FACILITATION OF SENSITIZATION OF THE FLEXOR WITHDRAWAL

REFLEX IN THE INTACT AND SPINAL RAT

by

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A Thesis Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF ARTS

In the Graduate College

THE UNIVERSITY OF ARIZONA

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ABSTRACT

Previous evidence indicated that sensitization of
the wiping reflex of the spinal and intact frog was
facilitated, that is its probability increased with repeated
elicitation over days. Similar results have been obtained
with various hind limb reflexes of the spinal cat when
temperature changes were used as stimuli. An attempt was
made in this study to determine whether, over brief periods
of time and relatively short stimulus periods, sensitization
of the flexor withdrawal reflex in the spinal rat to
repeated electric shock would be facilitated during a sub-
sequent series of stimuli. Both spinal and intact rats were
subjected to two 20 minute periods of one stimulus per 25
seconds, the periods being separated by a 25 minute recovery
period. Intact rats were compared to spinal rats to
determine if facilitation of sensitization was dependent on
the fact that animals were intact. Results showed that
facilitation of sensitization during the second block did
not occur in spinal rats but did in intact rats. It was
possible that extraspinal, possibly hormonal, or supra-
spinal neural influence caused this difference.

INTRODUCTION

Numerous behaviors fall under the heading of be-
havioral plasticity (Thompson and Spencer, 1966). The pro-
cedure of pairing two or more functionally different stimuli
produces a complex form of plasticity often described as
conditioning or learning. Repeated presentation of the same
stimulus induces a simple form of plasticity such as adapta-
tion, fatigue, habituation, or sensitization. To investi-
gate the physiological functions which subserve these be-
havioral changes has been one of the major activities of
the physiologist and the psychologist.

In order to achieve a physiological understanding of
these simple and complex forms of plasticity, three basic
biological models can be used. One involves the use of
intact but phylogenetically lower animals with more simple
response mechanisms. The second is to use the organism at
an early developmental and less differentiated stage. The
other is to use in vivo or in vitro portions of the whole
animal. This last category may include the spinal prepara-
tion, the insect limb with its associated ganglia, and even
single cells which have been used to demonstrate an analog
of a behavioral change as complex as operant conditioning.

The reason for the use of various model systems has
been, on the one hand, the less complexity they offer and,

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on the other, the hope that knowledge of their workings can lead to a basic understanding of the behavior of the whole organism. Thus for a given behavioral plasticity, if a causal chain or even a physiological correlate can be determined, we might explain and predict parsimoniously the learning, habitutation, or sensitization attributable to the intact subject.

A deductive logic for the use of biological models would assume the existence of a continuum of complex to simple systems. First observe the stimulus-response relationships belonging to the most complex model and then look for these relationships in less and less complicated models. The aim is to establish the least complex structure necessary for a given behavior to occur while maintaining the same processes as in the intact organism. Using, for example, a specific response plasticity of a limb, study it first in the intact animal, then in the spinal preparation, in groups of cells where possible, and eventually in the simplest models of individual cells and their components. This trend has been followed in general for the classical conditioning paradigm beginning with its discovery in the intact animal, then to its appearance in the limbs of the spinal animal, and subsequently to its localization in a block of interneurons in the cord.

Models would also be useful in studying the intriguing hypothesis that the processes underlying complex

behavioral plasticities such as learning may depend on the more basic or simple processes involved in habituation and sensitization. Increases in response amplitude to an unconditioned stimulus during classical conditioning or increases in response probability to a discriminative stimulus during operant conditioning may be determined by sensitization. Habituation could be, also, the basis for extinction. Only by utilizing models would we be able to differentiate and compare processes too molecular to be distinguished behaviorally.

Studying the characteristics of the simple processes of habituation and sensitization would prepare those interested better to handle questions such as the above. For this reason the present work focused on simple rather than complex processes, specifically sensitization, and on its development in the spinal rat. Before discussing specific questions about sensitization, defined as an increase in response amplitude or frequency induced by the repetition of a uniform stimulus, habituation or a decrement in response must first be mentioned. Habituation, like sensitization, depends only on a repeated stimulus, and because it has been studied much more extensively, it suggests questions to be asked of sensitization.

Thompson and Spencer (1966) provided a summary of parametric data concerning habituation. The repeated application of a stimulus, unless it is very intense,

results in a response decrement of responding which recovers
if the stimulus is withheld. The more rapid the rate of
stimulation the more rapid is habituation. Habituation can
proceed below the zero response level and shows generaliza-
tion to similar or cross modal stimuli. A phenomenon termed
dishabituation occurs when single intense stimuli are given
during habituation resulting in the recovery of the
habituated response. The response changes that occur during
both habituation and dishabituation are altered upon re-
peated application of the conditions used to obtain them.
Habituation occurs faster and the dishabituating stimulus
becomes less effective the more it is used.

