Autonomic Correlates of Conditioned Changes Generated by an Explicitly Unpaired Procedure

by

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Introduction

Overview of classically conditioned heart rate

Classical conditioning of the cardiovascular system has been a popular area of interest for the last two decades in psychology and physiology. Divergent findings concerning the direction of cardiovascular responses have caused some controversy about the parameters and interpretations of studies in this area. The heart rate (HR) conditioned response (CR) based on a shock unconditioned stimulus (US) can take different forms (Fitzgerald & Teyler, 1970). Some of this variation may be linked to the different species examined, as accelleratory CRs have frequently been seen in pigeons (Cohen & Durkovic, 1966), dogs (Black, Carlson & Solomon, 1962) and monkeys (Klose,Augenstein, Schneiderman, Manas, Abrams, & Bloom,1975) and deceleratory CRs have been observed in rats (Fitzgerald & Teyler, 1970), cats (Hein, 1969; Howard , Obrist, Gaebelein, & Galosy, 1974) and rabbits (Schneiderman, VanDercar, Yehle, Manning, Golden & Schneiderman, 1969). It has been suggested (Kazis, Milligan, & Powell, 1973; Teyler, 1971) that direction of HR CRs may be related to differences in the kinds of adaptive behavior different animals exhibit in response to danger. Animals such as rabbits or rats, which show freezing in response to stress might be expected to show decelerative HR CRS, whereas animals which show flight or attack behavior are more likely to show accelerative CRs.

Opposing HR CRs within the same species have been found to occur with a shock US. Black, Carlson and Solomon (1962) and Dykman, Gantt,

and Whitehorn (1956) reported decelerative CRs and accelerative CRs in dogs. Similar differences have been seen in rats (Black & Black, 1967; Bloch & LaGarrigue, 1968; Teyler, 1971; Martin & Fitzgerald,1981) although in restrained rats the direction of the HR CR has uniformly been decelerative (Fitzgerald, Martin & O'Brien, 1973). However, that restrained rats sometimes show accelerative HR responding to a CS has also been reported (Cunningham, Fitzgerald and Francisco, 1977). For example, in a recent investigation, rats showed a decelerative HR CR to a CS regularly paired with a shock US and then HR acceleration to a different nonreinforced CS that was given in an explicitly unpaired relationship with the shock US (Cunningham, et al, 1977). To account for the opposing HR responses the authors suggested that the HR deceleration reflected the action of an excitatory conditioning process and the HR acceleration, a separate and distinct conditioned inhibitory process. The broad objective of the current study was to provide additional information on the Cunningham, et al. hypothesis by determining whether the opposite HR responses are mediated by different segments of the autonomic nervous system. If so, this information would provide evidence in support for the notion that there are two separate systems underlying the responses seen to a CS+ and those seen to a CS-.

The nature of conditioned inhibition

Rescorla (1966, 1967, 1968, 1969) defined conditioned inhibitors as those stimuli which through a particular relationship with the US acquire the capacity to control a response tendency opposite to that occurring to a stimulus having a history of excitatory conditioning.

the salient points of these criteria are that the (inhibitory) experience must be with the same US as that forming the basis for the conditioned excitor and the tendency controlled by the supposed conditioned inhibitor must be opposite to that controlled by the conditioned excitor.

Rescorla (1975), in later writings concerning inhibition, stressed the importance of the background with which the inhibition must be measured. He noted that..."the identification of a stimulus as an inhibitor requires the presence of something to inhibit. In the absence of excitation one would not necessarily expect an inhibitor to have an effect identifiably different from that of an untrained, neutral stimulus." Broadly speaking, Rescorla's formulation was an extrapolation of what Pavlov (1927) proposed many years before. Pavlov's "conditioned inhibtion" however, referred to inhibition acquired as a result of a particular paradigm, while Rescorla used "conditioned inhibition" synonymously with learned inhibition.

Traditionally, many learning theorists have ascribed to the "pair-inf" viewpoint of classical conditioning, which holds that it is the contiguous presentation of both the CS and US that forms the association that leads to excitatory conditioning. Rescorla (1966, 1967, 1968, 1969a and b) contended that it was the existence of a positive contingency between the CS+ and US rather than the contiguous presentation of the two stimuli that produced learning. For him, the CS+ signals the occurrence of the US. Furthermore, the probability of a US is greater following CS onset than at any other time. Similarly, operations involving a negative contingency between a CS (CS-) and US were thought to result in the development of an inhibitory tendency.

In these cases, the CS- signals the nonoccurrence of shock, as US probability is greater in the absence of the CS- than in its presence.

Procedures that may lead to the development of conditioned inhibition due to the presence of a negative contingency include four basic paradigms: Pavlov's "conditioned inhibition" paradigm, backward conditioning, discrimination training, and the explicitly unpaired "control" procedure. In the review that follows, classical conditioning studies bearing on the issue of conditioned inhibition will be grouped according to these four paradigms. No attempt will be made to survey transfer-type experiments in which classical conditioning manipulations are assessed in the context of ongoing instrumental behaviors.

Typically, tests of inhibition have been restricted to such procedures as summation (combined-cue) or retardation of conditioning (Hearst, 1972). In the summation test, the CS- and CS+ are presented together and inhibition is claimed if responding to the combination is less than would normally occur to CS+ presented by itself. Retardation of acquistion refers to the impaired development of a CR to a former CS- that is now regularly paired with a US.

Inhibition has also been measured using reactions that go in opposite directions. In his 1975 book, Gray reviewed the Soviet literature and reported several uses of the "reaction-of-the-reverse-sign", which he described as opposing reactions elicited by a given CS. He cited a study by Bunyatyan (1952), in which an increase in blood glucose was conditioned to a CS. Later during extinction the response changed to a decrease in blood glucose.

Ilina (1959) also noted a reaction-of-the-reverse-sign. In this study a flash of light directed toward the dark-adapted eyes of human

subjects was used as a US. After conditioning, a CS came to elicit an increase in the absolute visual threshold of the photochemical conditioned reflex. Ilina found a decrease in this threshold when the subjects were presented with an extinguished or differential CS.

Gray also cited a study done by Rescorla and LoLordo (1965) in which the reaction-of-the-reverse-sign was inherent in the procedure but not acknowledged as such. The response measure was Sidman avoidance in rats in a shuttlebox situation. The data demonstrated a decrease in the rate of avoidance responding to the CS- and an increase to the CS+. In some respects, reverse-sign reactions are similar to the opposing HR responses that occurred to CS+ and CS- in the Cunningham, et al. (1977) study.

As will become clear in the review of studies that follows, special tests for the presence of inhibition (summation, reversal) have not always been employed. This is especially true of earlier work carried out in Pavlov's laboratory. Nevertheless, such studies have been included to provide a historical perspective on the question of conitioned inhibition. Many of the discrimination experiments that will be mentioned here did not involve tests of inhibition but do provide information on the question of response direction to a regularly reinforced CS+ as opposed to a consistently nonreinforced CS-.

Conditioned Inhibition studies

Pavlov (1927) described conditioned inhibition as a case of differential inhibition in which a compound stimulus is not reinforced after reinforcing singly one of the components. As a result of the procedure, the previously reinforced stimulus loses some of its positive

effect. Pavlov detailed numerous examples of the procedure. A typical example was an experiment executed by Nikolaev. An alimentary conditioned reflex was established to a rotating object (CS+). When the CS+ was combined with a tone and not reinforced there was a weakening of the salivary response as compared to the previous response. This scheme has been repeated exhaustively with various modifications by other Soviet investigators.

