omy and Electrophysiology of the Dorsal Column-Medial Lemniscus System." It has been prepared by one of us (A.C.N.) whose training and research experience have been in sensory physiology. The review will be distributed both by the Government Printing Office and the UCLA Brain Information Service (BIS). It will be kept up-to-date by the author, the new material being distributed by BIS. Specific inquiries in this field, both factual and bibliographic, are also being handled by the BIS. The preface to this review will include a more detailed account of the proposed method for updating.

The author of each review will accept comments from qualified individuals, particularly those whose work is cited in it. When appropriate, the text could be amended to take account of the comments. Thus the text is intended to reflect the views of all those concerned with the topic, not merely those of the author.

The Brain Information Service plans to offer to the scientific public additional reviews in the basic neurological sciences.

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Thermoregulation and Norepinephrine

Simmonds and Iversen (*1*) have shown that the radioactivity of tritiated norepinephrine (NE) which was injected intracisternally in rats declined significantly in the whole hypothalamus after the animals were warmed to 32°C. In so doing they suggest that hypothalamic NE may regulate heat loss under normal physiological conditions in the rat and indicate that this finding is consistent with the amine theory of thermoregulation proposed by Feldberg and myself (*2*). Unfortunately, the interpretation of their results constitutes an oversimplification and may even be incorrect.

If one assumes that an action of a given transmitter substance can be mimicked by the intraventricular application of this substance, then a 5-hydroxytryptamine (5-HT) mechanism in the hypothalamus of the rat, rather than a noradrenergic one, mediates heat loss systems (*3*). We have found that 5-HT, injected into the cerebral ventricles of unrestrained rats, produces a dose-dependent, long-lasting fall in temperature. The precursor of this indole amine, 5-hydroxytryptophan (5-HTP), also evokes the same degree of hypothermia. On the other hand, NE given in low doses by the same route causes a dose-dependent rise in temperature. Also, the precursors of NE, dopamine and L-dopa (dihydroxyphenylalanine), produce the same type of elevation in temperature although their action is somewhat more sluggish. Feeding often accompanies the NE hyperthermia, but the pharmacological specificity of adrenergic thermogenesis is further substantiated by the fact that isoproteronol, a β-adrenergic agonist, causes only the rise in temperature when it is injected intraventricularly (*3*). In view of these findings, it is essential that a shift in the amount of radioactivity of labeled 5-HT be demonstrated in relation to changes in environmental temperature. This would serve as a logical control to the specific nature of NE, even though the tissue content of ^{3}H-NE in the hypothalamus may not reflect the actual presynaptic release of this "candidate transmitter" to activate postsynaptically the heat production pathways.

The experiment of Simmonds and Iversen was based on a result of Feldberg and Lotti (*4*) who reported that intraventricular NE causes a transient hypothermia. We could confirm this finding, only if the catecholamine was given in high doses. The discrepancy between our two studies may be due to the fact that Feldberg and Lotti restrained their rats, and this condition may have interacted with an action of NE, particularly since "emotional hypothermia" can develop in association with restraint (*5*). What then do the results of Simmonds and Iversen mean?

The only experiments done thus far on the hypothalamic "mapping" of temperature responses to NE and 5-HT were in monkeys, and these amines were found to act mainly within the anterior, preoptic region (*6*). Moreover, "push-pull" perfusions of the monkey's hypothalamus revealed that an increase in 5-HT release occurs only in the anterior, preoptic region during exposure to cold stress (*7*). Because the anterior region constitutes only one-eighth of the entire hypothalamus (*8*), and because so many other systems traverse the area comprising the other seven-eighths of this diencephalic structure, it is difficult to imagine that the decline of ^{3}H-NE from the whole hypothalamus could be attributed solely to an alteration in environmental temperature. Aminergic systems in different regions of the hypothalamus are already thought to be involved in many other functions, including feeding (*9*), drinking (*10*), hormonal release (*11*), emotional or affective states (*12*), levels of arousal and activity (*13*), and rewarded behavior (*14*). Among other effects, heating a rat to 32°C may simply (i) elevate its thirst drive, (ii) decrease its food drive, (iii) make it placid, (iv) lower its level of arousal, or (v) interefere with its motivational state. Any one of these processes could override and thus mask the actual effect of elevated temperature on the afferent impulses to the anterior, preoptic area (*15*). In conclusion, a biochemical assay of the whole hypothalamus may have little value for establishing a relation between a single function and a specific chemical change in this entire structure.

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15. A second and perhaps equally important anatomical error was the failure of Simmonds

and Iversen to include, for scintillation counting, the preoptic area in their critical hypothalamic sample. It is commonly recognized that this rostral diencephalic area is a region of great importance in vertebrate thermoregulation.