The concept of dishabituation as a temporary
destruction of habituation was questioned by Thompson and
Spencer (1966) and was shown to be an independent process
occurring under appropriate conditions, simultaneously with
habituation. They noted that the response amplitude of
the flexion reflex in spinal cats, increased by a single
brief dishabituating shock train, decayed again to prior
habituated levels. This decay was spontaneous and occurred
without further habituating stimuli. Because decay did not
depend on rehabituation it was concluded that an independent
and incremental or sensitizing process occurred which has
its own decay parameters. Sensitization (a term replacing
dishabituation) was shown, like habituation, in most

instances a central rather than a peripheral phenomenon, cf. adaptation or muscle fatigue.

Since these original studies, an ther paradigm has been shown to result in a response increment (Thompson and Spencer, 1966). The procedures employed were very similar to those for developing habituation, with critical differences being in stimulus intensity and frequency. At frequencies which produce habituation, high intensities induce sensitization. With a given stimulus strength low frequencies favor response increments (Groves and Thompson, 1970). This method of producing sensitization by repeated stimuli rather than by a unitary stimulus is at present the most frequently used.

Habituation and sensitization occur in a variety of responses, both behavioral and physiological (Groves and Thompson, 1970). These range from the orienting response, through various limb reflexes measured usually as tension produced or EMG discharge, and into the electrophysiological data obtained from individual neurons. Unlike habituation, which shows an exponential decline, sensitization occurs first as an initial "hump" above the initial response level. This declines with further stimulation but may never reach control levels again if the appropriate stimulus intensity and frequency are maintained.

Once the independence of habituation and sensitization was established questions could be asked as to whether

sensitization would show analogs of any habituation param-
eters. Generalization of sensitization by measurement of
cross modal increases in the tonic excitability provided by
bladder distension were reported by Griffin and Pearson
(1968b). The response to repeated blocks of stimuli
intense enough to produce sensitization has not been studied
directly. Since dishabituation habituates, one expectation
was that sensitization occurring to repeated stimuli should
also habituate. Contrary to this hypothesis was an ob-
servation by Franzisket (1963) that the proportion of
stimuli to which reflex wiping occurred in both spinal and
intact frogs increased the more blocks of stimuli presented.
One stimulus block was given per day. Kozak, Macfarlane,
and Westerman (1962) saw similar increases in the duration
and decreases in latency of various withdrawal reflexes of
the spinal cat to noxious stimuli (heat or cold). Increases
in some aspect of sensitization are suggested at least for
some time periods on the order of days. It is not neces-
sarily true that the facilitation of sensitization ex-
cludes habituation of sensitization. There may be a more
rapid decrease after the initial hump appears but this peak
or hump may reach higher levels with subsequent blocks of
trials. It could also be possible that a facilitation of
sensitization is only a long term process requiring long
intervals of hours or days between blocks of stimuli, and
may itself be a form of temporal conditioning. The

intention of the present study, however, is to look at the course of response increments (sensitization) with relatively brief intervals between blocks of stimuli to determine if facilitation or habituation of sensitization over these short periods will occur. This was attempted using the withdrawal reflex of the spinal rat.

As in any situation where we wish to generalize processes from simple to complex structures a certain amount of care is necessary. Irwin (1972) has indicated that we often search for a physiological correlate of behavior where it is easiest to do so such as on the level of enzymatic activity or in the alteration of nucleic acids. These he suggests may mislead because they are oversimplifications in the sense that the change that we are looking for may be on the level of cell group interactions, for example changes in patterns of inhibition and facilitation of neuron firing. This kind of problem can be reduced by making sure that a phenomenon is produced fully in the more simple as well as the more complex models used. With this approach the entire system required for a change rather than only part of it would be studied. To this end the present study compared intact rats with their spinal counterparts.

On the basis of the obtained results conclusions would be made regarding the use of more simple procedures which induce sensitization and habituation, and less complex

models to explain these plasticities or learning in the intact animal.

METHOD

A total of six adult male albino rats weighing from 175 to 250 grams were used throughout the various phases of the experiment. They were maintained on ad lib water and food.

Approximately one hour prior to testing stimulating electrodes consisting of 32 gauge stranded steel wire were sutured into the skin on the bottom of the heel of the right or left hind foot 3 to 4 mm. apart. Surgery was performed while the animals were under ether anesthesia. The resistance between the two electrodes, once they were in place, ranged from 10K to 15K ohms depending upon the subject. Immediately after placement, the electrodes were secured into place and all exposed metal insulated with General Electric silicone sealant. About ½ hour was allowed for recovery from the ether before any stimuli were presented.