Frolov found a diminution of the conditioned salivation response after continued nonreinforced presentations of a metronome CS+ in tandem with a second stimulus. There initially was no reduction to the presentation of the CS+ and CS-. The CS- appeared to develop inhibitory properties as a result of repetitions without reinforcement. Another study by Kasherininova, found similar results. One dog was trained to salivate to a tactile stimulus which resulted in a response of 29 drops of saliva. After 25 nonreinforced presentations of this stimulus in combination with a metronome stimulus, only three drops of saliva were elicited by the stimulus combination. Pavlov (1927) cited other studies carried out by Krjyshkovski, Leporsky, Ponisvosky, Babkin, and Chebotareva which had similar results.

In more recent work (Szwejkowska & Konorski, 1959) salivary CRs were established in two dogs to a CS+, which was a bell combined with bubbling water. When this stimulus compound was presented in tandem with a metronome and whistle without reinforcement, there was a 50% diminution in responding.

Marchant, Mis and Moore (1972) utilized three CSs in a conditioned inhibitory paradigm of the rabbit nictitating memebrane response (NMR).

A light (CS_1) was paired with shock, while the light presented along with a tone (CS_2) was not. The third CS (CS_3) was presented as a control, randomly. The test phase consisted of nonreinforced presentations of the three CSs and pairwise combinations of these stimuli (CS_1CS_2, CS_2CS_3, CS_1CS_3). It was determined that the combinations of the inhibitory CS_2 (tone) and the control stimulus (CS_3) had less of an effect on the eyelid CR than the control stimulus presented alone. The authors proposed that this was due to the active inhibitory properties of the third CS.

Rescorla, Wagner and colleagues (cited in Rescorla & Wagner, 1972) also examined conditioned inhibition in the context of the rabbit nictitating membrane response. Their results suggested that the addition of a nonreinforced stimulus led to the generation of inhibitory tendencies. Furthermore, the authors found that the amount of inhibitory potential accruing to the inhbitory stimulus was a function of of the associative strength that was established to the excitatory stimului.

Other recent investigators have reported differentiation in responding due to a conditioned inhibition procedure (Giavelli, Astorga, & Santibanez, 1977; Diaz, Rossel, & Santibanez, 1969), with the HR changes to the inhibitory combination being in the same direction but of lesser magnitude than the HR CR to the excitatory stimulus. In both cases cats received presentations of a CS+ (tone of 500 Hz) reinforced with a paw shock US, nonreinforced trials of a CS- (tone of 1000 Hz), and nonreinforced pairings of the two stimuli presented in tandem. In both cases, subjects were found to respond to the CS+

with a deceleration in HR. A cardiodeceleration was also noted to the CS- and the inhibitory combination, but it was of lesser magnitude.

Backward Conditioning

Another procedure that has been used in studies of inhibition is backward conditioning.

Razran (1956) defined backward conditioning as a technique in which the CS is activated a short time after the US. The activation of the CS may occur a short time after the cessation of the action of the US or a short time after the beginning of such action. Kimble (1961) had stated that with only one or two exceptions, attempts at backward conditioning have met with little success and that the small amount which does occur is probably the result of pseudoconditioning rather than the development of a true conditioned association between the CS and US. It has also been suggested that the backward conditioning procedure leads to the acquistion of inhibitory characteristics (Razran, 1956; Kimble, 1961; Pavlov, 1927).

Pavlov (1927) found that in the training of a salivary CR in dogs, hundreds of backward reinforcements did not appear to have any facilitory or inhibitory effects when the backward CSs were applied simultaneously or in close succession to CSs of the previously developed forward CRs. Pavlov was in favor of a closer examination of the backward conditioning phenomenon as he believed that stimuli which do not become conditioned quickly acquire inhibitory tendencies.

Razran (1956) reviewed the literature up to 1956 and concluded that some claims of inhibitory properties accruing to CSs in the backward conditioning procedure have not been born out. He cites a

study by Anokhin (1927) on dogs in which five backward light combinations greatly reduced the forward CR to the light and considerably reduced the CRs to two other CSs. Seven backward trials with a different CS however, had no such effect. The investigator concluded that the light being a weaker CS, naturally induced a greater amount of inhibition.

Also cited was a study by Podkopayev (1928) in which backward light combinations presented to two dogs inhibited the subsequent formation of a former CR to the light. Lastly, work by Rite, in 1928, was reviewed. After forming forward CRs in dogs to some CSs, the investigator next reversed the order of the presentation of the stimuli using the same CS, then tried the forward order again. Rite found that the backward combinations did not completely abolish the forward CRs to the same CSs but that the magnitude of the forward CRs was reduced. Backward conditioning had no effect on subsequent formation of forward CRs to the same CSs.

From a perusal of studies done later in this time period, Razran concluded that backward conditioning was a genuine CR associative phenomenon that was obtainable and maintainable under special conditions (regarding CS strength and length of delay between US and CS). Razran cited studies by Petrova (1933) and Stroganov (1940) in which the CS after backward conditioning presentations appeared to develop inhibitory properties.

In an experiment described by Siegel and Domjan (1971), rabbits in one group were given 550 presentations of CSs and USs in a backward fashion before receiving 50 paired presentations of these same stimulus elements. This backward conditioning group had the slowest

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developemtn of the eyelid closure CR in the paired training phase as compared to other groups that received either 550 preexposures of the CS, 550 preexposures of the US, both the CS and US randomly, or neither the CS or US. It was suggested that stimuli negatively correlated with the US (as in the backward conditioning group) acquire active inhibitory conditioning.

In a later study by the same group (Siegel & Domjan, 1974), rabbits received preexposures of backward conditioning trials of the CS and US (0, 5, 10, 25, or 50 trials) before receiving forward pairings of the stimuli. It was found that acquisition of the eyelid CR was increasingly retarded with greater amounts of backward conditioning preexposures. However, only the two extremes were found to be reliably different.

Plotkin and Oakley (1975) also found that acquisition of the rabbit eyelid CR was retarded as a result of previous backward stimulus presentations and concluded that this retardation may have resulted from conditioned inhibition which developed to the CS.

Discrimination Conditioning

Discrimination (differential) conditioning is a procedure in which CS+ presentations are reinforced by the US, and CS- presentations are not. Rescorla (1969a) suggested that the ..."CS in a differential conditioning paradigm is a special case of a negative CS-US contingency; the probability of the US is lower in the time following CS-onset than at any other time during the session and that ..."it is the negative contingency between the CS and US that is critical". Inherent in this arrangement is a background level of excitatory conditioning, as reinforced conditioning trials (CS+/US) are interspersed randomly

with the nonreinforced trials (CS- alone).

That inhibitory properties can develop to a nonreinforced stimulus in the context of differentiation is suggested by the results of several studies. Konorski and Szwejkowska (1952b) reported evidence that nonreinforced presentations of a CS- which was randomly interspersed with a reinforced CS+ retarded the subsequent acquistion of an excitatory CR to the previously unpaired CS. The authors suggested that the repeated nonreinforced presentations of the CS- endowed that stimulus with strong inhibitory properties.

The studies that follow provide evidence on the question of response direction to CS+ and CS- during classical discrimination conditioning. The experiments were not concerned with the presence or absence of inhibition to CS-, therfore no special tests for inhibition were included.

Yamaguchi and Iwahara (1974) found differences between the HR responses to a CS+ and CS- in rats. While there was no statistical verification of this finding, the authors stated that the control rats, which received differential conditioning without a drug treatment, in general responded to the CS+ by decreasing HR and to the CS- by increasing HR.

