Histidine had the fastest mobility (21 cm), followed by the peptides containing a free α-amino group: L-alanyl-L-histidine (15.8 cm), L-histidyl-L-alanine (15.3 cm), and glycyl-L-histidine (18.5 cm). The free β-amino group of β-alanyl-L-histidine caused a reduction in mobility to 9.7 cm, and the γ-amino group of γ-aminobutyryl-L-histidine resulted in a mobility of only 1.2 cm. A mixture of 50 nmole of carnosine and 50 nmole of homocarnosine gave well-separated intensely stained red spots when sprayed with the diazotized sulfanilic acid reagent (Fig. 1, lanes 1 and 9). Extracts of olfactory bulb (Fig. 1, lane 2) and of olfactory epithelium (Fig. 1, lane 5) each gave one intense spot corresponding to carnosine and in the bulb, a faint spot at the position of homocarnosine. The major spot comigrated with authentic carnosine as indicated by the intensification of the major spot (Fig. 1, lane 8) when the standard mixture of carnosine and homocarnosine was added to the bulb extract. An extract prepared from olfactory bulbs removed 15 days after the zinc sulfate peripheral deafferentation procedure gave only very faint reactions with the diazo reagent, indicating a striking decrease in the content of carnosine after deafferentation (Fig. 1, lane 7). Extracts of cerebral hemispheres lacking the olfactory bulb (Fig. 1, lane 3) gave only a very faint reaction with the diazo reagent, and extracts of lung (Fig. 1, lane 4) were essentially nonreactive. Extracts prepared from skeletal muscle (Fig. 1, lane 6), a known source of carnosine, gave a single red spot at the same position as authentic carnosine and the major spot from the olfactory bulbs (Fig. 1, lanes 1, 2, and 9).

The electrophoretic results confirm and extend the chromatographic analyses (Table 1). They demonstrate that in the olfactory pathway carnosine and not homocarnosine is the major histidine peptide. Amino acid analyses after hydrolysis overnight in 6*N* HCl at 110°C also confirmed this since histidine and β-alanine were produced in essentially equimolar amounts with only traces of γ-aminobutyric acid. In addition, the virtual absence of carnosine in the lungs (Fig. 1), a source of respiratory epithelium, further supports the concept that the carnosine in the nasal olfactory epithelium is located in the receptor neurons and not in other cell types. Strong confirmation of this postulate was the decrease observed in the carnosine content of the olfactory bulb after peripheral deafferentation.

High concentrations of carnosine were found in the primary olfactory pathway and decreased after peripheral deafferentation, a pattern that precisely matches the localization and behavior of the unique marker protein of the primary olfactory pathway (*6–8, 10*). The relation between carnosine as a possible neurotransmitter, the olfactory marker protein, carnosine synthetase (*11*), carnosinase, and the function of the primary olfactory chemoreceptor neurons remain to be determined (*12*).

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11. Recently we have observed that peripheral deafferentation also results in a virtually complete elimination of carnosine synthetase activity [assayed according to the method of S. D. Skaper, S. Das, F. D. Marshall, *J. Neurochem.* **21**, 1429 (1973)] from the olfactory bulb, while it has no influence on several other enzyme activities (unpublished observations, F. Margolis, J. Tarnoff, and D. Armona).
12. After this report was accepted for publication we learned that A. Neidle and J. Kandera [*Trans. Am. Soc. Neurochim.* **5**, 169 (1974)] had reported that carnosine was present in high concentration in the olfactory bulb.
13. I thank Dr. S. Stein for performing the amino acid analyses on the hydrolyzed samples of olfactory epithelium.