Surgery for the spinal subjects, using ether as anesthesia, involved exposure and removal of the dorsal spinous process of T10 without cutting the dura. A suture was placed around the exposed spinal cord and pulled tight but without cutting it. This was followed by actual sectioning of the cord just below this point with scissors. Two weeks for one and three weeks for the other subject were allowed for recovery.

The single intact chloralosed animal (100 mg/kg one hour prior to testing) was included to explore the possibility of removing "emotional" but not necessarily all supra-spinal components of the intact subjects' response. However numerous respiratory problems occurred and very little data uncontaminated by this problem were obtained.

During the test periods each subject was restrained in a wire mesh tube adjustable to the length of the animal and closed at both ends. Both hind limbs extended through holes large enough to allow free movement of the limb. For all intact subjects the leg not being observed was held in its resting position with masking tape to prevent it from interfering with the movement of the leg being tested.

Just above the foot a counterbalanced lever was attached to the leg and at the point of attachment was padded with plastic foam. The lever was then passed through a ball bearing pivot and its other end was attached to a vane which passed vertically over a photocell. In this way the amount of light incident to the photocell was a direct function of the movement of the leg. The voltage output of this device was amplified and recorded on a Grass model 5 DC amplifier and pen recorder. It was necessary to weight the leg in order to reduce the total excursion of the reflex and to force the limb back to the same resting position between stimuli. This was accomplished by hanging lead weights from the lever in the same vertical plane as leg movement. A

stop was placed in a position to prevent the weight from continually exerting a force on the limb at rest. For the intact unanesthetized animals 64 grams were used. Only 31 grams were required for the spinal subjects and no weights were used for the intact chloralosed subject. Relative to the intact animals, less weight was used for the later two treatments due to the lower tension produced by the stimulus.

The stimuli, presented at a rate of 1 per 25 seconds, were obtained from a Grass model S4 stimulator held at a constant voltage that differed with treatment. For each of the three intact subjects stimulus intensity was 48V, for the chloralosed subject 96V, and for the spinal subjects the maximum output of the stimulator was used, 144V. These different voltages were necessary in order to obtain some sensitization from each preparation.

Sensitization was operationally defined as a response increment at some point during the first block of stimuli relative to the average of the responses to the first five stimuli. In order to achieve this increase different stimulus intensities were needed. For the intact group 48V or from 3.5 to 5.0 ma. was sufficient but for spinal animals an intensity of 144V or 10.5 to 15.0 ma. was necessary. An intermediate intensity of 96V (approximately 9.0 ma.) produced sensitization in the chloralosed subject. All of these were minimum values required for the reliable

production of sensitization. Below these habituation, or a decrement only, was generally observed.

Electrode resistance was measured at random intervals during testing and was found to drop approximately 15% during repeated stimulation. This problem is considered in the discussion. For each subject regardless of treatment, a series of from 5 to 10 low intensity stimuli (0.5 to 15V) were presented to determine threshold before and immediately after each block of sensitizing stimuli. During the single test period two blocks of trials were given to every subject with 50 stimuli per block. A 25 minute recovery period was given between blocks. During this time electrode resistance recovered to or close to its original level. The latency and duration of the first three responses to the sensitizing stimuli of all subjects were recorded at a high paper speed to allow comparison of these data between groups.

RESULTS

The main difference between the individual flexion responses of the intact and spinal subjects occurred in the amplitude of the response. The range of movement for all three intact animals was from 0.4-2.8 cm. with 64 grams opposing flexion while the spinal group lifting only 31 grams had a range from 0.0-1.05 cm. For comparison the subject maintained under chloralose anesthesia with no additional weight would respond with a movement of between 0.1-1.5 cm.

For both the intact and the spinal groups each response consisted of multiple contractions or response peaks before relaxation. Chloralose reduced the number of peaks in the intact animal to only one brief flexion. Because of this response multiplicity only the magnitude of the first peak was used for graphical representation and data analysis. The latency to this first response after each of first five stimuli for all but the chloralosed subject (where the paper speed was too slow to allow accurate measurement) was from 28 to 54 msec. The total duration of movement for intact and spinal groups was at least one and usually no more than two seconds for these same initial responses.

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The form of each response curve is generally the same within the spinal or intact group but quite different between groups (Figures 1 and 2). Not only was there a maintained increment in responding over both blocks for the intact animals relative to the spinal and anesthetized subjects, but the former group showed a more complex pattern involving drops (valleys) and rises (peaks) in responding over repeated stimuli. The order of occurrence of these points was consistent from subject to subject but they did not necessarily occur during the same five-response average. A visual comparison of seven distinct points, each as marked in Figure 2, could be made. The control point was the average of the first five responses. This was followed by a drop (#2) then a peak (#3) or response maximum. The final five response average in the first block was considered point 4. In the second block, the first five responses were point 5 then a second peak was #6 with the average of the last five to be #7.