In a study executed by Powell and Lipkin (1975), rabbits trained in a discrimination procedure responded to both the CS+ and CS- in a decelerative manner, as measured by percent change from baseline. The deceleration increased in magnitude to the CS+ over acquistion trials, and was found to be reliably different from the decelerative responding to the CS-. During the latter portion of the experiment

however, HR to the CS+ accelerated, until it reached a level well above baseline (3-4% accelerative change) while HR to the CS- remained decelerative (CS- changes averaged about a 2% decrease in rate). The authors reported a significant interaction of stimulus type and sessions suggesting that the change in HR CR topography over sessions was reliable.

Katcher, Solomon, Turner, LoLordo, Overmier and Rescorla (1969) noted opposite responding in one surgically intact control dog in a discrimination paradigm. The dog displayed a cardiodeceleratory overshoot to the CS- which increased over trials, while maintaining an accelerative HR to the CS+ during stimulus onset.

Another recent report (Hoffman, 1978) demonstrated cardiodecelerative HR CRs to a CS+ and a small accelerative-decelerative type of reaction to the CS-. Heart rate accelerations occurred to CS- on early trials, but these reactions were reduced in magnitude as training progressed. In a reversal test, the HR CR to the inhibitory CS- was a consistent cardiodeceleration.

Downs, Cardozo, Schneiderman, Yehle, VanDercar, and Zwilling (1972) gave rabbits discrimination training using two tones of different frequencies as the CSs. Subsequently four stimulus alone trials of both CSs were presented as test trials. Animals in the saline control responded to both conditioned stimuli in a cardiodecelerative manner. Though of similar direction, clear differentiation in responding was noted to the two tones. Opposite responding was not evident anywhere in the procedure.

Similar findings were noted in another study with rabbits (Schneiderman, et al., 1969). Animals responded to both CS+ and CS- in a

cardiodecelerative manner. While the response topography to the individual stimulus elements varied, they were of similar direction, with no opposite responding evident.

Dykman and Gantt (1959) presented two separate tone stimuli, one paired, the other unpaired, with a shock US to one dog. The percentage of HR acceleration to the excitatory CS (CS+) was 100% while to the CS-, it was 53%.

Yehle, Spaulding and Hsiu-Ying (1970) witnessed discrimination of HR responding within the first day of training. Rabbits displayed decelerative CRs to both CS+ and CS- but the response magnitudes were reliably different, percent HR change from baseline to CS- being smaller than that to CS+.

Lockhart and Steinbrecher (1970) reported similar findings to the studies just cited. Rabbits responded to both a CS+ and CS- in a cardiodecelerative manner. Differential responding was found to be significant in groups which received ISI (interstimulus intervals) of 5-sec or .5-sec, but not in the 10-sec treatment.

Church, LoLordo, Overmier, Solomon and Turner (1967) trained curarized dogs in a discrimination procedure. An analysis of variance based on the CR magnitude scores for trials with CS+ and trials with CS- indicated that discriminative responding did occur. On close examination of the figure, it appears that opposite responding in HR occurred to the CS+ and CS- during selected time intervals, for the groups that displayed a low cardiac base rate. Statistical verification of this observation however, was not available. In groups that exhibited medium and high cardiac rates, opposite responding was not in

evidence. Caution should be exercised in interpreting these findings, as all dogs were curarized prior to discrimination training.

Smith and Stebbins (1965) reported differentiation in HR responding to two light stimuli of different colors in five out of six monkeys. It was not clear in the figure which HR tracings were considered the pre-CS baseline, especially since stimulus lights were on for 56 seconds, but it is evident that opposite responding did not occur. In fact, little change in HR to the CS- is indicated in the figure.

In a study examining the HR discrimination conditioning on pigeons (Cohen & Durkovic, 1966) differentiation in responding to two different light stimuli was established but the HR changes were generally accelerative. Cardioacceleration to the CS- was found to be of lesser magnitude than the tachycardic response shown to the CS+.

In an investigation of the relationship of HR conditioned responding and movement in rats (Martin, 1975), it was revealed that discrimination training generated decelerative HR CRs to both CS+ and CS-, the response to the CS+ being of greater magnitude.

Decelerative HR CRs of different magnitudes to CS+ and CS- (with response to CS+ being more pronounced) were also noted in a study on rabbits (VanderCar & Schneiderman, 1967). The response was examined as percent change from prestimulus baseline in the decelerative direction.

Results reported by Lynch (1966) were in accordance with the aforementioned studies. In this experiment, nine dogs were given discrimination training. Because of variability in responding over days, subjects were discussed individually. Most animals showed a

greater cardiac reaction to CS- (acceleration). Opposite responding to the CS+ and CS- was not apparent anywhere in the discrimination phase of the study.

Mack, Davenport, and Dykman (1961) reported similar findings. Six dogs received discrimination training and responded to CS+ and CS- with cardioacceleration. It was noted that frequency of HR differentiation in the subjects was 70% but it was apparent that the responses were alike directionally.

In another study, HR, expressed as percent change from a pre-CS baseline, was determined in rabbits to be decelerative in response to CS+ and CS- (Kazis, Milligan, & Powell, 1973).

The list of HR discrimination studies is exhaustive. Parameters and direction of HR CRs differ, but the majority of the results have indicated a similarity of direction in the responses evoked to CS+ and CS-. Several studies mentioned demonstrated decelerative HR CRs and some have shown cardioaccelerative CRs. Direction of the HR CR to CS+ is not the issue, however. The notion that should be stressed is that most often these studies have failed to demonstrate opposite directionality of HR CRs within a discriminiation conditioning procedure. Taking this one step further, the lack of opposite responding in most of the HR discrimination studies suggests that the classical discrimination procedure may not be a good method for generating inhibition. This possibility would be consistent with recent views regarding procedures that can generate inhibition (Rescorla, 1969).

Explicitly-unpaired procedure

Another procedure has been found to generate opposite responding

to a nonreinforced CS. This procedure is the explicitly unpaired method which refers to the presentation(s) of a CS alone or explicitly not paired with the US. Rescorla (1967) noted that the most typical method involves the presentation of the CS and US in the same session but never close together in time. Like discrimination and backward conditioning, this design was originally intended as a control for nonassociative effects. In keeping with Rescorla's notion concerning the development of conditioned inhibition due to the presence of a negative contingency, it would be predicted that the explicitly unpaired procedure would bring about the growth of inhibition. Instead of the CS being a signal for the US (as in excitatory conditioning) it can become a signal for the absence of the US.

Some evidence has been reported that does not substantiate the claims for the generation of inhibition from the explicitly unpaired procedure, at least in terms of response direction to CS- versus CS+.

Furedy, in a series of studies, directed his inquiry towards the generation of inhibition by the explicitly unpaired procedure. In a 1971 study, he compared the performance difference between responses seen to a CS+ to those seen in an explicitly unpaired procedure (euCS-) and a truly random design (trCS-). Using human subjects, Furedy measured skin resistance response (SRR) and induced plethysmograph pulse olume (PVR). In brief, he saw reliable discrimination between the CS+ and the two CSs-. The performance difference between the CS+ and a truly random CS- (termed CS+: trCS-) exceeded the difference between the CS+ and the euCS-, which did not lend support to the tenet that the explicitly unpaired procedure generates inhibition. In a second exper-

iment, Furedy used a methodology with minor variations (stimulus interval, US duration and intensity, etc.) and found no significant differences between CS+: euCS- and CS+: trCS-.

