30. august 2007

Gold Symposium I

June 20, 2007

The applicability of metallic gold as a remedy for inflammation and pain

Institute of Anatomy, Aarhus University, Denmark

Abstracts

In vitro liberation of charged gold atoms

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Abstract

The present study demonstrates that cultured macrophages are able to liberate gold ions from metallic gold surfaces by dissolucytosis. Using the ultra-sensitive autometallographic (AMG) technique, we demonstrate that murine macrophages grown on a surface of metallic gold liberate gold ions. Ultra-structural AMG reveals that the gold ions are located in an ultra-thin membrane-like structure, “the dissolution membrane”, intervened between the macrophages and the metal surface. The presence of AMG silver enhanced gold nanoparticles in the dissolution membrane proves that the release of charged gold atoms takes place extracellularly. The dissolution membrane is most likely secreted and chemically controlled by the dissolucytes, here macrophages, and the membrane is essential in the dissolution of metal implants and particles which cannot be phagocytosed. Our findings

support the notion that whenever a metallic gold surface is attacked by dissolucytes, gold ions are liberated and taken up by surrounding cells. As gold ions can suppress the inflammatory process, it is reasonable to expect that when dissolucytosis takes place in the living organism the liberated gold ions will cause local immunosuppression.

Gold and the immune system – a history of suppression and stimulation

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Abstract

Gold as a beneficial remedy was used already in ancient Egyptian and China. In the 19th century gold chloride was used for syphilis treatment, and Robert Koch discovered a bacteriostatic effect of gold cyanide on the tubercle bacillus. Although the use of gold as a tuberculostatic was not successful, it led to the use of gold for rheumatoid arthritis, a chrysotherapy used since the 1930´s and until today. The main compounds are hydrophilic gold(I) oligomeric ring or chain structures, gold(I)thiolates (AuSR) –SR being thiomalate and thioglucose, respectively, reacting extensively with cysteines in proteins/peptides but also being oxidised to gold (III) complexes. In general some 60% of the patients exhibit a significant but slowly developing effect of the gold thiolates. Among cellular-molecular mechanisms indicated are: a)irreversibly stripping of peptides from the MHC-molecule on antigen-presenting cells; b)preventing in synovial cells NF□B activation which blocks IL-1-□-induced hyaluronan synthetase and COX-2 transcription (reducing PGE2 release) and other proinflammatory genes. However, up to 15-45% of the patients exhibit adverse immune-mediated side effects leading to symptoms from skin, kidney, liver, lung and blood causing cessation of therapy. Experimental studies show that gold thiolates may induce antinuclear autoantibodies and systemic immune-complex disease strictly regulated by MHC-class II genes. In vivo studies have demonstrated a stimulating effect on Ig-production using low doses of gold. Gold particles have been used as an adjuvant for vaccination, and are in this setting able to stimulate induction of both T-cells and antigen-specific antibodies. In the general population sensitizations to gold is frequent and correlates with dental and other implants of gold, although clinically relevant hypersensitivity is less common.

Anti-inflammatory effects of metallic gold particles injected into a focal brain injury

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Abstract

The effect of gold ions on inflammation in the central nervous system has to our knowledge never been studied. However, a few years ago it was demonstrated that gold ions are liberated from gold implants placed in the brain and it was stated that the released gold ions accumulate in glia cells and neurons adjacent to the implant.. The present study aim at evaluating whether the dissolucytotic released gold ions 1) contrive anti-inflammatory effects in the brain, and if so 2) whether the degree of immune suppression suggest clinical dimensions.

Mice were injected 25-45 µm gold particles into the neocortical target area just before it was cryo-lesion and the inflammatory responses was compared with cryo-lesioned controls.

We found: 1) a reduction in the number of activated microglia cells in the damaged area 2) an up-regulation of the neuro-protective proteins MT (I+II). Additionally, we recorded an increase in the number of astrocytes in the region and reduced apoptotic activity.

It can be concluded that gold ions liberated from metallic gold particles have a pronounced anti inflammatory effects on local inflammation in CNS and that it might be worthwhile studying the clinical possibilities of this discovery.

Use of local gold implants in general practice

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Abstract

Local gold treatment with implantation of small pieces of 24 carat gold has been successfully used in veterinary medicine for almost 30 years.
Inspired by the veterinarian's good results (1-4) three Danish physicians in 1997 initiated similar treatment on human patients suffering from certain painful conditions in the locomotor system.

