

Women with Fibromyalgia Have A Real Pathology Among Nerve Endings to Blood Vessels in the Skin.

A rational biological source of pain in the skin of patients with fibromyalgia

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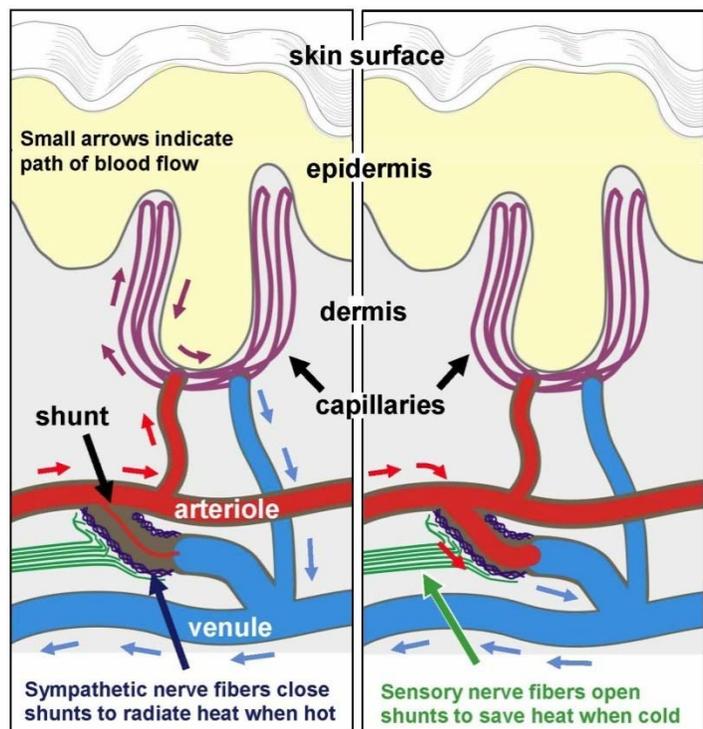
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As anyone who has fibromyalgia knows, the widespread deep pain and fatigue can be very debilitating. But even worse can be the uncertainty about the disease itself. The diagnosis can be difficult and subject to doubt because not much shows up in clinical tests. Often the diagnosis comes down to ruling out everything else. There are indications that the source of pain and fatigue is due to hypersensitivity of nerve cells within the central nervous system (called central sensitization), but why this may be occurring is unknown. Otherwise, no specific pathology has been identified that could be the source of the problem, which in itself can fuel self doubts. Distressingly, even when fibromyalgia has clearly been diagnosed, none of the FDA approved therapeutics provides predictable or sustained relief, if they provide any relief at all, and even then the side effects of drowsiness, depression and the like can be worse than the disease.

A Real Pathology Discovered in the Skin

Scientists at Integrated Tissue Dynamics LLC (Intidyn) and Albany Medical College (AMC) have made a major discovery that should provide a more certain diagnosis of fibromyalgia, significant insight into the source and symptoms of the disease, and new strategies for its prevention and treatment. The discovery has been published in the June issue of the journal Pain Medicine (the journal of the American Academy of Pain Medicine) where it was featured on the cover and accompanied by a laudatory editorial by Robert Gerwin, MD, of the Johns Hopkins University School of Medicine.



The research team was headed by neurologists Charles Argoff, MD, and James Wymer, MD PhD of AMC and James Storey, MD, of Upstate Clinical Research Associates, who did the clinical assessments, and by neuroscientists Phillip Albrecht, PhD, Quanzhi Hou, MD PhD, and Frank Rice, PhD, of AMC and Intidyn who analyzed the nerve endings in the skin. To analyze the nerve endings, the analytical team used their unique expertise and microscopic technology to examine small skin biopsies collected from the palms of fibromyalgia patients, who were being diagnosed and treated by Drs. Argoff, Wymer, and Storey. The skin biopsies were about one half the size of a pencil eraser. The study was limited to women, who have over twice the occurrence of fibromyalgia than men.