Later studies done by this group (Schiffman & Furedy, 1972; Furdy, 1974; Furedy & Schiffman, 1971, 1973) using the same basic design as the 1971 study, verified the earlier findings. The difference in responding to the CS+ as compared to the trCS- either exceeded or was not signifcantly different from the difference between the CS+ and the explicitly unpaired CS-. In no case did CS+: euCS- exceed CS+: trCS-.

Fitzgerald and Hoffman (1976) examined the influence of preconditioning exposure of a CS on conditioned heart rate in rats. Three experimental groups were assigned either 0, 10, or 50 CS alone preexposures and then given 30 CS-US acquistion trials. Controls received the same number of CS preexposures but the 30 later trials were explicitly unpaired. All of the experimental groups displayed a decrease in HR to the CS that was significantly different from the response seen in the controls. In the unpaired groups, the response was a small increase in the HR above baseline.

A study (Fitzgerald & Martin, 1971) which compared the effectiveness of aversive conditioning across various interstimulus intervals, did not find opposite responding between explicitly unpaired controls and experimental groups. The response seen for the controls was decceleratory but it was smaller than that seen for the conditioning groups.

Fitzgerald and Teyler (1970) administered explicitly unpaired trials as a sensitization control in a study examining trace vs. delay conditioning procedures over six US intensities. Following 20 CS alone presentations, the experimental group received 30 acquisition trials

(CS-US) and then 30 extinction trials. Two control groups were given similar trials but with the CS and US explicitly unpaired. The results indicated that the experimental groups HR CRs were decreases across all US intensities which were significantly different from the responses of the control groups. A 5.0 mA shock control group exhibited a slight cardioacceleration to the CS-. In a .4-mA control group, HR hovered near baseline or slightly below.

Ftizgerald, Martin, and O'Brien (1973) utilized an explicitly unpaired procedure as a control in a study of vagal involvement in the decelerative HR CR. The response of the experimental-saline group was a consistent cardiodeceleration while in the sensitization-saline group, HR hovered near baseline. However, a closer look at the figure indicates that for the control-saline group the HR response was a cardiodeceleration in the first part of the CS- that gave way to a cardioacceleration toward the end of the CS-. The accelerative component apppeared to be absent in a vagal blockade control group suggesting that the acceleration may have been mediated by vagal withdrawal.

Evidence for the development of opposing HR responses from the explicitly unpaired procedure was seen in a study by Holdstock and Schwartzbaum (1965). Rats were divided in to four groups, each containing four subjects. Two of the groups received paired CS-US trials and the remaining two groups explicitly unpaired trials of the CS and US. In the explicitly unpaired procedure, the click CS was followed at randomly determined intervals ranging from 30 to 75 seconds by the US. The two conditioning groups responded to the click CS in a cardiodecelerative manner while the controls displayed an accleration. The opposite response of the control groups relative to that of the experi-

mental groups suggests that some association may have been formed which might have been due to the presence of a negative contingency rather than the absence of any connection between the two stimuli.

Direct evidence that the explicitly unpaired procedure may be a generator of inhibition comes from the study of Cunningham, Fitzgerald and Francisco (1977), mentioned earlier. Thirty-two rats were given 24 CS+ (tone) - US(shock) pairings and then randomly assigned to either of two groups. One group received 90 explicitly unpaired presentations of another CS (CS-) and the shock US. The stimulus events were delivered in a random order at intervals of 120, 150, or 180 seconds (mean= 150) with the stipulation that no more than three CSs- or three USs were allowed to occur in a row. Rats assigned to the second group received the 90 CSs- and USs delivered in a truly-random fashion, such that chance pairings could occur. Subsequently both groups were given 12 CS+/CS- trials (combined cue) followed by 24 reversal conditioning trials using CS- to assess any inhibitory properties that might have accrued over training to the CS-. Heart rate to the CS+ was a decrease in all phases. The response of the explicitly unpaired group to the CS- was acceleratory while in the truly random group it was deceleratory. The authors suggested that the tachycardia seen in the explicitly unpaired group may have been based on a conditioned inhibitory process in that :(a) the HR response to the CS- developed over trials in a manner analogous to a conditioned reaction, (b) the direction of the response was opposite to the excitatory decelerative HR CR produced by the paired CS+ and (c) the CS- came to elicit an increase in HR on the basis of the same US that had

earlier generated the decelerative CR to the CS+. Additional evidence in favor of inhibition in the explicitly unpaired group was seen in the reversal phase, as conditioning of a decelerative HR CR to the CS- that had earlier been used in the explicitly unpaired procedure was retarded compared to what was obtained to the truly random CS-. These results are all in keeping with the formulation for a conditioned inhibitor (Rescorla, 1969b).

A comparison of inhibition procedures on HR in rats was made by Hoffman (1978) involving combined cue and reversal conditioning tests. Briefly, the author sought to compare the effects of conditioned inhibition, discriminiation, and explicitly unpaired presentations of a CS and US on HR in restrained rats. Only the results of the explicitly unpaired group will be reviewed here. After 24 paired presentations of a tone CS and a shock US, rats were given 96 explicitly unpaired presentations of a light CS- and shock US. Following drug administration (ethanol), the subjects received combined cue trials (four tones, four lights, 12 tone- light) and then reversal training in which the putative inhibitory light CS- was paired with the shock US. Decelerative HR CRs were seen to develop to the reinforced CS+ (tone). Conversely, the explicitly unpaired group showed HR accelerations to the CS- (light) that increased in magnitude over trials. Positive evidence of inhibition was obtained during reversal conditioning but not during the combined cue trials. Hoffman concluded that inhibition developed to the explicitly unpaired CS-.

In another recent work (Stainbrook, 1978) which examined conditioned inhibition of HR, three inhibitory training procedures were used.

Initially, 30 CS+ -US pairings were given to 88 rats. Subjects were then divided into one of three groups which were given presentations of (1) 54 explicitly unpaired CSs and USs, (2) 54 truly random (TR) presentations of the CS- and US or (3) 54 CS- trials with no USs. Following the 54 trials, the groups were tested using an inhibition of delay procedure, an induction procedure, and reversal conditioning to the CS-. A decelerative HR response was seen to the CS+. During the following unpaired phase, an increase in HR was seen in the explicitly unpaired group, while the response in the truly random group was small and variable, and in the CS- alone group, cardiodecelerative. In the reversal phase, acquistion of the HR CR to CS- was retarded in the explicitly unpaired group and also slightly in the truly random group.

In summary, several experiments with rats have shown that explicitly unpaired CS- and US presentations following regular excitatory conditioning can lead to accelerative HR responding to CS-. Moreover, conditioning of a decelerative HR CR to the CS- was found to be impaired during reversal conditioning. Both of these outcomes support the possibility that the CS- had acquired inhibitory capacities. Additional evidence for this view would be provided if it could be shown that the accelerative responding to CS- was controlled by segments of the autonomic nervous system that were different from those involved in the decelerations to CS+. Such a distinction would point toward two divergent precesses, one inhibitory, the other excitatory, instead of a single process that might vary in strength. Although autonomic control of decelerations to CS+ in rats has been found to be vagal

in origin using pharmacologic blockade techniques, conparable studies of the accelerations to CS- have not been reported. The following section is concerned with autonomic functioning of HR in rats and in selected other species.