5 March 1974

Illusory Correlation of Brightness Enhancement and Transients in the Nervous System

Abstract. *Short light flashes can appear brighter than longer flashes. This brightness enhancement has often been attributed to neural transients occurring shortly after stimulus onset. This attribution assumes an equivalence between the totality of the response to a stimulus of a given duration and the instantaneous response at a given time after stimulus onset. Recordings from* Limulus *photoreceptors indicate that this attribution is an example of illusory correlation.*

Illusions have the defining characteristic that they still elicit the illusory response from an observer even though the observer has carried out the measuring operations that reveal the illusion. Cognitive analogs of illusions occur when two classes of observations are believed to be correlated when they are not in fact related. These "illusory correlations" are often the result of associations arising from similarities between the words that describe the two classes. Illusory correlations have been so named because they share the defining characteristic of illusions, namely, that they do persist even though empirical evidence to the contrary has been provided (*1*). We now report the presence of an illusory correlation between data obtained in psychophysical and in neurophysiologic experiments on vision. This illusory correlation derives from the associative similarity of two operationally distinct parameters, namely, "stimulus duration" (a parameter in psychophysical experiments) and "time after stimulus onset" (a parameter in neurophysiologic experiments). Data which might have revealed this illusory correlation have been available for almost a half century (*2*); to our knowledge, the connection of these earlier data with the illusory correlation presently under consideration has not been noted. An analogous difficulty involving spatial rather than temporal parameters has recently been noted (*3*).

The two phenomena involved in this illusory correlation are subjective brightness enhancement and transients in the nervous system. Brightness enhancement occurs when one varies the duration of a light stimulus whose luminous intensity remains constant for the duration of the stimulus; one then finds that the subjective brightness of the stimulus varies in a complex fashion (*4*). Figure 1A illustrates the general form of the relationship between stimulus duration and subjective brightness. The overshoot of brightness at inter-

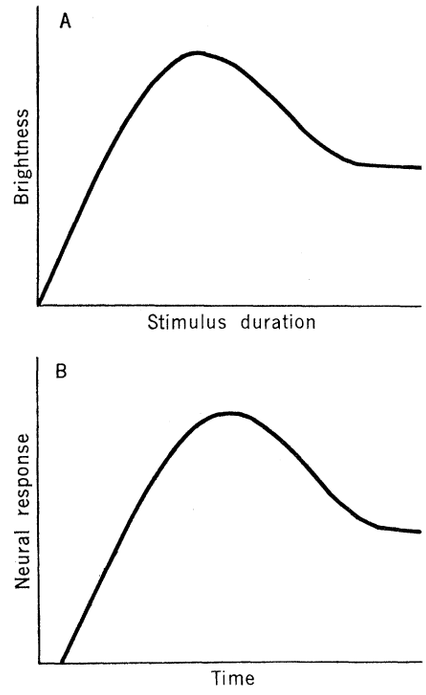

Fig. 1. (A) Subjective brightness as a function of the duration of a light stimulus of constant luminance. (B) Neural response (either spike frequencies or the amplitude of graded potentials) as a function of time after the onset of an indefinitely prolonged light stimulus. Both functions are schematic and intended to illustrate results obtained with relatively intense stimuli.

mediate durations is called brightness enhancement (sometimes called the Broca-Sulzer effect). The enhancement phenomenon is intensity dependent; the results shown in Fig. 1A are obtained at relatively high stimulus intensities. Lower intensities produce a monotonic rise in brightness as duration is increased. The duration that produces the maximum enhancement is also intensity dependent, varying from about 250 to 50 msec (*4*).

An apparently correlated phenomenon occurs when one measures the electrical activity of certain single cells in the visual system. Figure 1B illustrates the general form of the results of such experiments (*5*). A visual stimulus turned on at zero time and kept on indefinitely produces (after a latent period) a neural response which overshoots and levels off at a steady value which is maintained as long as the stimulus is maintained. This overshoot is intensity dependent, occurring only at relatively high intensities. The time after stimulus onset that produces the maximal response is also intensity dependent and varies over a range that is numerically comparable to the stimulus durations that produce the maximum brightness enhancement. Depending upon the preparation and the location of the recording electrode, the neural response can be an increase or a decrease in the membrane potential or in the frequency of action potentials (or spikes).

