SCIENCE

FRIDAY, APRIL 15, 1921

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THE PHOTOCHEMISTRY OF THE SENSITIVITY OF ANIMALS TO LIGHT[1]

I

AN analysis of sensory stimulation, in order to be objective, must take its data from the relations between the properties of the stimulating agent and those of the responses of the animal. If the analysis is to be quantitative as well as objective, not only should the response be a qualitatively invariable reflex but, together with the source of stimulation, it should be capable of precise and easy control.

There are a number of animals which possess such characteristic responses. Typical of these are the ascidian, *Ciona intestinalis* and the long-neck clam, *Mya arenaria*. Both of these animals, when exposed to light, respond by a vigorous retraction of the siphons. It has therefore been possible to investigate quantitatively the properties of their photic sensitivity, and as a result to propose an hypothesis which accounts for this type of irritability in terms of an underlying photochemical mechanism.

I propose now to describe briefly the evidence which has been accumulated in this connection, and to present the outstanding features of the proposed hypothetical mechanism.

II

The photosensory activities of these animals possess four striking and important properties. (1) When exposed to light, the animal

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[1] Delivered at the Symposium on General Physiology held by the American Society of Naturalists on December 30, 1920, at its Chicago meetings. The paper was illustrated with a number of charts which are not reproduced here. They may be found, together with the data on which this summary is based, in a series of articles in the *Journal of General Physiology* from 1918 to the present time.

responds only after a measurable interval, which is usually longer than one and a half seconds. This interval is called the reaction time. (2) The animals will respond to light only when there has been a decided increase in its intensity. (3) Once a response has been secured to a given illumination, the continued application of the same intensity fails to produce any additional effect. (4) If, following this, the animal is placed in the dark, it very soon recovers its sensitivity to the light which had previously become ineffective.

It is apparent that these four characteristics are not confined merely to these two species of animals. They belong generally to all animals which are sensitive to increased illumination. Their analysis is therefore of more than immediate interest. Their presence and their quantitative aspects have determined the nature of the hypothesis proposed, and they in turn find their explanation in terms of the hypothesis. It will therefore be well to consider these four outstanding characteristics in greater detail.

III

The reaction time is the interval from the beginning of the exposure to the beginning of the response. In *Ciona* this may vary from 2 to 10 seconds, and in *Mya* from 1.5 to 4 seconds, depending on circumstances such as temperature, intensity of light, and duration of exposure. If these are kept constant, the reaction time is constant.

Fortunately this reaction time is made up almost entirely of the time lost in the sense organ. For example, mechanical stimulation produces the same reflex as illumination. Yet the retraction of the siphons occurs so rapidly that it is not possible to measure it with a stop watch. The adjustor and effector processes, therefore, take almost no measurable time, and the reaction time is confined to the processes which take place in the receptor. This is, to say the least, highly convenient.

The reaction time, however, is not a simple interval. The total exposure to light, which it represents, is not necessary. If the animal is exposed for, say, half the reaction time, it will still respond *in the dark* at the end of the usual reaction time. By proper methods it is possible to reduce the exposure and at the same time to measure the reaction time. It is found that for each intensity of light there is a minimum exposure which will cause a response at the end of the usual reaction time. This short exposure is the sensitization period. Exposures longer than the sensitization period make no change in the duration of the reaction time; exposures shorter than the sensitization period prolong the reaction time, as will presently be described. That portion of the reaction time during which the animal is in the dark, or during which the exposure to light is not necessary, is called the latent period. Normally, therefore, the reaction time is composed of two parts: a sensitization period and a latent period.

The whole matter is strikingly illustrated with *Mya*. Here the sensitization period is extremely short. With a strong light it is only a few hundredths of a second long, whereas the latent period comprises most of the reaction time, which in such a case is about one and a half seconds.

The sensitization period varies with the intensity. The latent period however, provided certain conditions are maintained, is constant for all intensities. At room temperatures the latent period for *Ciona* is 1.76 seconds; for *Mya* it is 1.31 seconds. Since it is our purpose to study the quantitative aspects of this photic sensitivity, it is apparent that the analysis of the reaction time into its two constituents is of first rate significance. The composition of the reaction time was first discovered with *Ciona,* and it immediately opened a hitherto inaccessible field of investigation.