Autonomic control of HR

Before conditioned changes can be examined using pharmacological operations, it is first necessary to define the system. In the rat, as in all mammals, the autonomic nervous system has two divisions, the sympathetic and parasympathetic components. Together they act to regulate the cardiovascular system tonically and enable it to respond to more phasic changes in the organisms environment. The heart is innervated by both systems. The vagus nerve, which is parasympathetic, serves as an afferent running from the baroreceptors (pressure receptors) on the carotid sinus and the aortic arch of the heart to the medulla. When the baroreceptors are stimulated by an increase in wall stretching, this information is transmitted via the vagus to the appropriate center in the medulla (dorsal motor nucleus or cardioinhibitory area). This brings about a reflexive decrease in HR due to a direct action on the heart along with a decrease in blood pressure due to inhibtion of vasoconstrictor activity (via sympathetic outflow). Fibers descending from the medullary centers are influenced by such supramedullary structures as the hypothalamus and limbic system. The cholinergic parasympathetic vagus terminates on nodal tissue of the heart (sinoatrial, atrioventricular), atrial myocardium, ventricular myocardium and on the coronary arteries. The cardiac sympathetics relaying from the sympathetic chain ganglion end on the right side on

the sinoatrial node,and on the left side on the AV node and AV bundle. The noradrenergic sympathetic receptors are of two types. Activation of the beta receptors causes vasodilation and has a positive chrontropic (increased HR) and inotropic (increased contractile strength, rate of pressure development, and ejection volume) effect. As relates to the vasculature, alpha receptors on activation, cause vasodilation, but they have few cardiac effects.

Cohen (1974) provided an excellent review of the literature concerning the autonomic control of cardiac events during classical conditioning. His overall conclusion points toward the vagal dominance in the cardiac CR in species such as cats, and rats which have a cardiodecelerative CR. In species that most consistently display cardioaccelerative CRs, he suggests the existence of dual control of the sympathetic and parasympathetic divisions. Controversy has arisen over the relative contributions of each of the components.

Autonomic control of HR responding to CS+ and CS-

As mentioned previously, conditioned HR decelerations to CS+ are consistently seen in restrained rats. This observation has led many investigators to the conclusion that HR CRs are under vagal control. Evidence for this conclusion came from a study by Fitzgerald, Martin, and O"Brien (1973). In their study, atropine, which is a potent parasympathetic blocker, almost completely eliminated the decelerative CR. The decelerative response that developed in the last half of the conditioning session was attributed to sympatho-inhibition. The authors suggested that during the developmental stage, the rats' decelerative CR may be mediated solely by the vagi but that once the CR is fully

established, there is a synergistic interaction between the vagal and sympathetic output. They cautioned however, that blocking the parasympathetic activity might have altered the relative contribution of the sympathetic component.

Hoffman and Fitzgerald (1978) saw both a deceleratory HR CR and a decrease in blood pressure CR and concluded that the cardiac response was not mediated through baroreceptor activity. Instead, the simultaneous decreases in HR and BP suggested that the batoreceptor reflexes may have been inhibited in the presence of the CS.

Papppas and DiCara (1973) studied the neural control of HR in rats receiving classical conditioning. Twenty-eight rats underwent neonatal sympathectomy by peripheral injection of a vehicle. At approximately 115 days of age, the rats were paralyzed with succinlycholine and administered atropine or saline. Rats were then classically conditioned using a light-tone CS and a shock US. The basal HR and unconditioned cardiac response to shock were unaffected by sympathectomy but the decelerative HR CR to the CS+ was abolished. A decelerative HR CR was seen in the vehicle-nonatropinized group. Atropine was found to eliminate the cardiodecelerative CR shown by the vehicle rats but did not alter the accelerative response of the 6-OHDA rats. The authors concluded that the conditioned cardiac deceleration in the rat is vagally mediated. Because the 6-OHDA rats showed an abolition of the blood pressure increase and the HR decrease to the CS+, it was concluded that the overall cardiodecelerative response was secondary to a prior blood pressure increase.

In a related study, Pappas, DiCara and Miller (1972) examined the effects of chemical sympathectomy via 6-OHDA on cardiovascular conditioning in rats. The principle question addressed in this investigation was whether acute sympathectomy would enhance vagally mediated cardiac decelerative effects to shock or to a conditioned stimulus, or whether reflex vagal bradycardia would be eliminated by 6-OHDA because the precursive pressor response was eliminated. They found no effect on baseline HR, an attenuated HR UR (unconditioned response) to shock but no overall effect on the CR. Responses were small and highly variable, and there was no significant group differences from baseline averages. The findings agree with the notion of vagal dominance in the maintenance of basal cardiac rate and the CR.

Although an abundance of literature exists devoted to the identification of the autonomic innervation of cardiac conditioned responding, there is a paucity of information concerning the autonomic correlates of conditioned cardioacceleration in a background of decelerative responding. It will be recalled that Cunningham, Fitzgerald, and Francisco (1977) observed a cardioaccelerative CR resulting from explicitly unpaired presentations of a CS and a US in a background of cardiodecelerative responding to another positively reinforced CS. The authors viewed the cardioacceleration to the explicitly unpaired CS as maybe reflecting the activity of a centrally located state that could interfere with conditioning of a cardiodeceleration to a CS+. Suggested as possible correlates to this response were: (1) an increase in sympathetic output that would act

antagonistically to that increased vagal firing known to be responsible for decelerative HR CRs to a CS+, or (2) a decrease in vagal firing which would lead the sympathetic system to overshadow the parasympathetic division. In both cases, the end result would be cardioacceleration.

The purpose of the current study was to determine the relative contributions of sympathetic and parasympathetic input in the control of HR acceleration to an explicitly unpaired CS- using pharmacologic blockade of normal autonomic functioning. A second objective was to see what effect the blockade would have on HR responding during a combined cue testing phase of the CS+ and CS-.

Methods

Subjects

Thirty, naive, female, Long-Evans hooded rats, 90-120 days old and weighing in the range of 200-300 grams were used in the study. The animals were purchased from the department of Animal Care at the University of Oregon Health Sciences Center and housed individually with food and water available constantly. A 12-hour alternating light-dark cycle was maintained and the experiment was conducted during the light phase.

Apparatus

The rats were restrained in inverted u-shaped acrylic animal holders (made by Narco Bio-Systems Inc.) with adjustable guillotine-type inserts at the ends. The holders were placed on the floor of a 25.4-cm wide x 20.5-cm long x 40.6-cm high aluminum enclosure located inside an Industrial Acoustics sound attenuating chamber. A 60-W houselight was recessed in the ceiling to provide illumination. White masking moise was delivered to a speaker mounted on the back wall of the chamber(70 dB, re 20 $\mu N/m^2$). One and five-kHz tone sound stimuli (CSs), at a sound pressure of 80 dB, (re 20 $\mu N/m^2$) were delivered through a 10.2 cm speaker mounted on the ceiling of the aluminum enclosure. The unconditioned stimulus (US) was a 1.0 second, 1.5 mA 60-cycle ac shock produced by a Grasson Stadler shock generator, and delivered through 20-ga hypodermic needle electrodes positioned on either side of the rats' thoracic cage.

