

PHARMACOLOGICAL BLOCKADE OF NEURAL TRANSMISSION: LESSONS FROM EXPERIMENTS INVESTIGATING CUTANEOUS BLOOD FLOW

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The spatial discrimination in the measurement of blood flow offered by laser-Doppler flowmetry, when coupled with the local application of specific agonists or antagonists, has led to new insights in our understanding of the mechanisms of control, both neural and local, of the cutaneous circulation in humans. The reflex control of that circulation involves both adrenergic vasoconstrictor nerves and a non-adrenergic active vasodilator system. The application of bretylium to a small area of skin by iontophoresis blocks transmitter release from adrenergic nerves in that area and allows unambiguous observation of vasodilator function. Through this approach it was discovered that both thermoregulatory reflexes and non-thermoregulatory reflexes (baroreflexes, exercise), control both the vasoconstrictor and the active vasodilator systems. Post synaptic blockade of both alpha and beta adrenergic receptors through intradermal injections of yohimbine and propranolol was effective in completely inhibiting the vasomotor responses to exogenous norepinephrine, but was only partially effective in inhibiting reflex vasoconstrictor responses to body cooling. This finding is highly suggestive of significant cotransmitter function in adrenergic vasoconstrictor nerves. Post-synaptic beta-adrenergic blockade through application of propranolol alone and testing with isoproterenol by intradermal microdialysis revealed the presence of beta-adrenergic receptors in the skin. The vasoconstrictor responses to local skin cooling were reversed by the local iontophoretic application of bretylium, indicating that the response is dependent on a functional vasoconstrictor system. The use of iontophoretically applied atropine eliminated the vasodilator response to exogenously applied acetylcholine, but was only partially effective in inhibiting the reflex vasodilator response to body heating. Reflex active vasodilation was completely inhibited by the intradermal injection of the presynaptic cholinergic nerve antagonist botulinum toxin. Taken together, these findings strongly indicate an important role for a cotransmitter released from cholinergic nerves as part of the mechanism for active vasodilation. Preliminary findings through the application of antagonists through intradermal microdialysis suggest VIP as a good candidate for the cotransmitter. Finally, the use of nitric oxide synthase inhibitors applied via intradermal microdialysis showed a partial inhibition of active reflex vasodilation and an almost complete inhibition of the vasodilator response to local warming, showing roles for nitric oxide in both local and reflex effects of heat on the skin.

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