in the brain were diagnosed as foci of metastatic adenocarcinoma.

The MDCK cells may be a useful tool in both renal pharmacology and oncology.

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Thermoregulation: Effects of Environmental Temperature on Turnover of Hypothalamic Norepinephrine

Abstract. *The hypothesis that norepinephrine is a transmitter in the temperature-regulating center of the hypothalamus is based on observations of changes in the rectal temperatures of animals after injections of norepinephrine into the hypothalamus. By introducing tritiated norepinephrine as a label into the endogenous norepinephrine stores in the brain and then measuring the disappearance of tritiated norepinephrine from discrete areas, one can monitor the activity of norepinephrine-containing neurons in those areas. In the rat exposed to heat, the turnover of endogenous norepinephrine appears to be increased selectively in the hypothalamus, whereas exposure to cold has no effect.*

The hypothalamus plays a role in temperature regulation, although the details of the regulating mechanisms are not fully understood (*1*). Feldberg and Myers (*2*) have postulated that the normal body temperature of a cat is maintained by a balance between the secretion of norepinephrine (NE) and serotonin in the hypothalamus. This hypothesis was initially based on evidence that serotonin, when injected into the anterior hypothalamus, caused shivering and that the shivering could be abolished by injection of NE into the same area. Injection of NE into the cerebral ventricles of rats elicits a biphasic response in rectal temperature (*3*). Low doses cause a transient fall in renal temperature followed by a rise, but with increasing dosage, the fall becomes more pronounced and more prolonged. Attempts to demonstrate temperature-dependent changes in the concentration of endogenous NE in the whole brain or hypothalamus of the rat have been unsuccessful (*4*), but increased activity of NE-containing neurons in several regions of brain has been reported in rats exposed to a temperature of 40°C (*5*). In the latter experiments, however, the inhibition of both central and peripheral synthesis of NE by α-methyltyrosine impaired normal thermoregulation.

As an alternative approach, we have attempted to obtain an index of the turnover of endogenous NE in the hypothalamus of rats exposed to different environmental temperatures. A small dose of ^{3}H-NE (*6*) (2.5 μc, 0.044 μg) was injected intracisternally (*7*), under ether anesthesia, into male Wistar rats (200 to 250 g). This dose was much less than that required to induce a change in the rat's body temperature (*3*) but was sufficient to label the endogenous NE stores throughout the brain (*8*). After ½ hour, when the rats had fully recovered from the anesthetic, they were placed in individual cages in an environment of 9°, 24°, or 32°C, controlled to within ±2°C. At 2, 4, and 6 hours after injection, rats were stunned and decapitated, their rectal temperatures having first been measured with a Grant thermistor thermometer. The brains were rapidly removed, rinsed, and chilled. Cerebellum and medulla were discarded since they contained a disproportionately high concentration of ^{3}H-NE due to their close proximity to the site of injection. The hypothalamus (mean weight, 66 mg) was dissected from the rest of the brain as described by Glowinski and Iversen (*8*), except that the rostral limit was placed at the caudal end of the optic chiasma to exclude most of the preoptic area. The rest of the brain (minus hypothalamus, preoptic area, cerebellum, and medulla) was taken as a whole. The tissues were homogenized in 15 volumes of 0.4*N* perchloric acid containing 0.1 percent ethylenediaminetetraacetate, and the ^{3}H-NE in the extracts was separated from its metabolites by cation-exchange chromatography (*9*). The amount of ^{3}H-NE present was estimated by liquid scintillation counting, the tissue content of ^{3}H-NE being expressed as disintegrations per minute (dpm) per milligram of tissue.

The disappearance of ^{3}H-NE from the hypothalamus and the rest of the brain is shown in Fig. 1. The tissue content of ^{3}H-NE at 4 and 6 hours after injection is expressed as a percentage of that at 2 hours. The values of rate constant (*k*) (*10*) derived from the slopes of these lines are given in Table 1. The disappearance of ^{3}H-NE from the hypothalamus at 32°C is significantly faster than at 24°C. This is associated with an elevation of 2.9°C ($P < .001$) in rectal temperature at 32°C. There was no significant difference in the rates of disappearance of ^{3}H-NE from the hypothalamus at 24° and 9°C, although rectal temperatures fell by 1.3°C ($P <$

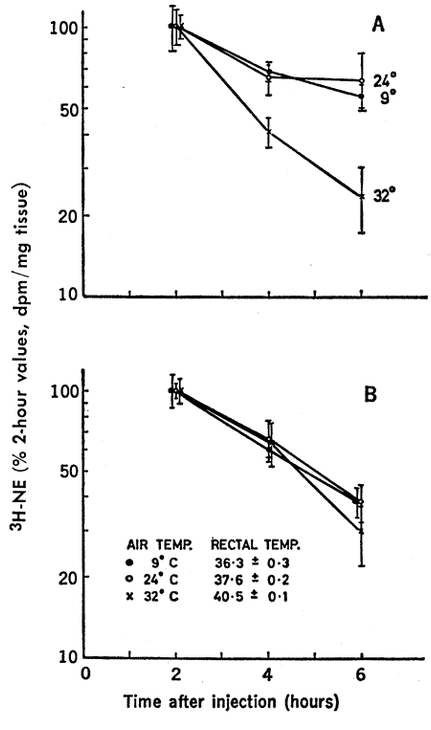

Fig. 1. Disappearance of ^{3}H-norepinephrine (NE) from hypothalamus (A) and rest of brain (excluding cerebellum and medulla) (B) of rats at various environmental temperatures. For the purposes of illustration, the ^{3}H-NE concentrations ± the standard error of the mean are plotted as percentages of the concentration at 2 hours. Each value is the mean for five to eight animals. Rectal temperatures are the overall means from rats killed at 2, 4, and 6 hours after injection.

