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TERMINAL PROGRESS REPORT
CHEMICAL STIMULATION AND ASSAY OF THE
HYPOTHALAMUS OF THE CONSCIOUS MONKEY

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During the period of this contract, research was undertaken which was devoted to an understanding of the fundamental neurochemical mechanisms in specific regions of the brain that control vital physiological and behavioral processes. The neurohumoral factors within the diencephalon that are responsible for body temperature, feeding, drinking and other vegetative functions were investigated.

The effect of protein synthesis inhibition by anisomycin on normal thermoregulatory processes and on the pathogenesis of fever was studied in the unanesthetized animal with a reversible protein synthesis inhibitor, anisomycin. When anisomycin was administered subcutaneously to the animal, the typical fever produced by an intravenous injection of the endotoxin, S. typhosa, was prevented. In addition, pre-treatment with this inhibitor delayed and/or blocked the fever which is ordinarily evoked by a direct injection of endotoxin into the anterior hypothalamic, preoptic area. Conversely, inhibition of protein synthesis did not prevent the rise in body temperature which is usually produced by an intrahypothalamic microinjection of either PGE₂ (prostaglandin E₂) or 5-HT (serotonin). Further, the inhibition of protein synthesis did not prevent the fall in body temperature which is usually produced by a hypothalamic microinjection of norepinephrine (NE) or dopamine (DA), again

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in the rostral area.

The normal thermoregulatory capacity of the animal was unaffected by the administration of anisomycin in that the animal was able to maintain its normal body temperature upon exposure to an ambient temperature of 10°C or 34°C. Our results strongly suggest that an intermediary humoral factor operates at the level of the thermosensitive neurons in the rostral hypothalamus to mediate fevers of a bacterial origin.

In another series of experiments the pharmacological effects of alcohol on body temperature were characterized. After a thermistor probe was inserted in the colon of the unrestrained rat and its body temperature had stabilized, either a saline control solution or 2.0 g/kg or 4.0 g/kg ethyl alcohol was administered by intragastric gavage. The temperature responses were recorded and the magnitude and direction of change was analyzed according to (a) the doses of alcohol administered, or (b) the ambient temperature to which the animal was exposed. The following observations were made:

- (1) at room temperature alcohol produced a dose-dependent decline in colonic temperature, which was enhanced if the ambient temperature was lowered but reversed when the ambient temperature was elevated;
- (2) exposure of the animal to a high or low ambient temperature prior to the alcohol gavage also affected the displacement of body temperature, as well as the direction of change;
- (3) the animal's temperature could be controlled precisely following a dose of alcohol, if the ambient temperature was systematically varied;
- (4) glucose loading of the animal prior to intragastric alcohol failed to alter alcohol's thermolytic effects;
- (5) equipotent doses of sodium pentobarbital and alcohol caused an identical impairment in thermoregulatory

function; (6) EGTA given intraventricularly prevented alcohol thermolysis but butaclamol, phentolamine and methysergide failed to prevent alcohol's effect on body temperature. It was concluded that alcohol acts as an anesthetic agent in that it blocks all thermoregulatory control functions, the physiological mechanisms for dissipation of body heat as well as for heat production. It appears that alcohol is neither a hyper- nor hypothermic agent, but rather is a poikilothermic drug.

Noradrenergic neurons in the hypothalamus are known to be involved in ingestive behavior. To investigate the relationship between these noradrenergic neurons and satiety signals from the intestine, stainless steel concentric cannulae were implanted in the animal's hypothalamus and intraduodenal catheters fixed in the animal's small intestine. Anatomical sites were identified where norepinephrine (NE) causes spontaneous feeding when injected into these loci. By means of the method of push-pull perfusion, the evoked release of the catecholamine could be measured. When a nutrient such as sustagen or glucose was injected directly into the duodenum, the release of norepinephrine was enhanced at sites in the lateral hypothalamus found to be insensitive to norepinephrine but the release was suppressed at medial sites reactive to norepinephrine. It was concluded that following the ingestion of food, signals from the duodenum are relayed to the hypothalamus, so that feeding is terminated by activation of noradrenergic inhibitory neurons.

