FDA about gastrointestinal adverse effects such as ischemic colitis that occurred in association with the use of Lotronex. There also have been 5 fatalities from complications of gastro-intestinal events, although Glaxo Wellcome has stated that it does not believe that a causal relationship to Lotronex has been established. Glaxo Wellcome has proposed a range of elements which the company believed would adequately and effectively address these risks. These included further label modifications, restricted distribution, on-going patient education, new clinical and epidemiological research, and use of an independent medical review board. The FDA, however, called these proposals inadequate and requested that Glaxo Wellcome voluntarily withdrawed Lotronex from the market. Glaxo Wellcome took a different view from FDA on the ability to educate physicians and patients about the management of potential adverse effects and benefits of Lotronex. However, Glaxo Wellcome representatives will immediately contact healthcare professionals to advise them of the discontinuation of distribution and marketing. Physicians should then begin contacting their patients to discuss a plan to transit them to alternative therapies. IBS is a chronic, recurring condition that affects an estimated 1 in 5 Americans. Although the cause is unknown, IBS is characterized by multiple symptoms that include chronic or recurrent abdominal pain and discomfort and irregular bowel function.
[http://www.medscape.com/MedscapeWire/2000/1100/medwire.1129.Lotronex.html]

Receptor Desensitization Linked to Morphine Tolerance

While still capable of developing physical dependence, mice lacking beta-arrestin-2 (beta-arr-2) fail to develop morphine tolerance. The main clinical implication of these findings is that inhibiting the process of G protein coupled

receptor desensitization can augment the efficacy of agonist drugs or endogenous agonists. With respect to morphine, inhibitors of the desensitization process will not only greatly potentiate the analgesic effects of morphine and reduce tolerance, but also, because of the lower doses of drug needed, will reduce unwanted side effects. The investigators found that unlike wild-type mice, which experienced a 50% drop in morphine responsiveness after a high priming dose of morphine, beta-arr-2 knockout mice maintained the same degree of responsiveness to morphine. Similar results were seen after daily administration of morphine. Chronic daily administration of morphine shifted the dose-response curve of wild-type mice in the direction of diminished sensitivity, the researchers noted, but had no effect on the dose-response of beta-arr-2 knockout mice. In contrast, both wild-type and knockout mice with prolonged exposure to morphine experienced withdrawal after administration of naloxone and showed increases in adenylyl cyclase activity, a hallmark of opiate physical dependence.
[Nature 2000; 408: 720-723]

Peptide Mixture Improves Cognition in Alzheimer's Disease Patients

Cerebrolysin, produced by enzymatic breakdown of lipid-free porcine brain protein to free amino acids and peptides, which has been shown in previous studies to improve various facets of brain function in Alzheimer's disease patients, appears to be safe and effective when used over a 4-week period to treat cognitive deficits and global function in patients with mild to moderate Alzheimer's disease. The study by Dr. Chul-Young Bae, of Pochon CHA Medical University, in Kyonggi-do, and associates, examined the effect of cerebrolysin on different primary and secondary outcome measures. Thirty-four subjects were administered intravenous 30 mL cerebrolysin in 100 mL saline 5 days a week for 4 weeks, while 19 subjects received placebo. According to the Alzheimer's Disease Assessment Scale-Cognitive subscale, patients in the treatment arm had a significant mean improvement of 3.23 points compared with a change of only 0.36 point in the placebo arm. On this subscale, 82.4% of cerebrolysin-treated patients improved versus 31.6% of placebo-treated patients. The authors noted that the 2.87-point benefit of cerebrolysin over placebo was comparable to results exhibited by the cholinesterase inhibitors tacrine, donepezil, and metrifonate. Similar findings were documented for the Clinical Global Impression of Severity/Change and the Mini-Mental State Examination.
[J Am Geriatr Soc 2000; 48: 1566-1571]