A method of treatment was developed suited for use in a doctor's clinic without sophisticated facilities.

In a 10 years period approximately 13.000 patients have been treated.
Based on reports from the treated patients after 6 or 12 months about 70 % of the patients experienced marked pain relief.

Two controlled, double-blinded clinical trials have been carried out, one of which showed significant effect of the local gold treatment, the other being inconclusive.
Further evidence based on clinical trials is needed to make local gold treatment generally accepted.

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Two years follow-up study of the pain-relieving effect of gold bead implantation in dogs with hip-joint arthritis

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Abstract

A total of 80 family dogs recruited from all part of Norway with pain and difficulties in moving due to canine hip dysplasia (CHD) were included in a six-month placebo-controlled, double-blinded clinical trial of gold bead implantation. Clinical examinations were performed when entering the trial, then at two weeks, three months and finally at six moths when the randomization code was broken for 78 dogs, whereof 36 in the gold implantation group and 42 in the placebo group. The results of the six month period revealed that 30 of the 36 dogs (83%) in the gold implantation group showed significant improvement ($p = 0.02$), included improved mobility and reduction in the pain signs, compared to the placebo group (60% improvement).

Seventy-three of the dogs that participated in the blind, placebo-controlled study were followed for an additional 18 months to evaluate the long-term pain-relieving effect of gold

bead implantation. In this long-term follow-up study, 32 dogs in the original placebo group had gold beads implanted at the end of the six months blinded study. When closing the study after further 18 months, 66 dogs with gold bead implantation and seven dogs representing the control group were followed. A certified veterinary acupuncturist used the same procedure to insert the gold beads as in the blinded study, and the owners completed the same type of detailed questionnaires. As in the blinded study, one investigator was responsible for all the assessments of each dog. The two-year follow-up study revealed that the pain-relieving effect of gold bead implantation observed in the blinded study continued throughout the two-year follow-up period.

Use of gold implants in the veterinary practice

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Abstract

Local Gold Treatment (LGT) has proved valuable in our clinic for the treatment of dogs and cats with arthrosis (arthritis deformans, degenerative joint disease). Approximately 80 % of our patients have had lifelong benefit from LGT based on clinical evaluation and reports/responses from the owners.

When evaluating the efficacy of the treatment it is important to consider that joints affected by arthrosis cannot, regardless of the chosen treatment, be cured. The effect of LGT is therefore often seen as improved quality of life (happier, more mobile and playful animals) while the animal e.g. still may walk with a limp. These improvements are therefore most likely caused by a release of pain in the involved joints. The practical aspect of LGT for arthritis/arthrosis in

small animals i.e. dog and cat is presented, based on pictures from LGT of a dog with arthrosis of the hip joints.

In dogs arthrosis appear in particular in the elbow, hip, stifle and hock joints and signs of growth disturbances both clinically and radiographically can be seen at a young age in animals predisposed to arthrosis especially in the elbow joint. These conditions quite often lead to the dogs limping when they are only 6 month of age. Gradually a severe arthrosis will develop, and affect the dog so seriously that its quality of life and utility for hunting et cetera will be affected.

Treatment with gold implants furnished with a highly extended surface (Berlock® Implant) has in our hands been found to be beneficial in chronic arthrotic conditions in the hip, elbow, stifle and hock joints, the vertebral column (spondylosis and L7-S1 instability) and we are presently involved in a study aiming at:

1) Mapping possible radiographic improvements of the LGT treatment
2) Examining the notion that metallic gold implants over time stay put in the tissue where they were implanted.

The effect of gold coating on experimental implant fixation

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Abstract

Inserting an implant in bone is a traumatic invasive procedure causing primary local inflammation with an increase in inflammatory markers. Gold salts have previously been used against rheumatoid arthritis due to their anti-inflammatory effects. Recent studies show that metallic gold releases gold ions if placed in an organism. We therefore hypothesized that Ti implants with a thin gold layer would have an increased biocompatibility by suppressing the inflammation and thereby a better implant fixation.

Nine dogs were used in the study. We inserted cylindrical plasma sprayed porous Ti implants with or without a thin gold coating in the proximal part of tibia. The implants were inserted press-fit. The study was paired with gold on one side and control implants on the contra-lateral side. Four weeks later the implants were evaluated by mechanical push-out test and by histomorphometry. Separate sections were also made for autometallography (AMG).