The responses of the spinal (Figure 2) and of the chloralosed (Figure 3) showed much less change over time and what change did occur was more rapid. For this reason all responses are provided in these figures. No statistical analysis was performed for these data.
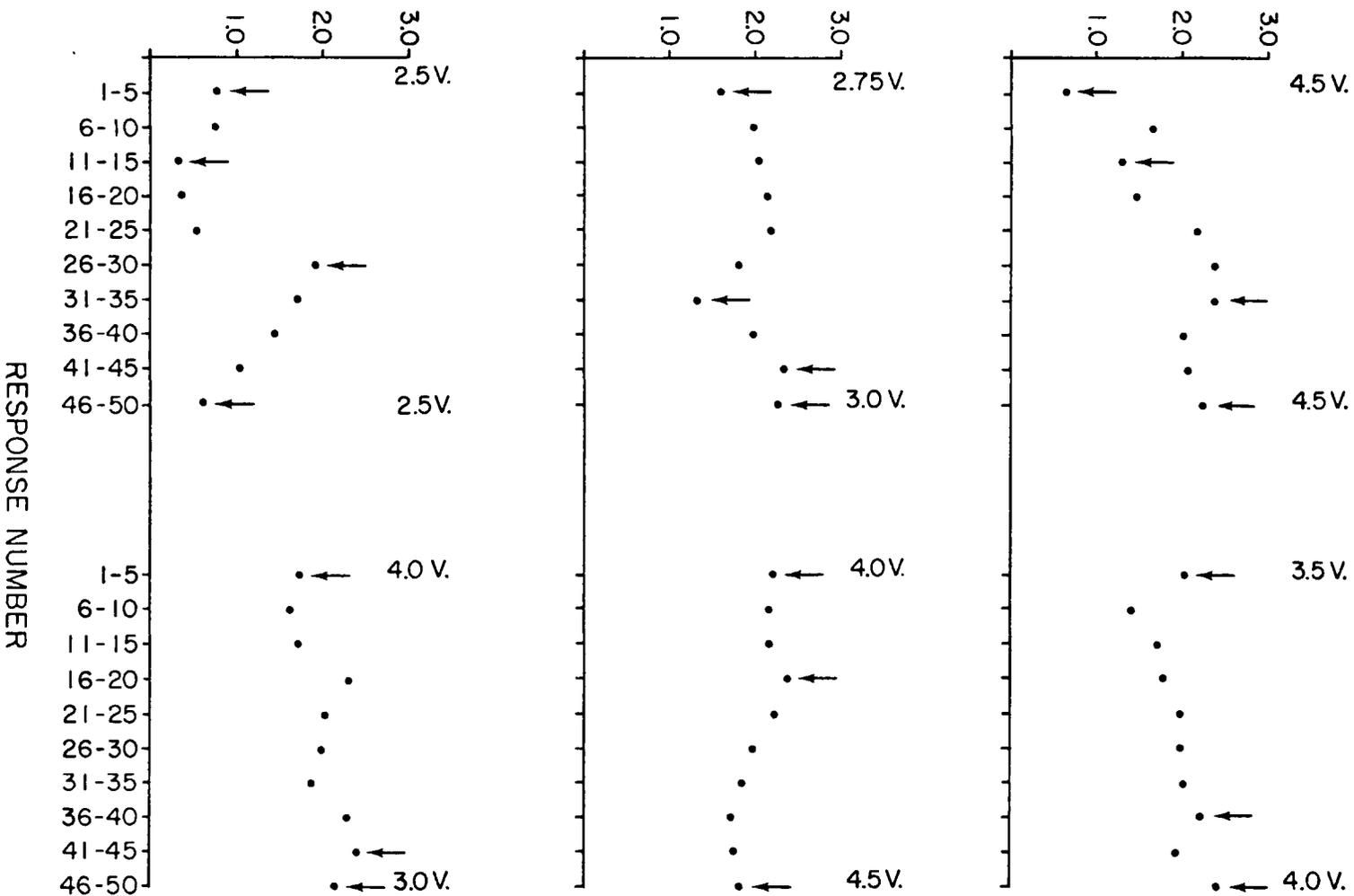