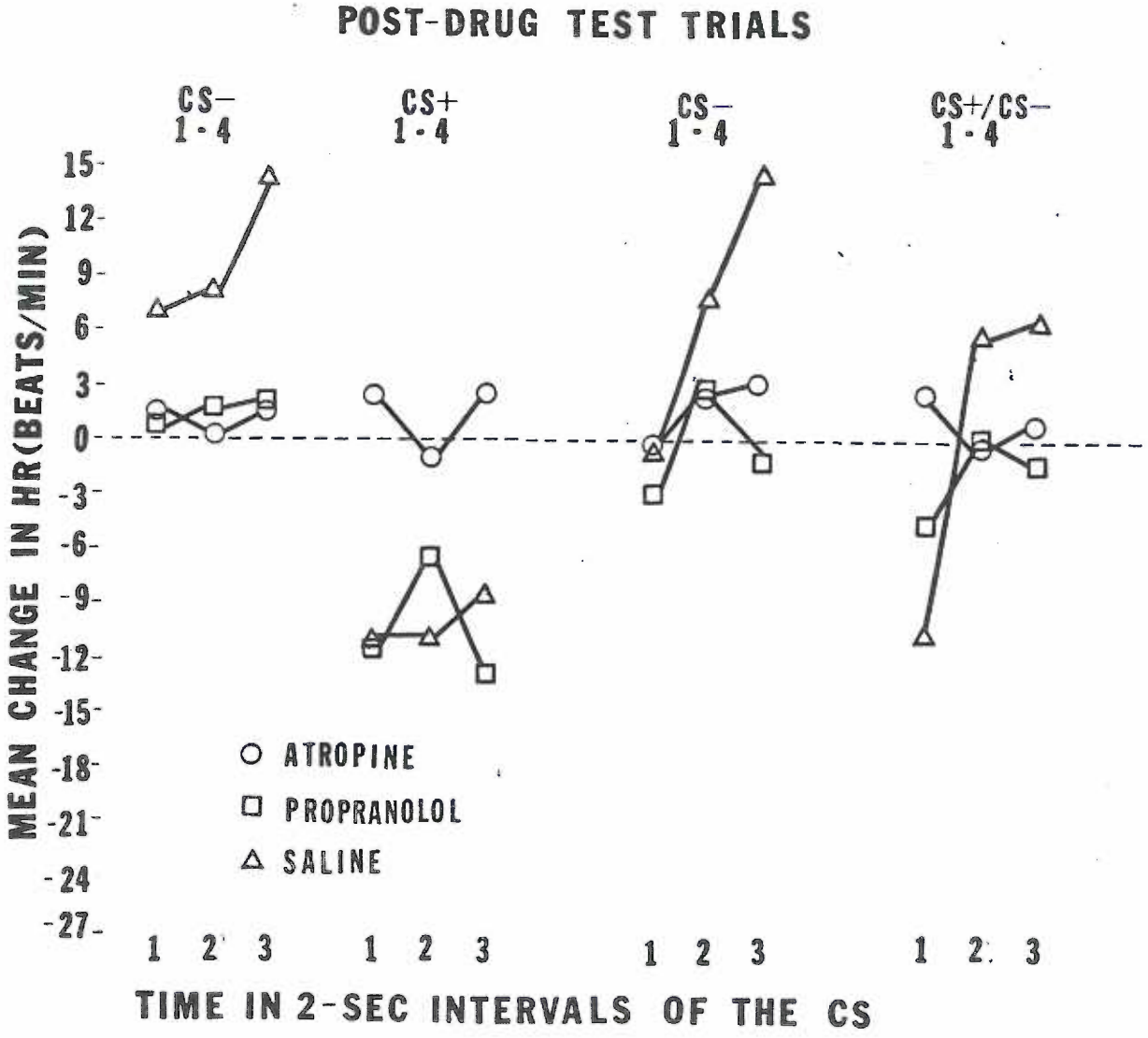
The electrocardiogram was recorded on a Model 5 Grass polygraph from the hypodermic needles. The number of heart beats in a trial

were tabulated automatically by an on-line recording system previously described in detail by Fitzgerald, Vardaris, and Teyler (1968). The system consists of a lever-type Microswitch mounted on a Plexiglas plate directly above the EKG polygraph pen with the arm of the switch connected to the tip of the pen. The position of the Microswitch was adjusted such that it was activated by the R wave of the QRS complex.

The CSs and US were started automatically by a film-tape programmer. The stimulus events and heart rate (HR) measurement intervals were timed by solid-state logic modules.

Procedure

The study was conducted in four successive phases, in two days. Each day was preceded by a 15- minute adaptation period. Pairs of rats were conditioned concurrently in separate identical chambers with trials alternating between the animals. During the first phase, which occurred on Day 1, all of the animals in each group received six habituation trials of both the CS+ and CS- presented alone (12 trials total) with an intertrial interval of 60, 90, or 120 seconds (mean= 90) followed by 30 pairings of the CS+ and US with an interstimulus interval of six seconds. Tones were counterbalanced such that for one half of each group the CS+ was the one-kHz tone and for the other half of the subjects, it was the five-kHz tone. In the second phase, also on Day 1, all groups received 20 presentations of the other CS (CS-) and of the shock US (in an explicitly unpaired fashion). The order of the CS- and US events in this phase was randomized with the restriction that no more than three CS trials or three US trials were allowed to occur consecutively. On the second day, Phase 2 continued with 30 explicitly un-


POST-DRUG TEST TRIALS
CS−
1-4
CS+
1-4
CS−
1-4
CS+/CS−
1-4
15
12
9
6
3
0
-3
-6
-9
-12
-15
-18
-21
-24
-27
MEAN CHANGE IN HR(BEATS/MIN)
ATROPINE
PROPRANOLOL
SALINE
1 2 3 1 2 3 1 2 3 1 2 3
TIME IN 2-SEC INTERVALS OF THE CS

paired presentations. The next phase, Phase 3, was designed to provide an assessment of the blocking agents on the HR response to the CS-. The two drugs administered were atropine sulfate, an antiparasympathetic agent, and propranolol hydrochloride, a beta-adrenergic blocker. One experimental group (n = 10) was injected with 10 mg/kg i.p. dose of atropine sulfate (1 ml/kg of a 10 mg/ml concentration). Another group (n = 10)received an i.p. dose of 2 mg/kg propranolol hydrochloride (1 ml/kg of a 2 mg/ml concentration). A control group received equal volumes of physiological saline. These doses have been found to effectively block parasympathetic or sympathetic transmission (Weiss, Lipp, Neubauer, & Feldman, 1976; Fitzgerald, Martin, & O'Brien, 1973). The half life of each drug is such that serum levels would be expected to remain high throughout the test phase of the study (Shand, Rangno, & Evans, 1972; Tipton & Taylor, 1965). Intraperitoneal injections were given immediately following the last trial of Phase 2. There was then an absorption period of 15 minutes to allow the drugs to reach maximum efficacy. Ten additional explicitly unpaired trials of the CS- and US were then presented. During Phase 4, which immediately followed Phase 3, all groups were given test trials with the previously excitatory CS+, the unpaired CS-, followed by combined cue trials with CS+ and CS- presented in compound. These trials consisted of presentations in a sequence of four CS+, four CS-, and four combined cue. Each stimulus was delivered for 6.1 seconds. These trials served as tests for the effects of the autonomic blockers on the accelerative HR changes to the CS- and on the CS+/ CS- compound. The intertrial intervals in all phases excluding habituation (CS alone) trials in Phase 1, were 120, 150, or 180 seconds (mean = 150),

Results

Although not plotted in any of the figures, the frequency of the auditory CSs was included as a factor in all analyses of variance. Drug treatment condition was included as a "dummy" factor in all analyses of variance (ANOV) of the predrug phases to determine whether chance differences existed between the groups prior to the administration of the blocking agents.