Biomechanical push-out tests showed approximately 50% decrease in mechanical strength in two out of three parameters. Histomorphometrical analyses showed a decrease in overall total bone-to-implant contact with 35 percent. AMG analysis revealed few cells loaded with gold close to the gilded implant surface.

The study demonstrates that gilding of implants indisputably affects mechanical strength and osseointegration. The possibility that a moderate use of metallic gold could prolong the period of satisfactory mechanical strength therefore cannot be excluded. An alternative coating technique could be to dot parts of the surface with gold leaving most part of the more biocompatible titanium surface of the implant exposed. This model will combine the

inflammatory suppressing quality of bio-liberated gold ions with titanium's biocompatible surface.

Induction heating of metallic gold in a MR-scanner system

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Abstract

The dissolucytotic process that takes place when gold implants are placed in the body is undoubtedly thermo sensitive. Based on a resent article in Nature that described radio frequency inductive heating of nano gold particles in an MR-scanner, we decided to uncover whether this approach could be used 1) as a non-invasive way of improving dissolucytotic release of gold ions from gold implants 2) to increase the temperature in cancer cells that had been loaded with gold nanoparticles bound to membrane translocating molecules.

A first step was to reveal the efficacy of low energy radio frequencies inductive heating of gold implants and gold nanoparticles. Non-invasive thermometry of the areas around the metal was used to establish temperature changes.

We found no significant global heating, but observed a trend towards an increase in temperature at micron distances from the metal surfaces. It is scientifically interesting therefore to evaluate what changes in the parameters that can increase the local heating to a level where it will facilitate dissolucytosis of gold implants and gold particles and cause cellular death in cells loaded with gold nanoparticles.

In vitro response to gold in allergic and non-allergic individuals

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Abstract

10 % of patients patch tested at out clinics have a positive reaction to gold. Most lack clinical symptoms, but allergic contact dermatitis (ACD) to gold is increasing. In our last study, 77 dermatological outpatients were divided into three groups depending on epicutaneous patch test outcomes; a group positive to gold (EPI+); a group negative to gold (EPI-); and a group with irritant reactions to gold (EPI-IR). Lymphocytes were stimulated in vitro with gold sodium thiosulfate (GSTS). Proliferation was assessed with the lymphocyte transformation test (LTT), and cytokine secretion with a multibead array (Luminex®), in order to evaluate whether an in vitro method with high diagnostic accuracy could be devised.

The EPI+ group showed a significantly increased secretion of Interferon (IFN)-γ, Interleukin (IL)-2 and IL-13, and significantly higher stimulation indexes for LTT, compared to the other two subject groups. Sensitivity and specificity were calculated for all methods individually and combined, but IFN-γ assessment alone was the most accurate method for identifying ACD to gold, with sensitivity and specificity of 81.8 % and 82.1 %, respectively. Interestingly, cells from the non-allergic group seemed to experience some inhibitory effects from the GSTS treatment, indicating previously known immunosuppressant properties from the gold ions.

Further studies are now being aimed at investigating the effects of gold treatment on lymphocytes from healthy, non-allergic subjects in vitro.

Chronic gold implantation: A promising alternative treatment of inflammation associated pain in humans and animals

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Abstract

Pain/nociception is an extremely important protective sensation that under physiological conditions is essential to humans and animals. However, in clinic the pain usually beyond its physiological role and evolve into refractory persistent or chronic conditions. Thus, finding an effective treatment, without tolerance and addiction, for persistent and chronic pain has become a hot topic for both basic researchers and clinicians.

The implantation of small pieces of metallic gold has been used as an unauthorized alternative remedy for osteoarthritis and pain. Recently, it has been found that gold ions are released from gold implants placed in experimental animals. This observation, in view of our knowledge of gold ions anti-inflammatory properties, suggests that metallic gold might be a way of reduces inflammation caused pain.

Using a novel electrophysiological approach that involves a simultaneous recording model and an array of other multi-disciplinary approaches including. immunocytochemistry and western blotting, we want to analyze the effect of metallic gold on pain and inflammation following complete Freund's adjuvant (CFA) injection into the left knee joint. The electrophysical activities at the spinal level will systematically analyzed in gold treated and control knees. If successful, the present study will open a new nontoxic alternative avenue for treatment of intractable pathological pain syndromes in humans as well as in animals.