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We have confirmed the increased rate of disappearance of tritiated norepinephrine (^{3}H-NE) from the hypothalamus at 32°C and have shown that it occurs in both anterior and posterior parts of the hypothalamus, but not in the preoptic area (*1*). Further responses obtained from rats exposed to 9°C, however, differed from those reported earlier. Instead of becoming hypothermic, the rats maintained normal rectal temperatures and, in addition, exhibited a significantly increased rate of disappearance of ^{3}H-NE from the hypothalamus. Again, both anterior and posterior parts of the hypothalamus were involved, but not the preoptic area (*1*). It appears, therefore, that the rats in the earlier experiments failed to thermoregulate effectively in the cold, and this was associated with a failure of hypothalamic NE to increase its rate of turnover. An increased turnover of hypothalamic NE is now obtained regularly in experiments at 9°C as well as in those at 32°C.

These results are consistent with the information presented by Feldberg and Lotti (*2*) and Myers and Yaksh (*3*) concerning the responses of rats to intraventricular injections of NE. Both groups of authors showed that NE could cause a marked hypothermia in doses only two and one-half to four times those required to produce a hyperthermic response. We therefore do not accept Myers' dismissal of the hypothermic responses to NE and suggest that hypothalamic NE may be involved in the responses to the rat to both heat and cold. In this connection, it would be interesting to know how the rat's rectal temperature responds to intraventricular NE when the animals are placed in either a warm or cool environment.

Myers' conclusion that "it is difficult to imagine that the [increased rate of] decline of ^{3}H-NE from the whole hypothalamus could be attributed solely to an alteration in environmental temperature" suggests that his concept of what constitutes a thermoregulatory response is somewhat narrower than ours. His list of "other effects" which may be influenced by environmental temperature and which may involve changes in NE turnover in fact describes a pattern of behavioral changes which assists the animal in reducing heat production and, in the case of the thirst drive, in maintaining its water balance during increased salivation in the heat (*4*). Such behavioral responses to heat may be just as important as vasodilation in reducing hyperthermia. There is also no evidence in the rat that either the preoptic or anterior hypothalamic area, or both, are the only sites of action of intraventricular NE in the temperature responses to the amine. Our results, indeed, suggest that NE in both anterior and posterior parts of the hypothalamus is involved in the responses to both heat and cold. Thus, it is not clear that the role of NE in the central regulation of body temperature can be regarded quite so simply as a "relationship between a single function and a specific chemical change."

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Histochemical Fluorescence as an Index of Spread of Centrally Applied Neurochemicals

Routtenberg *et al.* (*1*) used fluorescence of biogenic amines to trace the movement of carbachol, norepinephrine, and dopamine from cannulas implanted in the caudate nuclei and septal areas of freely moving rats. They concluded that their results (i) "support the view that the ventricle transports chemicals applied to brain tissue," and (ii) "are clearly relevant to discussions of widespread behavioral effects of neurochemicals applied to the brain." We question the validity and generality of these conclusions.

Routtenberg *et al.* tested three neurochemicals but obtained clear results with only one, dopamine. Their technique was inappropriate for a study of the diffusion of carbachol, and their inability to obtain any significant effect with norepinephrine is described as "somewhat puzzling." Yet the studies which have demonstrated behavioral effects of centrally applied neurochemicals have largely used carbachol and norepinephrine, not dopamine (*2*, *3*).

The criticism made by Routtenberg *et al.* (*1*) of the generalization to other substances of findings regarding diffusion of microinjected dyes (*4*) is thus applicable to their own work, since they used the diffusion pattern of one substance as an index of the diffusion of two other structurally different substances. Their data seem insufficient to support their generalized conclusions.

The amount of crystalline chemical used by Routtenberg *et al.* is estimated at approximately 10 μg. The amounts used in the studies of behavioral effects typically range from 0.5 to 5.0 μg, and in some of the most extensive work 1.0 to 3.0 μg was used (*2*). Grossman reports optimum behavioral effects with less than 0.5 μg of carbachol (*2*). Thus, Routtenberg *et al.* have introduced at least twice the usual dose, and up to 20 times as much, a procedure which must result in greatly increased osmotic pressure and diffusion of the injected substance. Coury, who used 1.0 to 3.0 μg (*2*), reports nonresponsive loci within 0.25 mm of responsive loci, for neurochemicals applied by an extendible cannula. Booth, applying solutions of neurochemicals via very fine cannulas (modified 27-gauge needles), reports distances between effective and ineffective sites between animals of as little as 100 μm (*4*). These data support the view that, within the usual dose ranges, diffusion through brain tissue is not a critical factor.

Although their conclusions include, at least by implication, the studies in which solutions of neurochemicals instead of crystals have been used, Routtenberg *et al.* do not specifically deal with these studies. Typically, the stimulus solutions are prepared as isotonic with 0.9 percent saline and contain a range of extremely low concentrations of the neurochemical, such as 0.5 to 72.0×10^{-4} mole/liter (*3*). Injected volume is usually 0.5 or 1.0 μl, giving a dose range of 0.5 to 72.0×10^{-10} mole. For carbachol, this represents a quantitative range of 0.009 to 1.300 μg, and maximum behavioral effects, as compared to those from placebo injections of isotonic saline, are usually obtained in the lower third of this