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Wasserman (*1*) draws an interesting comparison between a subjective wavelength-dependent brightness enhancement to relatively brief pulses of light and the enhancement of luminance flicker that we found in color-opponent primate retinal ganglion cells (*2*). We did not mention this in our report because we wanted to stress our main theme, that color opponent cells play a role in both color and luminance contrast detection.

The effects Wasserman refers to and our electrophysiological ones are probably related. This is still difficult to establish, however, because there are differences in the results obtained not only between the psychophysical and electrophysiological experiments but also among different psychophysical experiments. The physiology could provide some clues to why such differences occur. In the primate retino-geniculate system, there is a great range in the strength of color opponent interactions a cell may show, especially among the largest fraction of cells, those which only show such interactions between the two mid-spectral or so-called red and green cone mechanisms. Some cells have a spectral cross-over point, that is, a spectral region where their response to light changes from excitation to inhibition, in the middle of the visible spectrum; others have their spectral cross-over point at one or the other end of the spectrum, and some have a cross-over point only when they are chromatically adapted (*3*). The cross-over point of any one cell also varies with both the spatial (*4*) and temporal (*2*) pattern of stimulation, and the entire ensemble of cross-over points of different cells subserving the same area of visual space also changes in a systematic way with distance from the fovea (*3*). The range of cross-over points among retino-geniculate cells may be responsible for the differences found in different experiments, since the wavelength-dependent enhancement depends upon these cross-over points.

In addition, as Wasserman mentions, there is a parallel retino-geniculate system of phasic cells, which also respond to luminance contrast and which do not show overt color opponent interactions (*5*). This phasic system has a retinal distribution different from the tonic one, described above, and consequently its contribution to luminance detection will change in different ways with changes in stimulus size or retinal position.

It is valuable to establish links between single unit neurophysiology and human perception, as Wasserman has attempted to do. Our results agree on an interesting point, namely that channels, in which color-opponent interactions occur, contribute to the perception of luminance contrast. In the visual cortex, there are two distinctly different classes of cells, those responding only to luminance and those responding only to color contrast (*6*, *7*). It is important to understand how these separate contrast detectors are synaptically constructed from the retino-geniculate input to visual cortex. Extant models of color vision imply that this segregation is already established in the retina, under the assumption that color-opponent cells handle color information and non-color-opponent cells handle luminance information (*8*). Recent evidence, however, suggests that color-opponent retino-geniculate cells affect both luminance and color contrast detectors in the visual cortex (*7*) and imply that previous models of color vision are incorrect. The use of color-opponent interactions in luminance contrast detection could have the advantage of ensuring a strong response to luminance across a wider range of spectrally different borders.

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3 November 1980

Calcitonin: Aversive Effects in Rats?

Freed *et al.* (*1*) report that injections of the peptide hormone calcitonin reduce food intake in rats after a latency of some hours after injection. They conclude on the basis of a conditioned aversion test that their result "appears not to be the result of illness or aversive effects." Unfortunately the test they chose can reveal only extremes of illness even when such illness is induced within minutes of the ingestion of the preferred novel solution. Freed *et al.*'s (*1*) rats were given access to water only 15 minutes per day and were tested 24 hours after their last drink and were given only a highly preferred taste to drink during the test. Any conditioned aversion would have to overcome both the extreme motivation to drink where the rat has no other choice and the strong preference for a sweet taste. It has been shown (*2*) that such a paradigm (called single bottle because the rat is offered only one bottle during the test) is much less sensitive than a two-bottle test. In a two-bottle test two novel flavors are used. One flavor is followed by an injection of vehicle on one day and the second flavor is followed on a subsequent day by an injection of the drug. On the test day, the rat is given a choice between the two flavors. In this way the rat is not forced to drink a flavor to which it has a conditioned aversion, because another source of water is available. That this is not merely a theoretical objection here may be shown by the case of cholecystokinin (CCK). Reduction in feeding after an injection of CCK was attributed to an induction of satiety (*3*) because CCK did not produce a conditioned taste aversion in the same test as used by Freed *et al.* (*1*). However, when we used a two-bottle test (*4*) a large conditioned taste aversion to CCK appeared. Further work (*5*) has shown that the sickness or malaise produced by the dose of CCK used to show food intake reduction was due to the nonphysiological amounts injected. There is a further problem with calcitonin. The food intake

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reduction was observed 4 to 9 hours later. "When calcitonin was given 1, 3, or 22 hours before, feeding was not substantially decreased." Increasing the period between the ingestion of a flavor and the induction of sickness decreases the conditioned taste aversion subsequently displayed (*6*). Delaying the injection of lithium chloride from 1.5 hours to 4.5 hours produced a fourfold decrease in the effectiveness of the injection as measured by intake suppression (*7*). Therefore, an amount of lithium chloride producing a similar decrease in food intake should have been injected at least 4 to 5 hours after a novel flavor had been presented. Should such a test still show no taste aversion, the conclusion that no sickness was present to cause the reduction in food intake would be made more plausible. However, some doubt would still remain because we do not know how the speed of onset of sickness influences the formation of conditioned taste aversion. Gradualness of onset may militate against the efficiency of a learned association.