Subjective brightness enhancement and such neural transients have generally been assumed to be related to each other. The intensity-dependent variations in brightness enhancement are believed to be the result of the intensity-dependent variations in the neural transients. This isomorphism between brain and behavior is so well known that it is difficult to find explicit and concise statements of it in the literature. Le Grand remarks that ". . . the general occurrence (especially at high intensities) of an initial frequency [of optic nerve spikes] which is much greater than the regular frequency of the discharges when the stimulus is constant, evidently arises from an autoinhibition which slows down the activity; the connection of this phenomenon with the Broca-Sulzer effect is obvious" (*6*). The use of this citation in the present context should not be taken as an animadversion upon Le Grand; the citation is unusual only in its explicit assertion of the relationship. Most authoritative discussions of this problem implicitly assume that the two types of data are related.

The problem that we wish to raise is that the independent variables in the two sets of experiments are not the same. In the psychophysical experiment, the independent variable is the *duration of the stimulus*; in the physiologic experiment, the independent variable is *time after stimulus onset*. This difference in the independent variables produces an associated difference in the dependent variables, since the former is the response to the totality of the flash while the latter is the instantaneous response as a function of time after stimulus onset. These operational differences between the two experimental situations require that their presumed relation be tested empirically rather than intuitively. Intuitive tests are the source of illusory correlations (*1*).

We therefore designed a neurophysiologic experiment wherein these two independent variables were dissociated and wherein the instantaneous response at a given time could be clearly distinguished from the totality of the response to a given duration. Since intensity is also an important parameter, we independently varied intensity over a wide range. We used a model preparation, namely, the photoreceptor of the lateral eye of *Limulus*, the horseshoe crab. Eyes were excised from animals,

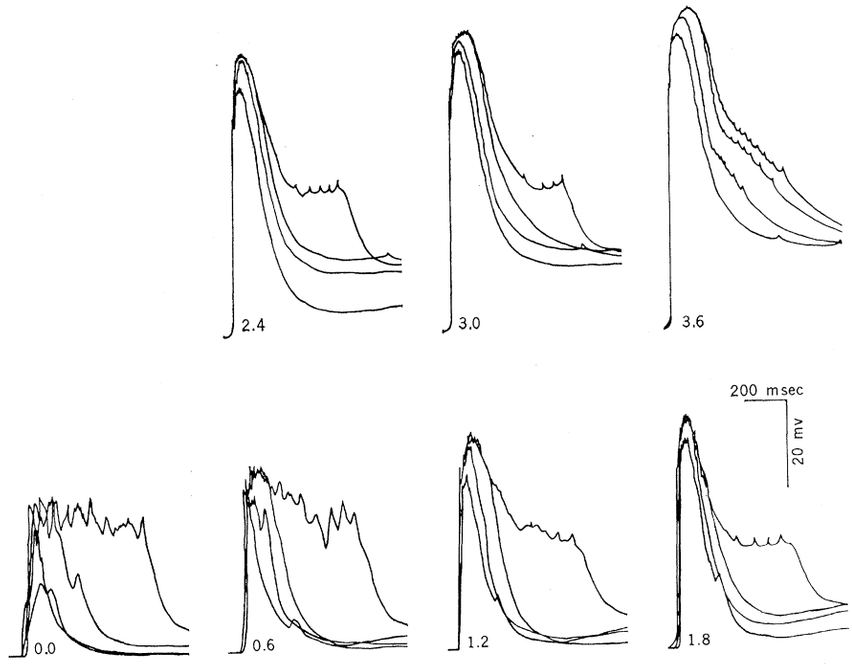

Fig. 2. Graded receptor potentials elicited by lights of varying intensity and duration. Each group of four graphically superimposed traces represents responses to lights of an intensity given in the figure in relative log units; the four responses within each group are stimuli of 10, 40, 160, and 640 msec. Longer stimuli produce longer responses. All response traces begin at stimulus onset.

and microelectrodes were inserted into single retinular (photoreceptor) cells in accordance with procedures which are described in detail elsewhere (*7*). These receptor cells produce graded depolarizations (reductions of membrane potential) in response to light. Optic nerve discharges (or spike frequencies) are linearly related to the depolarizations induced in the receptor cell (*8*). The receptor cells were kept in a constant state of dark adaptation by regularly applying a constant test stimulus. The response to the test stimulus provided a control against possible changes in the viability of the receptor during the experiment.