IV

The second characteristic of the sensitivity of these animals is the fact that they will respond to light only when it is increased. This initial action of the light must be on a photosensitive substance contained in the sense organ. It is necessary to determine whether this action of the light on the sensory process possesses the ordinarily well-demonstrated characteristics of photochemical reactions. Photosensitive chemical reactions have been studied extensively, and certain of their properties have been found to be commonly distributed. One of these is that a definite quantity of radiant energy is associated with a definite photochemical effect. This is the well known Bunsen-Roscoe law, which states that to produce a given effect the product of the intensity and the time of exposure of the light is a constant.

Tested by this standard, the action of light in the sensory responses of *Ciona* and *Mya* is photochemical in nature. With *Ciona,* in the production of a response, the sensitization period varies inversely with the intensity, and their product is constant and equal to 4,746 meter-candle-seconds. The same is true for *Mya.* To produce the minimum stimulating effect the intensity must vary inversely as the exposure, the product of the two being in this case only 5.62 meter-candle-seconds.

Another common property of photochemical reactions is that they possess a low temperature coefficient. Whereas ordinary chemical reactions are markedly accelerated by an increase in temperature, photochemical reactions proceed at pretty much the same rate over wide ranges of temperature. Experiments show that the temperature coefficient for the action of light on the sensory activity of *Mya* is 1.06 for a rise of 10° C. This value is so characteristic for endo-energetic photochemical reactions that, combined with the applicability of the Bunsen-Roscoe law, it can lead to but one conclusion. That is that the initial effect of the light in photic stimulation is a rather simple photochemical phenomenon. These results further indicate that in order to produce a photosensory effect a definite amount of a photosensitive substance must be broken down by the light.

V

The third point which was made with regard to the sensory responses of these animals is that the continued application of the light fails to elicit any additional effect. This has been tested with intense sunlight and with artificial light of over 10,000 meter-candles intensity. The result is always the same. After the first retraction of the siphons, the animal comes into sensory equilibrium with the light. The siphons are slowly extended, and the animal appears to act as if there were no light present.

This brings us to the fourth characteristic of photic sensitivity—the one which has served as the key to the whole situation. This is the fact that when an animal has come into sensory equilibrium with a bright light, it may be made to recover its sensitivity to light by being placed for some time in the dark. The rate at which this recovery takes place is of significance, and has been carefully investigated in the case of *Mya.*

An animal is exposed to an intense light for an hour. It is then suddenly darkened, and at regular intervals its sensitivity is determined by measuring the reaction time to a light of low intensity. What one finds is this. For about three minutes the animal is still insensitive to the particular intensity used. On the fourth minute its first response appears. The reaction time when measured at this time is nearly twice as long as usual. Measured at regular intervals, the reaction time is found to decrease continuously during the next thirty-five minutes. At first this decrease is rapid, then slow, until after thirty-five minutes or so it ceases entirely, and the reaction time is at its minimum for that intensity.

The course of dark adaptation is very orderly. It is similar in the case of *Ciona,* except that it is much slower, requiring about three hours for completion.

What is the significance of these regular changes? Physically they mean that during dark adaptation the quantity of light required for a response is much greater than normal, and that this quantity decreases at first rapidly, then more slowly. The effect of the light we have shown to be the photochemical decomposition of a sensitive substance in the receptor. Therefore the amount of decomposed photosensitive material necessary for a response during dark adaptation is at first large, and gradually becomes smaller and smaller until it reaches the normal amount for that intensity.

VI

These phenomena, and many others, can be explained in terms of a simple hypothesis. In producing sensory equilibrium, the light decomposes a photosensitive substance, and at the same time causes a loss of sensitivity. The removal of the light results in a characteristic return of sensitivity. This is probably because new photosensitive material is being formed. If we assume that the action of the light is to break up the sensitive material into its precursors, and that in the dark these precursors reunite to form the sensitive substance, all of our data may be explained in terms of the kinetics and dynamics of chemical and photochemical reactions whose general properties are well known and mathematically predictable.