What the team uncovered was an enormous increase in sensory nerve fibers at specific sites within the blood vessels of the skin in the palms of the hands. These critical sites are tiny muscular valves, called arteriole-venule (AV) shunts, which form a direct connection between arterioles and venules. The discovered pathology involving the nerve endings to the shunts provides a logical explanation not only for extreme tenderness in the hands, but also for the widespread deep pain and fatigue symptomatic of fibromyalgia.

AV Shunts Are Like Thermostats in the Skin

To understand what the scientists believe is the nature of the problem affecting fibromyalgia patients, let's think about a problem that most of us have experienced at one time or another with our cars. You wake up in the morning. It's cold and damp. You go out to start your car, turn the key, and the engine sputters and runs a bit rough. You back out of your driveway and the engine stalls, and then again at a stop sign. It finally warms up and starts running more smoothly. As you go about your errands, you smell coolant fluid and notice that the engine temperature warning light is on. The engine is now overheating. What's wrong with your car? You take it to a mechanic who tells you that you need a new THERMOSTAT? What's a thermostat?

Discoveries From Fibromyalgia May Have Far Reaching Implications

AVS		
26 yr Control	24 yr Fibromyalgia	
vasoconstrictive NPR-positive endings		
vasodilatory CGRP-positive endings		

- Research findings indicate that sensory nerve endings on arterioles and arteriole-venule shunts (AVS) play an important role in regulating dilatation.
- The shunts play a critical role in apportioning blood flow between the skin and muscle for thermal regulation (like the thermostat in a car cooling system) and management of metabolism.
- The pathologies of the AVS in fibromyalgia may result in muscle ischemia and the symptoms of widespread deep pain and fatigue.

The diagram illustrates the analogy of a car cooling system. A radiator (Skin Capillaries) is connected to an engine (Heart) via a water pump. A thermostat (AVS) is positioned between the radiator and the engine. A motor (Muscle) is connected to the thermostat. The diagram shows how the thermostat regulates blood flow between the skin and muscle.

Here's the problem. Your car has a cooling system with hoses that run between the engine and a large, flat honey-combed part called the radiator that is located at the front of the engine compartment. The coolant circulates between the engine, which gets hot, and the radiator which spreads the coolant out into thin tubes where the air flowing over the radiator carries away the heat. The coolant system has a pump to circulate the coolant between the engine and the radiator. The radiator also has a fan, so if the coolant gets very hot, it increases the air flow to facilitate the cooling process. However, when you start your engine, it won't run properly until it warms up, so you don't want the coolant to go to the radiator right away.

The thermostat is a valve that regulates the flow of coolant between the engine and the radiator so everything functions properly. When the engine is cold, the thermostat keeps the coolant in the engine until it warms up. Then the thermostat allows the coolant to go to the radiator so the engine doesn't become too hot. Finally, the thermostat balances the flow between the engine and the radiator to maintain just the right operating temperature whether you are going downhill when the engine doesn't have to work very hard or uphill when the engine is straining.

Another factor that influences the operation of the thermostat, is whether it is cold or hot outside. In other words, the engine isn't the only source of heat, and the radiator isn't the only source of cooling. On a hot day, much more coolant has to be sent to the radiator to compensate for the high air temperature, and it is much more likely that the radiator fan will turn on to increase the air flow. On a cold day, it will be more important to keep heat in the engine. Simple, huh?

The AV Shunts Help Balance Our Body Temperature and Metabolism

The circulatory system of our body works much the same way to regulate our body temperature. For us, it is extremely important to maintain a constant internal (core) body temperature (98.6°) for our most delicate organs to work properly. A sustained decrease (hypothermia) or increase (hyperthermia and fevers) of just a few degrees can permanently damage the brain, kidneys and liver. So how do we maintain our core body temperature?