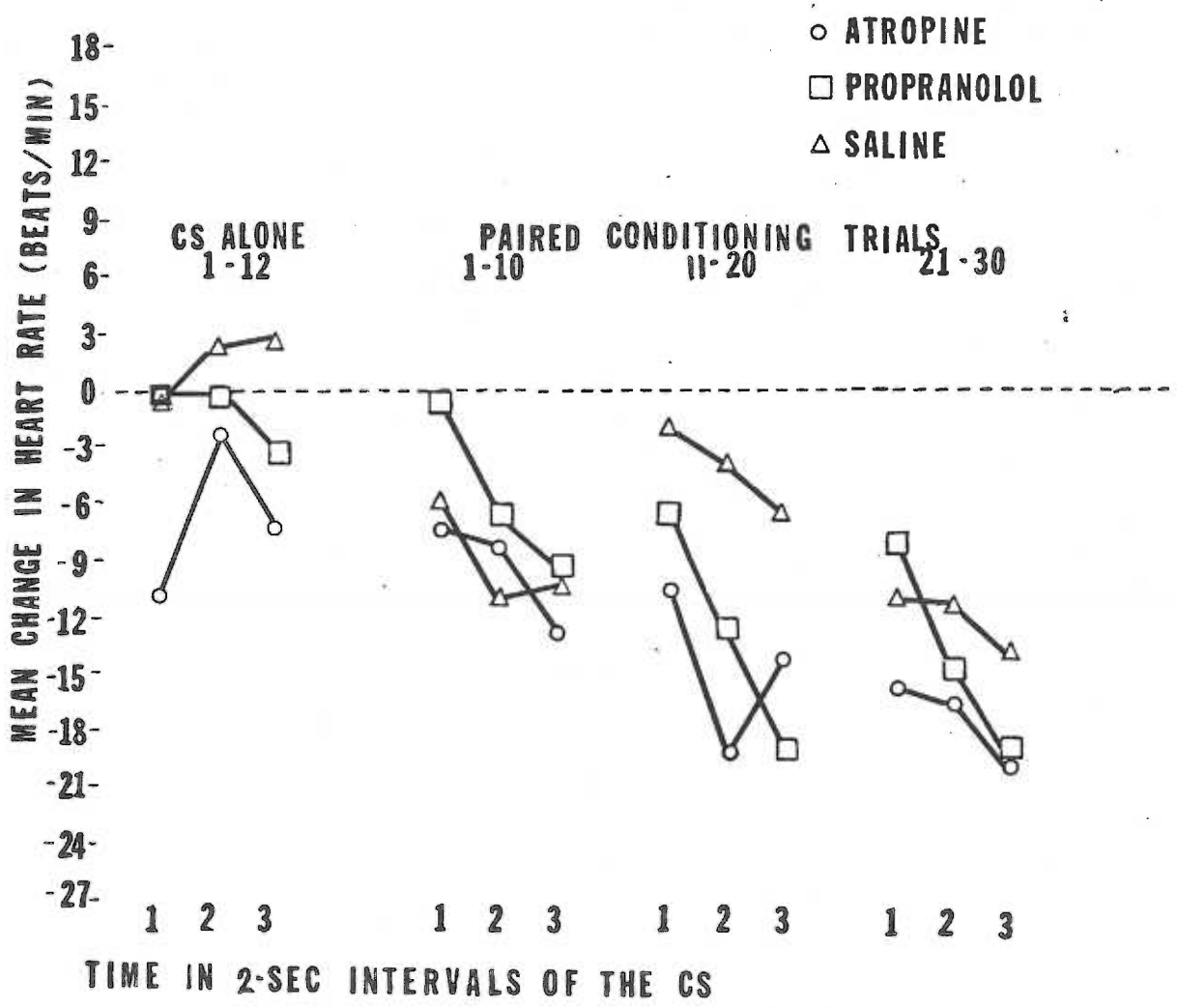
Preconditioning CS alone trials

The HR responses of the three groups over the six trials with each CS are shown on the left of Figure 1. The results were collapsed over the two CSs after it was determined that inital responding did not vary significantly with the frequency of the CS. From Figure 1 it may be seen that the HR responses of two of the groups were small magnitude decelerations and accelerations whereas those of the third group were consistent decelerations. However, the only significant effect that was produced as detected by a four-way ANOV (groups x CS frequency x measurement intervals x trial blocks) was that of measurement intervals, $F(2, 48)= 3.88$, $p< .05$.

Paired conditioning trials

The responses of each group in successive 2-sec intervals of the CS+ averaged over three blocks of 10 paired conditioning trials each are plotted on the right of Figure 1. It may be seen that all of the groups developed decelerative responding to CS+ over the course of the paired trials. The pattern of the responses was such that maximum decelerations occurred toward the end of the CS+. Although the

Figure 1. Mean CS minus pre-CS HR responses to six CS-, six CS+ alone trials averaged over 12 trials; mean HR change to 30 paired CS+/US trials. Drug treatment in these phases is a "dummy" factor.