The Effect of Metallic Gold on Wound Healing in C57bl6-mice

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Abstract
Metallic gold hold several properties which may prove to be beneficial in optimizing wound healing. The gold ions released by dissolucytosis from the gold surface have been proved to have anti-inflammatory property and gold surfaces has been shown to process oligodynamic qualities i.e. they are weakly bactericide (McKhann et al. 1948, Muller 1985).

The dissolucytotic *in vivo* and *in vitro* liberation of gold ions from metallic gold implants and gold particles have recently been scientifically proven and this discovery strongly suggest that implanted metallic gold will cause a local immuno-suppression which will be beneficial to wound healing (Danscher 2002, Larsen et al. 2007). We have also observed that gold particles have inhibitory effects on the production of granulation tissue (Danscher et al. unpublished observations). If this observation holds true the use of gold particles as a treatment of e.g. cheloid might be interesting.

The use of implant-models in wound healing research is well-established. By using an implant-model it is possible to clearly distinguish newly formed granulation tissue from “pre-existing connective tissue. The expanded polytetrafluoroethylen (ePTFE) tube is a particularly attractive model for use in humans and animals. The ePTFE-tubes allow in growth of granulation tissue. This approach is frequently used because it is safe, minimally invasive and enable measuring of matrix deposition (Wicke et al).

The experiments will be performed on male C57 bl6 mice. Under anaesthesia ePTFE-tubes containing either gold or control material will be placed subcutaneously. After 7-14 days the ePTFe-tubes will be removed by making a small incision in the skin overlying the tube and the

tube is pulled out. Thereafter the mice will be killed by transcardial perfusion. Skin and connective tissue from the wound area, liver and kidneys will be removed for histological examination. The volume of granulation tissue will be estimated by means of stereology and the hydroxyproline content of ePTFE-tubes will be measured by the Woessner-method.

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About the Dermagold project: “Cutaneous immuno-modulation by metallic gold”

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Abstract

Gold has throughout history had a place in treatment of illness. Prior to the advent of “biological” drugs in the last decade, systemic gold therapy was relatively common. It is indeed still used to some extent but variable effect and the occurrence of side effects restrict its use. In alternative medicine and in other cultures, gold therapy has a more prominent role. At a basic research level, gold ions have many demonstrated effects on cellular mechanisms.

It is generally accepted that some of these are potentially beneficial in a therapeutic situation since they are immuno-suppressive/immuno-modulatory. Animal research has shown that macrophages in a process termed “dissolucytosis” mediate the liberation of gold ions from metallic gold in vivo, in various organs, and in vitro in cell culture systems. The gold ions are demonstrated to reach cells such as mast cells and macrophages and may thus well have useful anti-inflammatory effects in a clinical situation. Indeed use of gold implants in vetinary medicine and in alternative treatments in humans gives som indication that this may occur. In the present study, the skin, arguably the body’s most accessible organ, will be the human site used to confirm the release of ions in conjunction with metallic gold application and to investigate anti-inflammatory effects on common skin inflammatory provocations and two model skin inflammatory conditions, psoriasis and lichen simplex chronicus. The study will be conducted in two phases, a pilot study and a main study with a concept- generation phase running in parallel. A second or supplementary ethical application will be made prior to the commencement of the main study, since findings from the pilot study and rationales for treatment principles will influence the conduct of the main study.

Applicability of gold implants as a pain reducing therapy of sport related damages – a pain score analysis

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Abstract

Prolonged overuse related tendon pain in the Achilles tendon is amongst the most frequent injuries in sport, but despite the fact that the treatment includes active rest, eccentric training of the calf muscle, NSAID, local steroid injection, sclerosing injections, shockwave, nitric oxide and surgery these tendon injuries have a poor prognosis with a high incidence of chronicity and recurrence and will often bring the athlete's sports activity to a premature end.

Ultrasound guided injection of corticosteroids are effective reducing pain and tendon thickness, but many athletes have relapse of symptoms 6 months after treatment. The aim of this pilot study is to examine the effect of ultrasound guided peritendinous implantation of gold in Achilles tendinopathy.

The effect is evaluated by ultrasonography (tendon thickness and neovascularisation), pressure algometry (pressure pain detecting threshold) and VAS (pain).