The gastrointestinal peptide hormone, cholecystokinin (CCK), is implicated in the state of satiety and in the internal mechanism responsible for cessation of feeding. CCK abolishes feeding if it is given systemically to a fasted rat or monkey. To determine a possible relationship between CCK,

NE and central ingestive functions, CCK was infused either intraperitoneally or at sites in the hypothalamus which had been shown to be sensitive to NE. If CCK was infused before a hypothalamic injection of NE, it blocked the animal's feeding response to NE. The intake of water, however, was not changed.

In further studies with the CCK-octapeptide, ^{14}C -norepinephrine was infused into the hypothalamus by means of push-pull guide cannulae which were positioned at loci known to release endogenous norepinephrine. Thus, it was possible to radio-label cellular stores of this amine. When CCK was given intraperitoneally, it evoked a release of the ^{14}C -norepinephrine at medial and rostral hypothalamic sites implicated in the physiological control of feeding. When the push-pull perfusates were analyzed by high performance liquid chromatography, it was verified that actual endogenous norepinephrine was released. These results indicate that intestinal CCK may act by way of an afferent input to the diencephalic noradrenergic feeding circuit, either through neurons responsible for initiating satiety or for the activation of feeding.

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PUBLICATIONS ARISING FROM U.S. NAVAL RESEARCH OFFICE

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December 1, 1979 - May 31, 1981

- Ruwe, W.D. and R.D. Myers. The role of protein synthesis in the hypothalamic mechanism mediating pyrogen fever. Brain Research Bulletin 5:735-743, 1980.
- Myers, R.D. and W.D. Ruwe. Fever: Intermediary neurohumoral factors serving the hypothalamic mechanism underlying hyperthermia. In Fever, edited by James M. Lipton. New York: Raven Press, 1980, pp. 99-110.
- Ruwe, W.D. and R.D. Myers. Fever produced by intrahypothalamic pyrogen: Effect of protein synthesis inhibition by anisomycin. Brain Research Bulletin 4:741-745, 1979.
- Weiner, H., R.D. Myers, C.W. Simpson, and J.A. Thurman. The effect of alcohol on dopamine metabolism in the caudate nucleus of an unanesthetized monkey. Alcoholism: Clinical & Experimental Research 4(4):427-430, 1980.
- McCaleb, M.L. and R.D. Myers. Cholecystokinin acts on the hypothalamic "noradrenergic system" involved in feeding. Peptides 1:47-49, 1980.
- Myers, R.D. and M.L. McCaleb. Feeding: Satiety signal from intestine triggers brain's noradrenergic mechanism. Science 209:1035-1037, 1980.
- Ruwe, W.D. and R.D. Myers. The role of protein synthesis in the hypothalamic mechanism mediating pyrogen fever. Brain Research Bulletin 5:735-743, 1980.
- Myers, R.D. Catecholamines and the regulation of body temperature. In: Handbook of Experimental Pharmacology, Vol. 54, edited by L. Szekeres. Berlin: Springer-Verlag, 1980, pp. 549-567.
- Myers, R.D. Hypothalamic control of thermoregulation: Neurochemical mechanisms. In: Handbook of the Hypothalamus, Vol. 3, edited by P.J. Morgane & J. Panksepp. New York: Marcel Dekker, 1980, pp. 83-210.
- Myers, R.D. Alcohol's effect on body temperature: Hypothermia, hyperthermia or poikilothermia? Brain Research Bulletin (in press 1981).
- Myers, R. D. The role of ions in thermoregulation and fever. In: Handbook of Experimental Pharmacology, A. S. Milton, Editor. Springer Verlag, Berlin (in press, 1981).
- Myers, R.D. and M.L. McCaleb. Peripheral and intrahypothalamic cholecystokinin act on the noradrenergic "feeding circuit" in the rat's diencephalon. Neuroscience 6(4):645-655, 1981.