For starters, our blood is the coolant and our heart is the pump. So where is the engine? The engine is mostly our muscles. For the most part, our organs such as the kidney, liver and brain don't generate a lot of heat, but our muscles do through physical exertion.

So here is the challenge to the proper functioning of our body. Just like a properly functioning car, we need to maintain a safe temperature depending upon whether the air temperature is hot causing us to absorb heat from our environment and become overheated (hyperthermia), or whether it is cold causing us to lose heat and risk hypothermia. At the same time we have to balance this with the heat that builds up within our muscles when we exercise.

But, we are also a lot more complicated than a car. Our blood is not only our coolant, it is also our source of nutrition. So, when we wake up and become active, we need to increase blood flow to provide more nutrition to our muscles, but when heat starts to build up in the muscles we need to shift more blood flow to our hands and feet to get rid of the excess heat. So we have to find just the right

balancing act to provide sufficient nutrition without building up too much heat. Wow! So blood flow has to be constantly shifted between the muscles and the skin to achieve the right balance. Our delicate organs are caught in the middle.

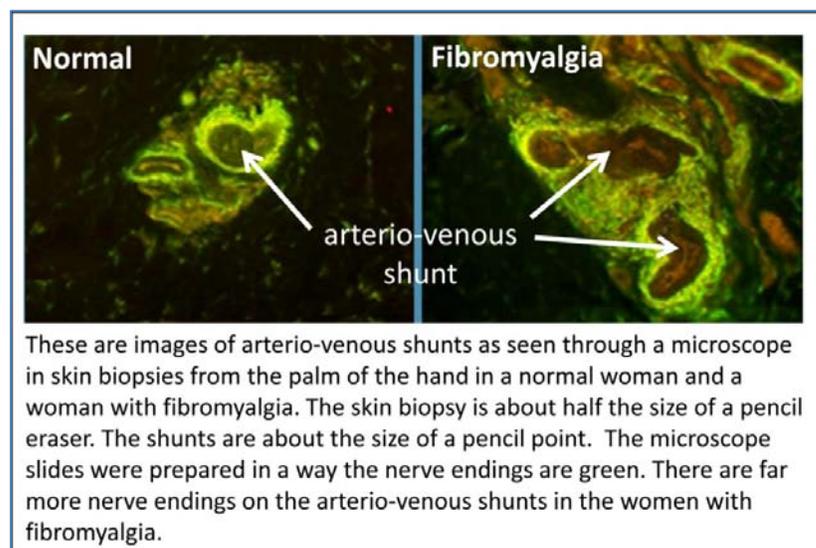
Fortunately, unlike delicate internal organs, the muscles and skin can withstand wide fluctuations in temperature and blood flow, so maintaining a constant core body temperature mostly involves balancing the blood flow between our muscles and skin. The skin can heat up by diverting blood flow from the muscles to get rid of heat, or skin can cool down to divert blood flow to the muscles to conserve heat.

So we can see the parallels between our cooling system and that of our car. We have accounted for the coolant (blood), the pump (heart), the engine (muscles), and the radiator (lungs and skin, especially that of the hands and feet). So *what* and *where* are the THERMOSTATS? Several lines of evidence indicates that the thermostats are the AV shunts which are particularly numerous in the palms of the hands and soles of the feet. These are precisely the structures where the AMC and Intidyn scientists discovered the pathologies in fibromyalgia patients.

So what are AV shunts? As we all know, oxygenated blood flows through our arteries which divide up into smaller arteries called arterioles and from there the blood flows into numerous tiny capillaries to supply tissues with nutrition, eliminate waste, and, as was just discussed, regulate temperature. From the capillaries the blood returns to small veins (venules) which then connect to larger veins. The AV shunts are small valves that connect directly between an arteriole and a venule. They have a thick muscle wall that can constrict (close the valve) or dilate (open the valve). **When the shunts are closed, blood flow is forced into the capillaries in order to dissipate heat. When the shunts are open, blood flow is diverted from the capillaries to conserve heat.**

AV Shunts Have Excessive Sensory Fibers in Fibromyalgia Patients

So what is the nature of the discovered pathology? This involves the nerve supply to the shunts which controls whether they are open or closed. One kind of nerve supply is called SYMPATHETIC, and when this is active it causes the shunts to constrict and close. The other nerve supply is called SENSORY, and this nerve supply plays a dual function. These fibers can not only detect activity in the blood vessels but they can also cause the shunts to dilate and open.