Tumor Suppressor Gene Expression Inhibits Angiogenesis in Murine Model

Expression of RB2/p130, a member of the retinoblastoma tumor suppressor gene family, inhibits angiogenesis and down regulates vascular endothelial growth factor expression in vivo. Using cell culture methods and a murine model, the investigators assessed the vascular-related effects of experimentally induced RB2/p130 gene expression in lung cancer and glioblastoma cell lines, and found that induction of RB2/p130 gene expression, achieved through a variety of techniques, inhibited angiogenesis in the murine model. This finding correlated with the results of in vitro and in vivo analyses that showed a down regulation of vascular endothelial growth factor protein expression when the gene was expressed. This study showed that the tumor used vascular endothelial growth factor to have the host cell produce vessels to feed it and the number of vessels that would form normally in the control tumor could be inhibited 10 times. RB2 has been shown to be one of the few molecules that can strongly inhibit the growth of tumor cells in animal tests, suggesting that it can be a new biological drug. The research's goal is still to seek FDA [US Food and Drug Administration] approval and to bring this entire system to patient trials. Eventually, especially for lung cancer, the researchers want to develop an easier way of delivering RB2, perhaps by aerosol and are in the process of designing small molecules to more efficiently deliver the small portion of RB2 necessary to inhibit tumor growth.
[Cancer Res 2001; 61: 462-468]

Mechanism of Action of IVIG Identified

Clearing the way for the development of new drugs to treat autoimmune disorders, researchers have determined the mechanism of action of intravenous gamma globulin (IVIG), long used to treat infectious and inflammatory diseases. In a mouse model of immune thrombocytopenia, they found that IVIG induced the expression of an inhibitory Fc

receptor, Fc-gamma-RIIB, on splenic macrophages and prevented platelet consumption. They treated mice with an antiplatelet monoclonal antibody, which mimicked a pathogenic autoantibody and induced immune thrombocytopenia. Disease was dependent on the presence of the Fc-gamma-RIII receptor, and either IVIG or its Fc fragments were effective in protecting against disease. Next, the researchers induced disease in mice whose endogenous Fc-gamma-RIII gene was replaced by the human Fc-gamma-IIIA gene, which was not expressed on neutrophils. The mice were still susceptible to disease, so the authors suggested that neutrophils were not necessary to induce disease. In addition, since splenectomy protected against disease, they suggested that splenic cells such as macrophages were necessary to induce disease. According to the results of previous studies, the effects of FcR-gamma-III were balanced by an inhibitory receptor, Fc-gamma-RIIB, so the researchers induced disease in mice lacking the inhibitory receptor. The mice were susceptible to disease and could not be protected by treatment with IVIG. Further investigation showed that in normal mice, IVIG treatment led to a 60% increase in the number of splenic macrophages expressing high levels of Fc-gamma-RIIB. These data support the conclusion that IVIG mediates its protective effect by its ability to induce the expression of inhibitory Fc-gamma-RIIB receptor on effector cells that will otherwise trigger clearance of the opsonized platelets. Although the experimental model is quite different from the clinical situation, in that IVIG is administered before the pathogenic autoantibody. Nevertheless, the study demonstrates that FC-gamma-RIIB is crucial for mediating the anti-inflammatory activity of IVIG and that modulating surface expression of Fc-gamma-RIIB is a viable strategy for treating autoimmune disorders. The way is now clear to develop potent drugs that can mimic the effects of IVIG on Fc-gamma-RIIB expression.
[Science 2001; 291: 484-486]

New Survey Illustrates Trends in Parkinson's Disease Treatment

According to survey results released on Monday by the American Parkinson's Disease Association, Inc. (APDA), nearly 92% of neurologists surveyed have shifted their prescribing behaviors during the past 3 years, with 85% now prescribing dopamine agonists as a first-line treatment of choice. The survey polled 205 practicing neurologists to determine their views and current prescribing behaviors of Parkinson's disease. There is an ongoing controversy in the medical community whether patients should be given levodopa or a dopamine agonist as an initial treatment for Parkinson's disease. Levodopa has been the "gold standard" for 35 years and is used in a majority of patients. Unfortunately, over time, levodopa can cause dyskinesias that can inhibit patients' ability to function. Dopamine agonists are a class of drugs that mimic the effects of dopamine in the brain by stimulating dopamine receptors; research shows that dopamine agonists may lower a patient's risk of developing the uncontrollable and irreversible dyskinesias often associated with levodopa therapy. Knowledge of Parkinson's disease has grown tremendously over the past few years. Recent controlled studies suggest that, in many patients, dopamine agonists are an excellent alternative to levodopa in the early stages of Parkinson's disease. These results indicate that the treating physicians are incorporating the results from recent trials into their clinical practice. The survey was conducted by Hospital Research Associates at the 52nd American Academy of Neurology (AAN) Annual Meeting in San Diego, California. Other survey results indicated:

- 93% of neurologists cite dyskinesias as a problem for Parkinson's disease patients on levodopa therapy.
- 76% believe initial therapy with a dopamine agonist helps delay the need to initiate levodopa therapy.
- 77% believe initial therapy with a second generation dopamine agonist helps delay the development of dyskinesias.
- 88% note Parkinson's disease patients are taking a more active role in the treatment of their disease.
- 79% choose to start treating younger Parkinson's disease patients with dopamine agonists.

[http://www.medscape.com/MedscapeWire/2001/0100/medwire.0109.Survey.html]

Perforin and Interferon-Gamma Contribute Independent Antitumor Effects

Perforin and interferon-gamma independently and equally account for the natural antitumor activity mediated by natural killer (NK) cells in mice. While perforin (pfp) expression has been

previously shown to prevent tumor initiation, growth and metastasis, it cannot account for all the tumor protection afforded by NK and NKT cells, the authors explain. The possible role of interferon (IFN)-gamma in the natural antitumor response has not been compared previously with that of pfp. The investigators examined the relative role of pfp and IFN-gamma in three distinct models of tumor immunity in mice. Mice deficient in either pfp or IFN-gamma developed significantly more metastases than did wild-type mice, but they developed fewer metastases than did mice depleted of NK cells. Mice doubly deficient in pfp and IFN-gamma proved as susceptible as NK-cell-depleted mice to tumor metastasis. The results in mice deficient for pfp, or pfp and IFN-gamma, indicated that this independent antimetastatic function of NK cells might involve both the cytolytic activity of pfp and antitumor activity of IFN-gamma. Both pfp and IFN-gamma deficient mice developed significantly more MCA-induced fibrosarcomas than did normal mice, the report indicated, and doubly deficient mice developed as many sarcomas as did NKT-cell-depleted mice. The authors demonstrated for the first time that in innate antitumor responses that involve relatively different contributions by NK and NKT cells, the killer cell pfp and cytokine IFN-gamma constituted independent mechanisms that together controlled tumor initiation and metastasis. The investigators indicated that future research efforts would be directed at defining how these antitumor effects were orchestrated.
[Blood 2001; 97: 192-197]

ZymoGenetics Researchers Identify New Molecule Related to Psoriasis

Researchers at Seattle, Washington-based ZymoGenetics, Inc. have identified a new member of the interleukin family of proteins that may be implicated in the development of psoriasis. The researchers discovered the human gene coding for the molecule, designated as interleukin 20 (IL-20), belonging to a class of cytokines responsible for regulating cellular processes in healthy and diseased tissues. The scientists further characterized the interaction between the IL-20 protein and a cell-surface receptor composed of two sub-units, named IL-20R alpha and IL-20R beta, which were present in human skin cells. In transgenic mice genetically engineered to overproduce IL-20 within their bodies, ZymoGenetics scientists observed that the mice developed skin similar to psoriatic skin lesions in human. In a culture study, the researchers also discovered that IL-20 appeared to stimulate the activation of human keratinocytes, cells presented in the outermost layer of the skin. Further analysis of human skin tissues for the presence of the two receptor subunits for IL-20 demonstrated that both molecules were present at very low levels in normal skin and also presented at much higher levels in psoriatic skin. The transgenic mice study indicateed an "interesting association" between IL-20 and psoriasis. The IL-20 molecule is still in the "research" stage of development. The company plans further animal studies to determine if inhibition of the IL-20 ligand can play a therapeutic role in regulating the pathogenesis of psoriasis. Psoriasis affects between 1% and 2% of the United States population, or about 5.5 million people. Although the disease occurs in all age groups and about equally in men and women, it primarily affects adults. People with psoriasis may suffer discomfort, including pain and itching, restricted motion in their joints, and emotional distress.
[http://www.medscape.com/reuters/prof/2001/01/01.15/20010112scie006.html]