Consider the kinetics of the formation of a sensitive substance from its precursors. The velocity of reaction at any moment will be proportional to the concentration of the precursors. Therefore these will disappear at first rapidly, and then more slowly according to the well-known expression

$$-\frac{dx}{dt} = k(a - x)^n,$$

where $(a - x)$ represents the concentration of precursors, and n the order of the reaction, the other symbols having their usual meaning.

It is certain that the reaction time, and therefore the amount of photochemical action necessary for a response, is not proportional to the concentration of sensitive substance in the sense organ, because during dark adaptation the former decreases while the latter increases. Moreover, it becomes apparent on second thought that the sensitive substance as such is not the effective agent; it is only after it has been decomposed by the light into something else that it can produce its effect. It is therefore more likely that the amount of decomposition represented by the reaction time (more accurately, by the sensitization period) will depend not on the concentration of sensitive substance, but on the concentration of its precursors.

Let us assume this to be true. The changes in the reaction time during dark adaptation should therefore parallel the progress made in the disappearance of precursor material during their combination to form the sensitive material. A superficial resemblance between the dark adaptation curve and the isotherm of a chemical reaction is at once apparent. The resemblance however is more than superficial. The curve which best fits all of the data on dark adaptation is actually the isotherm of a bimolecular reaction, represented by the expression

$$k = \frac{1}{at} \cdot \frac{x}{a - x},$$

which is the integral form of the equation above when $n = 2$; a represents the initial concentration of precursors, x the concentration of sensitive substance at the time t, and $a - x$ is the concentration of precursors at the same time. This means that there are *two* precursors (P and A) whose concentration is decreasing because they are combining to form the sensitive substance S. The process which goes on in the sense organ may then be written

$$S \underset{\text{“dark”}}{\overset{\text{light}}{\rightleftharpoons}} P + A$$

with a full consciousness of the quantitative significance of the expression.

VII

The dynamics of this reversible photochemical reaction account for the prominent characteristics which we have described for the photosensory process. The response to an increase in illumination, the applicability of the Bunsen-Roscoe law, and the low temperature coefficient are all inherent to the light reaction, $S \rightarrow P + A$. Sensory equilibrium corresponds to the well-known stationary state which results when the opposing light and "dark" reactions become balanced, and no fresh decomposition products can be formed by the light. Dark adaptation very obviously is a clear function of the unopposed "dark" reaction.

More than this, however. Certain predictions may be made on the basis of this reversible reaction. Several of these have been investigated with complete success. To mention just a simple example: the "dark" reaction, $P + A \rightarrow S$, is an ordinary chemical reaction; its temperature coefficient should therefore lie between 2 and 3. This is equivalent to saying that the temperature coefficient of dark adaptation should lie between 2 and 3 for 10° C. This is precisely what has been found to be true. The temperature coefficient of dark adaptation for *Mya* is 2.4. This concept of a reversible photochemical reaction has therefore been fruitful in accounting for the known properties of photosensory stimulation, and has served to suggest the investigation of other properties. The results of these have in turn corroborated the original explanation.

VIII

So far we have considered the events which take place during the sensitization period only. The photosensory responses of these animals, however, involve the very definite existence of a latent period. In fact, in the case of *Mya*, most of the reaction time is merely latent period and nothing more. Fortunately this part of the reaction time has also yielded to quantitative methods of analysis, and as a result we can now offer an explanation of photoreception which covers not only the sensitization period, but the latent period as well.

At the beginning of this paper, in defining the different parts of the reaction time, I pointed out a significant fact. It is that if the exposure of an animal to light is made shorter than the sensitization period at that intensity, the reaction time—and consequently the latent period—is prolonged. This indicates that there is some interrelation between the two portions of the reaction time. Experiments were therefore made in which animals were exposed for varying periods of time, all less than the sensitization period. It was found that the duration of the latent period varies inversely with the length of the exposure to light.