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We have performed several studies similar to those suggested by Deutsch (*1*) and have been unable to produce a statistically significant conditioned taste aversion by administration of calcitonin. We therefore continue to believe that the inhibition of feeding produced by calcitonin cannot be explained by the production of illness or nausea. But, this is not to say that it would be impossible under any conditions to demonstrate that calcitonin can produce a conditioned taste aversion. We do not believe that absolutely no sickness is present, but only that any sickness that is produced by calcitonin is insufficient to account for the inhibition of feeding.

One of our studies was somewhat similar to those referred to by Deutsch (*2*). We used two flavors (black walnut and chocolate), one of which had previously been paired with the administration of calcitonin; the other had previously been paired with the administration of vehicle. When the animals were subsequently presented with a choice between the two flavors, neither flavor was significantly preferred (Fig. 1). There was, however, a nonsignificant tendency for a decreased consumption of black walnut extract in the animals for which black walnut extract had been paired with calcitonin. There was no apparent aversion when calcitonin had been paired with chocolate. Perhaps a significant conditioned aversion would be revealed by this procedure if large numbers of animals were tested.

In another experiment, we administered calcitonin 3 hours before the first exposure to saccharin (backward conditioning) (*3*) and we were again unable to demonstrate a conditioned aversion. Finally, we gave animals access to saccharin for a 6-hour period after they received calcitonin. When subsequently tested for their preference of saccharin

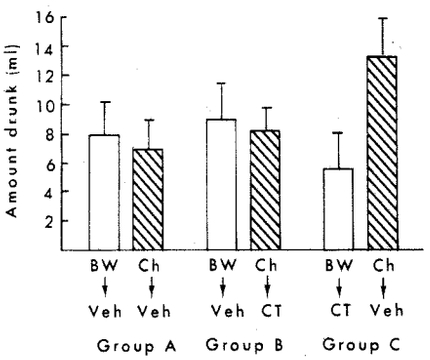

Fig. 1. Amount of black walnut-flavored (*BW*) solution and chocolate (*Ch*) solution (McCormick extracts; diluted 40:1) drunk by animals given simultaneous access to both solutions for 60 minutes (mean ± standard error). The animals previously had been given access to each solution and had then been injected with either synthetic salmon calcitonin (*CT*) (Armour Pharmaceutical; 50 U/kg, subcutaneously) or vehicle (*Veh*), as indicated by the arrows. Thus calcitonin was paired with chocolate for group B, with black walnut for group C, and with neither solution for group A ($N = 10$ per group). Animals were tested while on a 23½-hour schedule of fluid deprivation. A two-way analysis of variance for one repeated measure showed no significant effects [for groups, $F(2, 27) = 1.02$, $P = .374$; for chocolate versus black walnut, $F(1, 27) = 0.68$, $P = .423$; for interaction, $F(2, 27) = 1.45$, $P = .251$]. A post hoc comparison for group C also did not achieve significance ($P = .065$, Scheffé). Finally, Wilcoxon matched-pairs signed-ranks tests were performed for each of the groups and none reached statistical significance ($T = 18.5$, $N = 9$; $T = 25$, $N = 10$; and $T = 10$, $N = 10$ for groups A, B, and C, respectively).

as opposed to water the calcitonin-treated animals increased their consumption of saccharin, but not as much as did the controls. (None of the differences were statistically significant.) Our studies thus far lead us to conclude that, although it might be possible to produce a conditioned taste aversion by administration of calcitonin, such an effect would certainly not be robust and is not easily demonstrated. We also point out that food-deprived animals that had received calcitonin ate avidly; as we noted in our original study (*4*), the animals that received 12.5 units of calcitonin per kilogram of body weight invariably began to eat within 10 seconds of food being introduced into their cages. Also, although the maximum effect of calcitonin occurred between 4 and 9 hours with a small (12.5 U/kg) dosage, larger dosages were effective over an entire 24-hour period. We have always used the largest dosage (50 U/kg) for conditioned aversion studies.

Conditioned aversions can be produced by moderate dosages of a wide variety of drugs, such as chlorpromazine, benzodiazepines, barbiturates, alcohol, ether, methaqualone, scopolamine, and the anorexogens amphetamine and cholecystokinin (*2*, *5*). Illness and nausea are not prominent features of the clinical pharmacology of these drugs, and some of these drugs can produce conditioned taste aversions in animals but do not decrease eating. It thus appears likely that any disturbance of homeostasis can produce a conditioned taste aversion. Therefore, although such studies may be informative, it would probably be unwise to attribute any pharmacological effect of a drug to nausea or illness (in the usual sense) solely on the basis of conditioned taste-aversion studies.

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