Table 1. Effect of environmental temperature (T_E) on rate of ^{3}H-NE turnover in rat hypothalamus. Rate constants (k) and half-time values ($T_{\frac{1}{2}}$) for ^{3}H-NE disappearance from hypothalamus and rest of brain were calculated (*10*) from data presented in Fig. 1. Values are given as mean ± standard error.

T_E (°C)	Hypothalamus		Rest of brain	
	k (hr^{-1})	$T_{\frac{1}{2}}$ (hr)	k (hr^{-1})	$T_{\frac{1}{2}}$ (hr)
9	0.120 ± .054	5.78	0.238 ± .045	2.91
24	.136 ± .062	5.09	.256 ± .049	2.72
32	.392 ± .060*	1.77	.318 ± .067	2.18

*$P < .01$ when compared with value at 24°C.

.005) at 9°C. The rate of disappearance of ^{3}H-NE from the rest of the brain was similar at all three temperatures.

Although there has been recent controversy (*11*) over whether the rate of disappearance of ^{3}H-NE from tissues can be used to calculate the turnover rate of endogenous NE, this technique can at least provide an index of the turnover of endogenous NE. Our results, therefore, suggest that there is an increased activity of NE-containing nerve terminals in the hypothalamus during heat exposure, but no change in the cold. The failure to detect any such change in the other brain regions studied indicates that generalized heat stress is not involved and that the hypothalamic changes probably reflect the activity of a part of the temperature-regulating mechanism. These findings are consistent with the theory of thermoregulation proposed by Feldberg and Myers (*2*) and provide the first evidence that hypothalamic NE may regulate heat loss under normal physiological conditions in the rat.

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Complement-Immunoglobulin Relation: Deficiency of C'1q Associated with Impaired Immunoglobulin G Synthesis

Abstract. *Concentration of the complement protein C'1q was determined immunochemically in serums of individuals with a wide variety of immunoglobulin abnormalities. A significant correlation was observed between decreased concentration of C'1q and deficient synthesis of immunoglobulin G; C'1q was particularly diminished in subjects with congenital, sex-linked (Bruton) agammaglobulinemia. In contrast, two to five times the normal concentration of C'1q was found in the serum of three patients with heavy chain disease (subtype immunoglobulin G3). No significant relation was found between C'1q and concentrations of immunoglobulins A and M.*

The C'1q subunit of the first component of human complement (C'1) (*1*) is a glycoprotein with a molecular weight of 400,000 and the electrophoretic behavior of a very slowly migrating γ-globulin (*2*). It carries the site through which C'1 combines with γ-globulin or with specific antibody, and, as such, C'1q constitutes an anti-γ-globulin factor. It is endowed with differential specificity for the immunoglobulins, reacting readily with immunoglobulins G1, G3, and M (IgG1, IgG3, and IgM), but only slightly with IgG2 and little or not at all with IgG4 and IgA. Although it is possible that C'1 q may be related to the immunoglobulins, immunochemical analyses have failed to establish such a relation.

Initially, C'1q could be measured only in relative terms either by its hemolytic activity or its ability to precipitate soluble γ-globulin aggregates (*3, 4*). It was markedly diminished in serums from three patients with Bruton agammaglobulinemia (*3*). When monospecific antiserums to C'1q were produced, it became possible to detect and to quantitate C'1q in serum as an individual protein (*5, 6*). Recently, the classical C'1 hemolytic activity was found lacking in a 3-week-old infant with Swiss type agammaglobulinemia (*7*); serum from this patient was markedly deficient in C'1q (*6*). These observations prompted the present investigation, which is

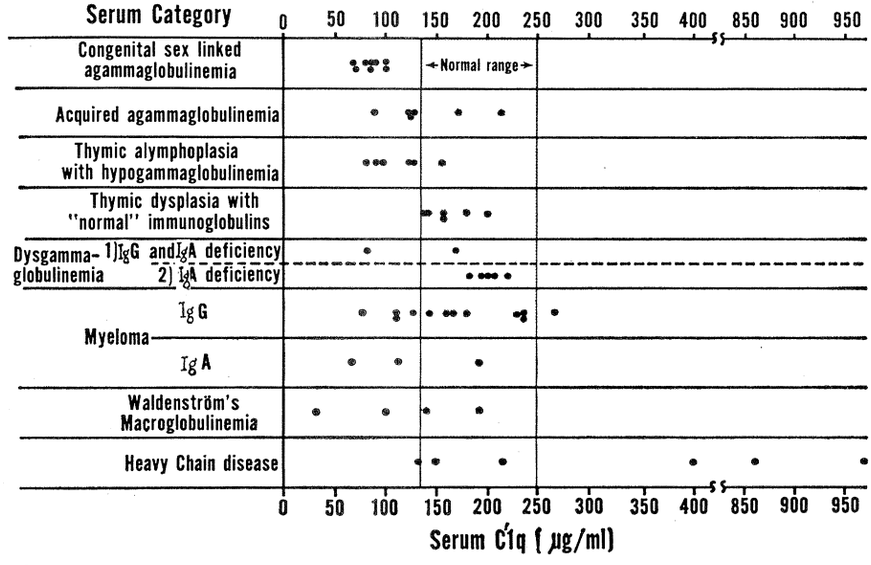

Fig. 1. Serum C'1q concentrations of 58 subjects with serum immunoglobulin abnormalities. The normal range of C'1q is between 134 and 246 μg/ml.