The results of a representative experiment are shown in Fig. 2. Each group of graphically superimposed traces represents responses to light flashes of a given intensity but of different durations. The intensities are indicated in relative log units in the figure; we also obtained responses to other intermediate intensities. Four different durations, namely, 10, 40, 160, and 640 msec, are illustrated; we obtained responses to intermediate durations as well. The responses to the different durations can be easily identified since longer durations always gave more prolonged responses. Each trace in the figure begins at the beginning of the light flash and each trace is a plot of the instantaneous response as a function of time after stimulus onset for a given stimulus. Each group of superimposed traces illustrates the totality of the responses as a function of stimulus duration for a given intensity.

The range of intensities employed begins below the level at which a clear-cut neural transient occurs (compare 0.0 log units). These responses to the weakest stimuli are quite irregular; this is characteristic of the response to weak stimulation in dark-adapted visual systems. Despite these irregularities, it is fairly clear that no appreciable transient occurs at the lowest intensity; progressive increases in intensity elicit a progressively clearer transient. Moreover, the longest duration produces a clear-cut plateau except at the very highest intensity where the cell has not yet equilibrated after the transient (compare 3.6 log units). Thus these data cover the entire range of stimuli that might be expected to produce a neural correlate of brightness enhancement.

Certain trends are clearly present in these data. First, longer stimuli always produce responses whose peak height (and hence whose associated maximum spike frequency) is greater than or equal to that produced by shorter stimuli. Second, longer stimuli always produce responses whose total area (and hence whose associated total number of spikes) is greater than that produced by shorter stimuli. Thus, the neural response to lights of varying durations is always monotonically related to stimulus duration. There is no correlate in these data of the psychophysical phenomenon of brightness enhancement even though we have clearly elicited neural transients and even though we have covered the entire range of appropriate stimuli. We have seen no exception to this generalization in any of our experiments. Although we have discussed only two features of the total response, namely, peak height and area, no other feature appears to violate this generalization (*9*). Latency appears to be independent of stimulus duration.

These data do not demonstrate that some other single-cell response might not be isomorphic with brightness enhancement although we are not presently aware of any nonillusory single-cell correlate of the Broca-Sulzer effect. But the mere presence of a neural transient at *any* level of the nervous system cannot be presumed to be related to the Broca-Sulzer effect. The search for the correlate of brightness enhancement cannot benefit from the assumption that stimulus duration is in any simple way related to time in the nervous system.

Such an assumption is likely to have frequently occurred in the analysis of other substantive problems because of certain differences in the methods employed in the two types of research: Psychophysical experiments manipulate duration because there is no reliable way of obtaining a continuous numerical description from a subject of the temporal course of perceptual events. On the other hand, physiologic experiments automatically provide a measure of activity as a function of time. A substantial additional investment has to be made to manipulate stimulus duration as a separate parameter. Other postulated psychophysiologic isomorphisms involving temporal factors might therefore be examined for the possible presence of an illusory correlation by exactly replicating the psychophysical procedure with the physiologic material.

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9. These data were collected as part of a study on the reciprocity of stimulus intensity and duration. Previous single-cell studies of reciprocity (*2*) contain data which can be subjected to the same analysis that we have here applied to our data. Such analyses corroborate and lend generality to our findings.
10. This research was supported by funds provided by the University of Wisconsin Research Committee. Earlier versions of this report were kindly read by L. J. Chapman, W. Epstein, and C. T. Snowdon.

8 November 1973

Maternal Lymphocytes: Suppression by Human Chorionic Gonadotropin

Adcock *et al.* (*1*) devised an ingenious theory of fetal protection based on the proposition that human chorionic gonadotrophin (hCG) is a constituent of the trophoblast surface and that it can inhibit maternal lymphocytic responses. They tested the latter part of the proposal by attempting to stimulate lymphocytes with phytohemagglutinin (PHA) in the presence of hCG. Since they observed apparent inhibition, they concluded that their original theory remains tenable.

There might be another explanation for their findings. That is, hCG, a protein that contains 31.3 percent carbohydrate, has little or no effect on the cells, but acts by combining with