The AMC and Intidyn scientists discovered that the AV shunts in the hands of fibromyalgia patients have an extremely excessive amount of sensory fibers. The excess sensory fibers provide a logical explanation for extreme tenderness in the hands of most fibromyalgia patients. Of perhaps more importance, the excess sensory fibers on the AV shunts could interfere with the regulation of blood flow throughout the body including deep tissues including the muscles. This interference could result in a lack of proper nutrition to the muscles during exercise leading to a build up of lactic acid that could contribute to wide spread aching and fatigue. Importantly, some of the molecular characteristics of the sympathetic and sensory fibers indicates that they communicate and regulate each other. Activity of the sympathetic fibers can likely reduce the activity of the sensory fibers and vice versa. These molecular characteristics explain why some drugs such as Cymbalta and Savella provide some relief to some fibromyalgia patients.

So what is next for the research team and fibromyalgia patients?

The study, which was supported by grants from Eli Lilly and Forest Laboratories, was limited to women since they are frequently afflicted by fibromyalgia. The Intidyn scientific team is collaborating with a nationwide network of chronic pain specialists to investigate whether the same problem is occurring with men who have fibromyalgia. This difference between genders may provide some insight into why the excess sensory fibers occur in the first place and why it is occurring specifically on the AV shunts. This research will hopefully lead to more effective preventative and therapeutic strategies.

About Integrated Tissue Dynamics LLC (Intidyn)

Integrated Tissue Dynamics LLC (www.Intidyn.com), located in Rensselaer, NY amid the Capital region's Technology Valley, provides flexible and scalable pre-clinical and clinical research and consulting capabilities on skin and nerve related chronic pain afflictions in collaboration with the pharmaceutical industry, government agencies, academia, and a network of pain specialists throughout the United States. The Intidyn ChemoMorphometric Analysis (CMA) platform can be used to detect chemical and structural changes in the skin and other tissues related to chronic pain, numbness, and itch associated with a wide variety of afflictions, including diabetes, shingles, complex regional pain syndrome, carpal tunnel syndrome, sciatica, fibromyalgia, psoriasis, chemotherapy, unintended side effects of pharmaceuticals, and others.

How to Support Further Research on Fibromyalgia and Other Types of Chronic Pain

Tax deductible donations to support the research of a nationwide network of pain specialists, which includes Drs. Argoff and Wymer at Albany Medical College, can be made to the **Clinical Pain Research Program at the University of California San Diego, an American Pain Society Center of Excellence, by contacting the UC San Diego Office of Development (giving.ucsd.edu; 858-534-1610; specify area of**

research) or UC San Diego Center for Pain Medicine (anes-cppm.ucsd.edu; 858-657-7072). This network, referred to informally as the Neuropathic Pain Research Consortium, includes top neurologists, anesthesiologists, and research scientists at leading universities and pain treatment centers in California, Illinois, Maryland, Massachusetts, Minnesota, New York, Utah, Washington, and Wisconsin.

Albrecht PJ, Hou Q, Argoff CE, Storey JR, Wymer JP, Rice FL (2013). Excessive Peptidergic Sensory Innervation of Cutaneous Arteriole-Venule Shunts (AVS) in the Palmar Glabrous Skin of Fibromyalgia Patients: Implications for Widespread Deep Tissue Pain and Fatigue. *Pain Medicine*, Vol. 14, Issue 6, Pages 895-915 .

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