Figure 1. Response averages for the three intact subjects including threshold voltage before and after each block of 50 stimuli -- The arrows indicate the points discussed in the text.
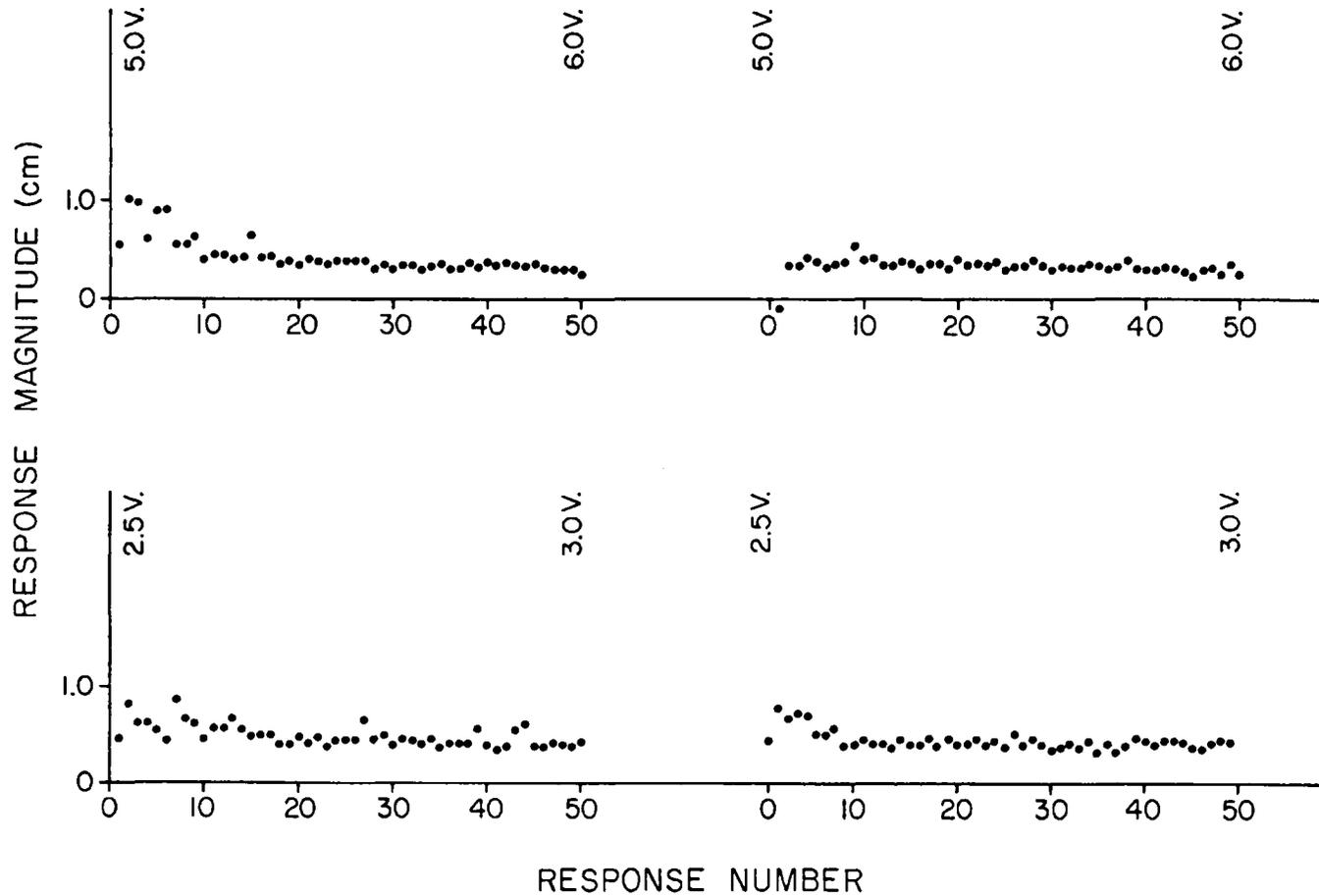
Figure 2.   The magnitude of each response (cm.) for the transected subjects
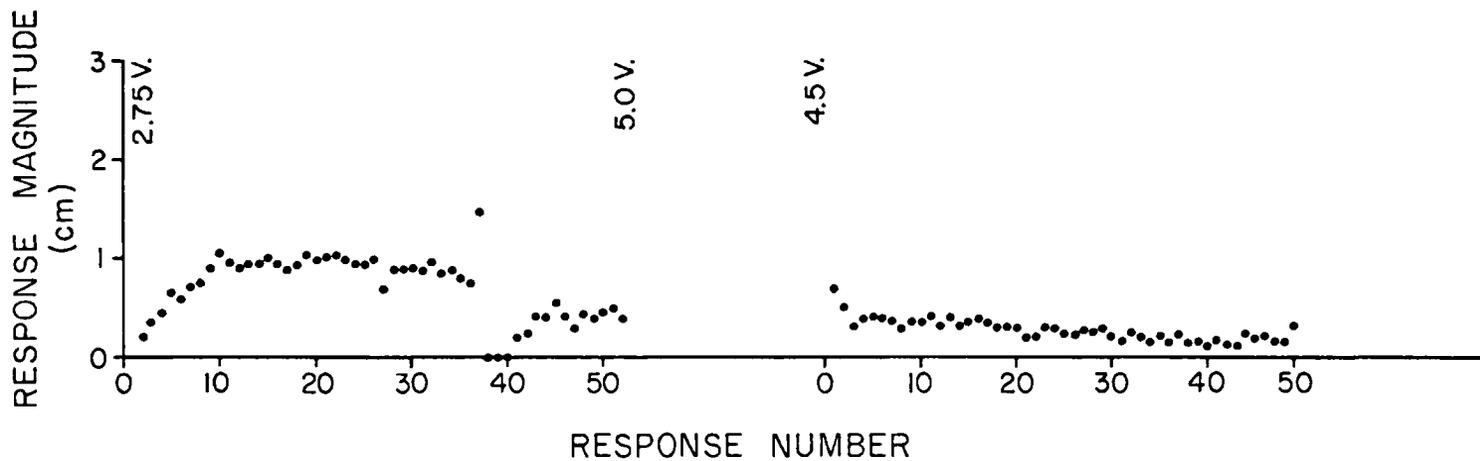including threshold voltage before and after each block.