New Hormone May Link Obesity to Diabetes

Using a murine model, Pennsylvania investigators have identified a fat cell-secreted hormone, which they named resistin (for resistance), that causes insulin resistance similar to what seen in type II diabetic patients. The researchers from the University of Pennsylvania School of Medicine in Philadelphia, screened for genes that were present during fat cell differentiation but down regulated in mature fat cells exposed to the antidiabetic thiazolidinedione class of drugs. From this search, they discovered resistin. In the animal model, the authors found that circulating levels of resistin were decreased when the anti-diabetic drug rosiglitazone was given. Normal mice treated with a recombinant form of resistin had impaired glucose tolerance and insulin action. Mice with genetic and diet-induced forms of obesity demonstrated elevated levels of resistin. In addition, in mice with diet-induced obesity, antibodies against resistin improved blood sugar levels and insulin action. In vitro adipocyte analysis revealed that resistin treatment impaired

glucose uptake, and neutralization of the hormone enhanced uptake. Resistin is a strong candidate to explain the anti-diabetic effects of thiazolidinediones, as well as a mechanism by which excess adiposity leads to insulin resistance. If the regulation and properties of human resistin are similar to those of mouse resistin, potential anti-diabetic therapies could include reduction of serum resistin level, neutralization of the biological activity of circulating resistin, and/or antagonism of resistin action directed against the cellular receptor(s).
[Nature 2001; 409: 307-31].

CDK Inhibitors Prevent Chemotherapy-Induced Alopecia in Animal Model

Several synthetic inhibitors of the protein kinase CDK2 safely prevent chemotherapy-induced alopecia in rats. Many chemotherapeutic drugs exhibit cell-cycle-specific cytotoxic effects, and inhibiting cell cycle progression of normal hair cells may reduce these cytotoxic effects. The investigators developed and tested several synthetic compounds designed to specifically inhibit CDK2. In SCID mice transplanted with human scalp, topical treatment with CDK inhibitors produced similar inhibition of cell cycle progression, the results indicated. Pretreatment of human diploid fibroblast cells with one CDK2 inhibitor reduced the cytotoxicity of taxol, etoposide, cisplatin, 5-fluorouracil, and doxorubicin by factors of 5, 1.5, 8, 4, and 5, respectively. Furthermore, in a neonatal rat model of chemotherapy-induced alopecia, topical treatment with CDK2 inhibitors protected 50% of rats from etoposide-induced alopecia and protected 33% from alopecia after cyclophosphamide-doxorubicin treatment. The leading CDK2 inhibitor caused no apparent toxic effects in either animal model or in normal rat skin treated with the compound. On the basis of the evidence, clinical trials in cancer patients to assess the efficacy of this approach to prevent chemotherapy-induced alopecia may be warranted.
[Science 2001; 291: 134-137]

Long-Term Use of Non-aspirin NSAIDs Reduces Colorectal Cancer Risk

Long-term use of non-aspirin nonsteroidal anti-inflammatory drugs (NA-NSAIDs) reduces the risk of colorectal cancer by half, independent of the treatment indication. Researchers conducted a population-based cohort study with secondary case-control analysis to examine the link between colorectal cancer risk and use of aspirin and individual NSAIDs, including the role of dose and duration. Using the General Practice Research Database in the UK, they traced 943,903 subjects who were between the ages of 40 and 79 years and who were free of cancer and colorectal adenoma from 1994 to 1997. They identified 2,002 incident cases of colorectal cancer. The incidence rate of colorectal cancer per 10,000 person-years was 7.3. After 6 months of continuous treatment, the risk of colorectal cancer was reduced in people who used NA-NSAIDs, with an adjusted relative risk of 0.5. High daily doses were associated with a slightly greater reduction than low-to-medium doses. One year after stopping NSAID treatment, the reduction in risk disappeared completely. According to the report, long-term users of aspirin at doses of 300 mg/day also had a reduced risk of developing colorectal cancer, with a relative risk of 0.6. However, there was no reduction in risk among those who used aspirin at daily doses of 75 mg and 150 mg. Based on these findings, 1-year treatment with NSAIDs would prevent one case of colorectal cancer in a population of 1,000 persons of 70 to 79 years of age.
[Epidemiology 2000; 12: 88-9]