The latent period, being the interval during which the animal may remain in the dark following the exposure, is certainly not a time during which nothing happens. We may be sure that a process takes place during the latent period which is in some way a vital link in the chain of events between the incidence of the light and the appearance of the response. Whatever this process may be, we can consider its velocity as proportional to the reciprocal of the duration of the latent period. When this is done, we find that the velocity of the latent period process is a linear function of the duration of the initial exposure to light.

During the exposure we know that the photosensitive substance S is decomposed. We may assume that for these extremely small exposures, the photochemical effect is directly proportional to the time of action of the light. It therefore follows that the velocity of the latent period process is a linear function of the photochemical effect during the exposure. In other words, the velocity of the latent period reaction is directly proportional to the concentration of freshly formed precursor substances P and A.

Such a relationship may be explained in several ways. The one finally chosen assumes that during the latent period an inert substance, L, is changed into a chemically active material, T, which then acts upon the nerve to produce the outgoing sensory impulse. This reaction, $L \rightarrow T$, is catalyzed by the presence of the freshly formed photochemical decomposition products, P and A, formed during the exposure to the light. The linear relation between velocity of reaction and concentration of catalyst is a very common one in catalyzed reactions.

In terms of this conception the latent period assumes a position of prime importance in the photosensory mechanism. The latent period reaction is all set and ready to go, and requires only that the light change S into P and A so that the latter can catalyze the transformation of L into T, which is the end-product of the sensory process. The whole photosensory mechanism may then be summed up in the two reactions

$$S \rightarrow P + A; \quad L\|P + A\| \rightarrow T,$$

in which the symbol $\|P + A\|$ means catalysis by one or both of the precursor substances. The first of the two reactions occurs during the sensitization period; the second during the latent period.

IX

This hypothesis of photoreception is rather concrete. The concreteness of the conceptions has however proved a useful tool in the acquisition of knowledge in this field. Time does not permit the description of experiments designed to test the hypothesis in numerous ways. I can, however, mention just a few to indicate its fruitfulness.

The latent period is assumed to be a simple, chemical reaction, perhaps as hydrolysis or an oxidation. Its behavior with the temperature should therefore follow quantitatively the rule deduced by Arrhenius for the relation between the velocity constant of a reaction and the absolute temperature. This means more than a mere determination of the temperature coefficient for 10 degrees; it means a continuous relationship between temperature and velocity, following certain theoretical considerations. Experiments showed that the reaction $L \rightarrow T$ follows this prediction accurately, and that the value of the constant, $\mu = 19{,}680$, for our reaction is in accord with those usually found for hydrolyses, saponifications, etc., in pure chemistry.

Another test concerns the interrelations between the exposure and the latent period. I have mentioned that the velocity of the latent period reaction is directly proportional to the exposure (t), provided the intensity (I) is kept constant. This may be written

$$V = k_1 t.$$

If now we keep the time of exposure constant and vary the intensity we find that

$$V = k_2 \log I$$

or that the velocity is proportional to the logarithm of the intensity. Ordinary mathematical reasoning indicates that if we combine these two equations—which means experimentally that we vary simultaneously both the time and the intensity—it should be true that

$$V = kt \log I.$$

Experiments prove that this expected relationship indeed holds good.

Still another and perhaps more significant application of the proposed hypothesis has been made. This concerns the dark adaptation of the human eye. A careful analysis of the data of dark adaptation in terms of the principles discovered in these investigations has shown that dark adaptation and protoreception in the human retina are fundamentally similar in principle to the process in *Mya* and *Ciona*. As a result there has been opened up a new field of investigation in retinal photochemistry which may some day enable us to possess a reasonable theory of vision.

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THE MECHANISM OF INJURY AND RECOVERY OF THE CELL[1]

Some of the fundamental ideas of biology are extraordinarily difficult to analyze or define in any precise fashion. This is true of such conceptions as life, vitality, injury, recovery and death. To place these conceptions upon a more definite basis it is necessary to investigate them by quantitative methods. To illustrate this we may consider some experiments which have been made upon *Laminaria*, one of the common kelps of the Atlantic coast.

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[1] Address for the Symposium on General Physiology at the meeting of the American Society of Naturalists, December, 1920.