Figure 3. The magnitude of each response (cm.) for the chloralose anesthetized subject including threshold values -- The sudden drop during the first session occurred when breathing was hampered.

DISCUSSION

Stimulus Problems

The stimulus may have become more effective in producing responses as it was repeated. As mentioned in the method section a decrease occurred in subject resistance while the stimulator held voltage constant and thus current levels were able to increase. The importance of this variable relative to that resulting from other factors must be assessed. The initial increment (sensitization) might be due simply to the increase in current level. With a gradually increasing stimulus, presumably the result of gradually decreasing resistance, response strength should increase. Even with this slowly increasing current baseline other changes both as decrements and increments were observed. The original subject resistance recovered over the 25 minute period between blocks of stimuli and so should not have been the cause of the increased flexion responses seen at the beginning of the second block. Additional support for this idea was derived from the fact that sensitivity as defined by threshold was actually reduced at the beginning of the second block. That is, threshold voltage for all but one intact subject was the same or higher at the beginning of the second block as compared to the beginning of the first block. It seems

justifiable therefore, to attribute these changes to factors
other than a simple change of stimulation parameters.

Intact vs. Spinal Subjects: Magnitude of Individual Responses

One of the most obvious differences between the
intact and spinal animals was the decreased magnitude,
relative to the intact group, of response for the spinal
group. This finding was in agreement with the hypo-
reflexivity to skin stimuli observed by Kozak and Westerman
(1966) in the 2 to 4 week post operative spinal cat. Only
after longer recovery periods of months were these
reflexes, which included various flexion responses, seen to
become normal. Also in accord with the present findings
were the data that the number of stimuli required to
habituate the flexion response was greater for intact than
for spinal rats transected 4 to 12 days earlier (Griffin
and Pearson, 1967).

Griffin and Pearson (1967) and Pearson and Wenkstern
(1971) both reported a significant decrease in the reflex,
the tension developed, and duration of EMG discharge, after
100 stimuli in intact rats. They used implanted skin
electrodes with stimulus parameters of 20 ma., 5 msec.
pulses at a frequency of 1 per 10 seconds. After 50 stimuli
a slight decrement was observed in EMG response latency with
very little change in tension and EMG discharge duration.
This result is in opposition to the present data where

significant increases were observed with a much lower
stimulus intensity (approximately 5 ma. at 50V) by the end
of the first 50 stimulus block. However it was possible
that at high enough stimulus levels a maximum is achieved
during the first few elicited responses and could subse-
quently only decrease. Since lower intensity stimuli were
used in the present experiment such a ceiling effect would
not have interfered with possible response increases.
Another possible cause of the maintained response increase
observed in Figure 1 may have been due to any treatment of
the subjects which increased their excitability. During the
present study the subjects were brought to the testing room
and restrained while still anesthetized. The room itself
was isolated from extraneous light and noise.

The obtained increase in response magnitude over
time for intact animals as opposed to the decrease dis-
cussed above, may have been due to a differential stimula-
tion of skin tissue or to changes in the type of nerve
being stimulated as the experiment proceeded.

Since studies measuring the flexor withdrawal reflex
quite often used electrical stimulation at intensities as
high as 20 ma. (Griffin and Pearson, 1968a; Pearson and
Wenkstern, 1971), a further question arises as to how wide-
spread throughout the tissue were the stimulus effects.
The stimulation of pieces of skin or whole nerves results
in the activity of sensory paths serving different reflexes

and, furthermore, with high intensities both low and high threshold neurons would be fired. This complicates the problem of the exact locus and mechanism for any plasticity observed and is a prime reason for the use of even less complicated models. These problems, though recognized, are generally not taken into account. In spite of this lack, work on a molar level is justifiable on the basis of the consistency and generality of the phenomenon of sensitization. Franzisket (1963) and Kozak et al. (1962) have observed sensitization, measured as an increase in probability of response, to stimuli less traumatic than shock (such as temperature, scratching, or rubbing). An initial hump in the amplitude of repeatedly elicited startle responses has also been shown (Groves and Thompson, 1970), showing that the sensitization phenomenon is not specific to the isolated cord. But the effects of interactions between these stimulus consequences and more involved procedures as required in searching for possible bilateral transfer of sensitization or even the effects of repeated production of sensitization are unknown.

Intact vs. Spinal Subjects: The Process of Sensitization

Figure 2 depicts each individual response obtained from the two spinal animals. In spite of the increased stimulus strength required to obtain a response there was only a brief initial period of oscillation and response

increase. The weak sensitization was followed by a con-
sistent and smooth decrease or habituation. During the
second block the form of responding showed none of the
maintained amplitude found in the intact subjects. If any
second block sensitization occurred it could be observed
only for subject #2 but decreased rapidly and never attained
greater strength than any response of the first block.
Since responding during the second block was almost imme-
diately at the same level as at the end of the first block,
apparently when habituation is once established in the cord
it has a longer lasting effect than concurrently induced
sensitization. This was true at least for the present
experimental conditions.

A question exists about the nature of the peaks and
valleys over repeated responding for intact subjects. In
the relatively gross behavioral system employed they could
be attributed to differential sensitization or activity
among the various flexors activated, which for some reason
is dependent on the integrity of the cord. Other literature
has suggested that this multiplicity of response might
occur in spinal animals, but if it has it has not generally
been reported. Kozak et al. (1962) indicated that syn-
chronous volleys in many nerve fibers elicited by shock can
produce an unexpected mixture of reflexes over time. Egger,
Adams, Bishop, and Cone (1973) saw, while studying plantar
cushion reflexes of the spinal cat at the ventral root, an

increase in response superimposed on the habituation
occurring after the initial sensitization hump.

Significance of Cord Damage and
Extra-Spinal Influences

Three major, though not necessarily exhaustive,
hypotheses could be offered to explain the difference
between the spinal and intact groups. Cord damage, supra-
spinal neural influence, and hormonal factors are all viable
explanations for failure to obtain second block facilitation
of responding in the spinal model.

It could be argued that transection damaged the cord
and hindered its ability to respond in a normal manner.
This conjecture is indirectly supported by the fact that
spinal animals never responded as strongly as the intact
group. However both transections were carried out at a
level high enough to avoid direct mechanical damage to the
lumbar cord and flexor withdrawal reflexes were obtained by
a toe pinch 30 minutes after transection. Another factor
against a damage hypothesis includes the observation that
some increment in response magnitude was followed by a
decrement in the spinal and chloralose anesthetized animal.
Damage and anesthetic appeared to reduce response strength
but not the ability to manifest at least some reflex
plasticity.

Lloyd (1941) noted that a conditioning shock to the
pyramidal tract (weak enough to cause no measurable ventral

root potential) facilitated the subsequent monosynaptic
ventral root discharge, reflecting activity of alpha motor
neurons, elicited by stimulation of dorsal root gamma
afferents. Later, due largely to the work of Lundberg and
his associates (Lundberg, 1964; Lundberg and Voorhoeve,
1962; also Patton and Amassian, 1960), some of the functional
effects of pyramidal activity of reflex paths have been
determined. This information could provide a possible basis
for the enhancement of spinal reflexes as a function of
pyramidal activity. Any stress or agitation developed by
the intact subjects as a result of their capability to feel
the stimulus shock could activate cortical or other supra-
spinal influences.

In general Lundberg (1964) indicated that in cats
stimulation of the pyramidal tracts, specifically cortico-
spinal via cortical stimulation, produced facilitation of
all polysynaptic excitatory and inhibitory spinal reflexes
studied. Thus a given reflex could be inhibited or
facilitated depending upon the specific interaction cortico-
spinal activity had with that reflex system. If the state
of the organism, such as increased "emotionality" presumed
to result from intense stimuli, a variable more relevant to
intact rather than spinal subjects, did vary then cortically
modulated pyramidal activity provides a mechanism for
modifying ongoing spinal reflexes. Unfortunately, pyramidal
activity has yet to be correlated with emotional states. In

terms of actual facilitation of reflexes rather than in-
hibition applicable to the present study, Lundberg and
Voorhoeve (1962) have made one relevant conclusion. With
supraliminal cortical stimulation, or that which is strong
enough to produce alpha motoneuron activity, excitatory
actions often dominated in flexor motoneurons and inhibitory
ones in extensor motoneurons. If the cortex were active in
a comparable way by the present conditions flexor responses
should be enhanced. Griffin and Pearson (1968b) did show
that the frontal cortex influences the development of
habituation of the flexor withdrawal reflex (duration of EMG
discharge). This reflex in rats occurred more slowly with
bilateral lesions of the frontal cortex than in intact rats,
or rats with unilateral lesions of the frontal cortex or
bilateral lesions of the somato-sensory cortex. What role
this area has on the development of sensitization is unknown.

Granit and Kaada (1952) have shown that output from
the cerebellum can influence both alpha and gamma spinal
motoneurons. Extrapyramidal influence is available from
other regions especially the reticular formation, the red
nucleus, and Dieter's nucleus acting respectively via the
reticulospinal, rubrospinal, and vestibulospinal tracts.
Magoun and Rhine (1946) observed inhibition and excitation
of stretch and flexion reflexes produced respectively by a
muscle tap or pinch as a result of electrical stimulation
of the reticular formation. Again the activity of these

systems have not been correlated with the emotional or activational states of the animals during the present experiment so the above can only be suggestive. It would be interesting behaviorally to induce operationally defined emotional states and study aspects of pyramidal activity as well as effect on the spinal reflex. Noting the importance of the pyramidal tract essentially in primates where mono-synaptic connections with alpha motoneurons are made, be-havioral studies using subliminal rather than supraliminal (see Lundberg and Voorhoeve, 1962) pyramidal stimulation during learned or operant extensions and flexions could be performed.

Another major influence could be through endocrine activity including the release of adrenal corticoids, catecholamines, and ACTH. While studying the blood plasma levels of epinephrine and norepinephrine, Mason, Brady, and Tolson (1966) noticed small increases for both of these hormones during free shock or horn sounding. These changes occurred within 10 minutes. Davson and Eggleton (1968) indicated that these catecholamines are released almost immediately by action of the splanchnics when "stressors" are applied. From Rothballer (1959) who reviewed the effects of catecholamines on the central nervous system, the following information can be emphasized. The stimula-tion of peripheral sympathetics or application of epine-phrine or norepinephrine to frog skin lowers threshold and

slows adaptation of tactile receptors. Regarding muscle, epinephrine can produce a 5% to 20% increase in the contractile force even in non-fatigued skeletal muscle with the effect appearing to be direct. Under certain conditions epinephrine will enhance conduction in peripheral nerves. Finally, Rothballer suggests that a certain baseline level of epinephrine is important in facilitating the action of acetylcholine but that large supraphysiological doses have the opposite effect. Furthermore the facilitory effect of epinephrine appeared to be specific to certain reflexes, in particular extensor reflexes. However, Curtis, Eccles, and Eccles (1957) found very little effect of epinephrine or norepinephrine on cord activity.

The effects of ACTH are similarly equivocal. Though it is released rapidly (10 seconds) to physiological stimuli (Gray and Munson, 1951), Nicolov (1967) showed that the IM injection of 2U/kg ACTH in intact dogs produced an increase in electrical activity of the cord within 15 minutes. In contrast, Krivoy and Guillemin (1961) saw no action of 50μg/kg IV ACTH to the spinal cat on ventral root potentials evoked by stimulation of the dorsal root.

Even though the precise effects of these hormones on cord reflexes has not been determined, there were activities described relating to receptor, cord, and muscle function which could have been involved in any stressful situation. The intact subjects in this experiment would be

subject more than the spinal group to these effects since stress resulting from foot shock has the entire CNS available through which hormonal release can be mediated. The only evidence that stress was developed was that the intact animals about half way through the first block of stimuli began to vocalize in response to each stimulus while spinal subjects were quiet. The similarities between this proposed hormonal facilitation of reflexes and neuronal sensitization are striking and call for further study.

In summary, it has been shown that in the intact preparation a sensitization of the flexor withdrawal reflex developed during a block of 50 stimuli and that during a subsequent block this increased response recovered quickly or was maintained. With spinal animals, on the other hand, sensitization was developed only with a much higher stimulus strength, and no such second elevation was obtained. These results suggest two main conclusions. First, accepting the previously mentioned findings of long term increments, this type of response increase does not appear with brief stimulation and recovery periods but only over repeated daily sessions with long recovery periods. Secondly, extraspinal influences, possibly either supraspinal or hormonal, developed to maintain the intact unanesthetized subject's response magnitude. Sensitization, which can be facilitated over a short period of time, may be a property of the intact animal only and not of the isolated spinal cord.

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