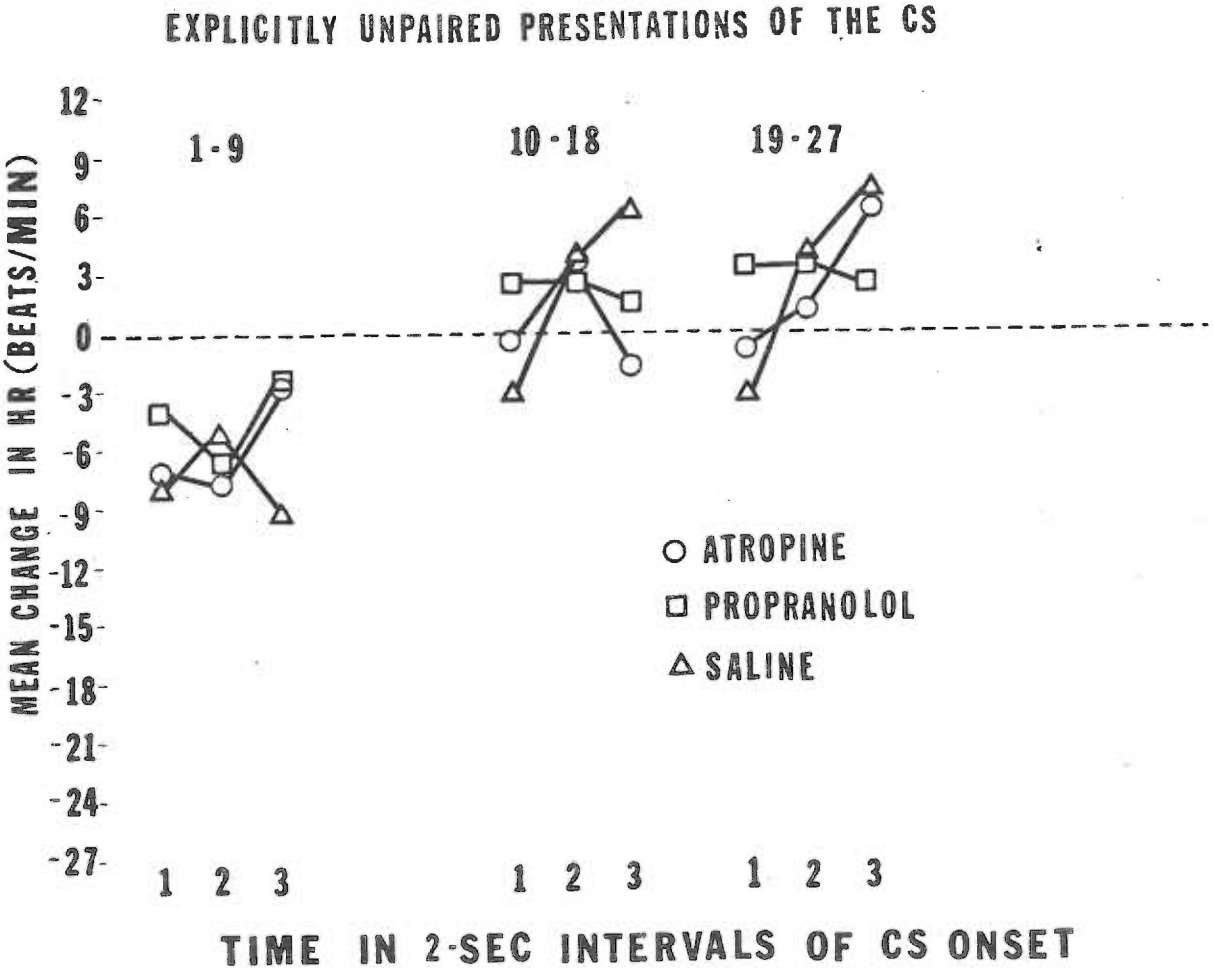

ATROPINE
PROPRANOLOL
SALINE
CS ALONE
1-12
PAIRED CONDITIONING TRIALS
1-10
11-20
21-30
MEAN CHANGE IN HEART RATE (BEATS/MIN)
18
15
12
9
6
3
0
-3
-6
-9
-12
-15
-18
-21
-24
-27
1 2 3 1 2 3 1 2 3 1 2 3
TIME IN 2-SEC INTERVALS OF THE CS

responses of the saline group appeared to develop more slowly than those of the other group, no group differences were obtained in a four-way (groups x CS frequency x measurement intervals) ANOV. The analysis did provide a significant trials effect, $F(2, 48)= 8.02$, $p < .01$, indicating that the change in responding over trials was reliable. There was also a significant measurement interval effect, $F(2,48)= 11.50$, $p < .01$, showing that HR changed reliably (in this case progressively more deceleration from the beginning to the end of CS+) during CS+.

Explicitly unpaired trials

Figure 2 shows the HR responses of each group in 2-sec intervals of CS- averaged over blocks of nine trials each. This figure reveals that the responses of the three groups were generally similar to each other. In most cases, HR was decelerative on the intial block of trials and became accelerative over the second and third block of trials. By the final trial block, maximum acceleration occurred in the third measurement interval in two out of the three groups. In the remaining group (propranolol), accelerative HR changes were relatively uniform over the CS- for the last two trial blocks. A four-way ANOV (groups x CS frequency x measurement intervals x trial blocks) provided a significant trials effect, $F(2, 48)= 14.39$, $p < .01$, showing that the change in HR across trials was reliable, and a significant measurement intervals effect, $F(2, 48)= 4.73$, $p < .05$, showing that HR changed reliably within the CS-. None of the effects involving groups was significant.

Figure 2. Mean CS minus pre-CS HR responses to 27 explicitly unpaired presentations of the CS. Drug treatment in this phase is a "dummy" factor.


EXPLICITLY UNPAIRED PRESENTATIONS OF THE CS
MEAN CHANGE IN HR (BEATS/MIN)
12
9
6
3
0
-3
-6
-9
-12
-15
-18
-21
-24
-27
1-9
10-18
19-27
1 2 3
1 2 3
1 2 3
ATROPINE
PROPRANOLOL
SALINE
TIME IN 2-SEC INTERVALS OF CS ONSET

Post-drug test trials

It will be recalled that each group received a total of 10 explicitly unpaired trials (6 US alone and four CS alone) immediately following the 15 minute post-injection-drug-absorption period. These were followed in sequence by four nonreinforced trials with CS+, a second set of our CS- trials (no USs were delivered at this time) and four combined cue trials with CS+ and CS- being given together. Due to an error in testing, two animals in the saline group failed to receive the four CS+ trials and four combined cue trials. Instead, they were given a long series of explicitly unpaired CS- and US alone trials. This meant that while their second set of four CS- trials was available for analysis, the trials were not exactly comparable to those given the other groups. Between-groups comparisons of the second set of CS- trials were carried out with and without the data from these two animals present.

First set of four CS- trials

The responses of each group on each of the trial types given in the post drug test phase are shown left to right in Figure 3. The far left of the figure reveals that accelerative responding, comparable to that occurring in the previous unpaired phase, was shown by the saline group on the first set of CS- trials. In the case of both drug groups, accelerative responding was reduced to near zero levels. The overall difference between the groups was shown to be reliable by a significant drug effect, $F(2, 24)= 3.68$, $p < .05$ in a three-way ANOV (drug x CS frequency x measurement intervals). A subsequent t test revealed that the saline group was reliably differ-

Figure 3. Mean CS minus pre-CS HR response to post drug test trials, consisting of four CS- (out of 10 explicitly unpaired presentations of the CS and US), four CS+ alone, four CS- alone, and four combined cue (CS+/CS-). Drug treatment was a factor in these phases.

ent from the drug groups ($p < .02$). The analysis also provided a significant CS frequency effect, $F(1,24) = 7.19$, $p < .05$, which was due to the fact that HR accelerations were larger to the 5-kHz CS- than to the 1-kHz CS-.

Four CS+ test trials

The next panel in Figure 3 indicates that atropine blocked the occurrence of the decelerative HR response to CS+ whereas propranolol did not. In the atropine group, HR in all threee measurement intervals was near baseline, not unlike what occurred in both drug groups in the preceding CS- trials. In the propranolol group, HR decelerations matched those of the saline-control group. Thus, while propanolol was effective in sharply reducing accelerative responding to CS-, it had no major effect on decelerative responding to CS+. A three-way ANOV (drug x CS frequency x measurement intervals) established that the overall differences among the groups was significant, $F(2,22)= 5.83$, $p < .01$.

Second set of four CS- test trials

The next to the last panel in Figure 3 depicts responding in 2-sec intervals of CS- averaged over the second set of four CS- alone trials. In keeping with what occurred to CS- previously, both drug groups showed a loss of accelerative responding to CS- relative to that exhibited by the saline-control group by the end of the trial block. However, in this case, the group differences did not reach significance, either with or without the two problem animals mentioned earlier included in the analysis. Inspection of each group demonstrated slightly more

decelerative responding in some of the animals in the propranolol group on the second set of CS- trials as opposed to the first set. This may be seen in the figure by noting that the first and third points for the propranolol group were decelerative.

Four combined cue test trials

The final panel in Figure 3 presents the responses of the groups in 2-sec periods of the combined CSs averaged from the four combined cue test trials. The most striking feature of this panel is the reaction shown by the saline-control group. For the first time in any phase of the study and for any group, the saline-control group displayed a major biphasic HR change consisting of deceleration to the onset of the CSs followed quickly by acceleration in the second and third measurement intervals of the CSs. By contrast, the HR changes of both drug groups were more gradual within the CSs and smaller in magnitude. The biggest change in the drug groups occurred in the first intervalm while the direction of the change being decelerative in the propanolol group and accelerative in the atropine group. A three-way ANOV (drug x CS frequency x measurement intervals) provided a significant drug x measurement intervals interaction, $F(4,44)= 3.64$, $p < .05$, in addition to a measurement intervals effect, $F(2, 44)= 3.76$, $p < .05$, establishing that the responses of the groups were reliably different from each other. A subsequent t test revealed that for the first measurement interval, the saline group was significantly different from the atropine group ($p < .04$).

Baseline heart rate

Pre-CS baseline HR of the groups averaged over various trial

Figure 4. Mean baseline heart rate (6-sec pre-CS) during all phases of the study.

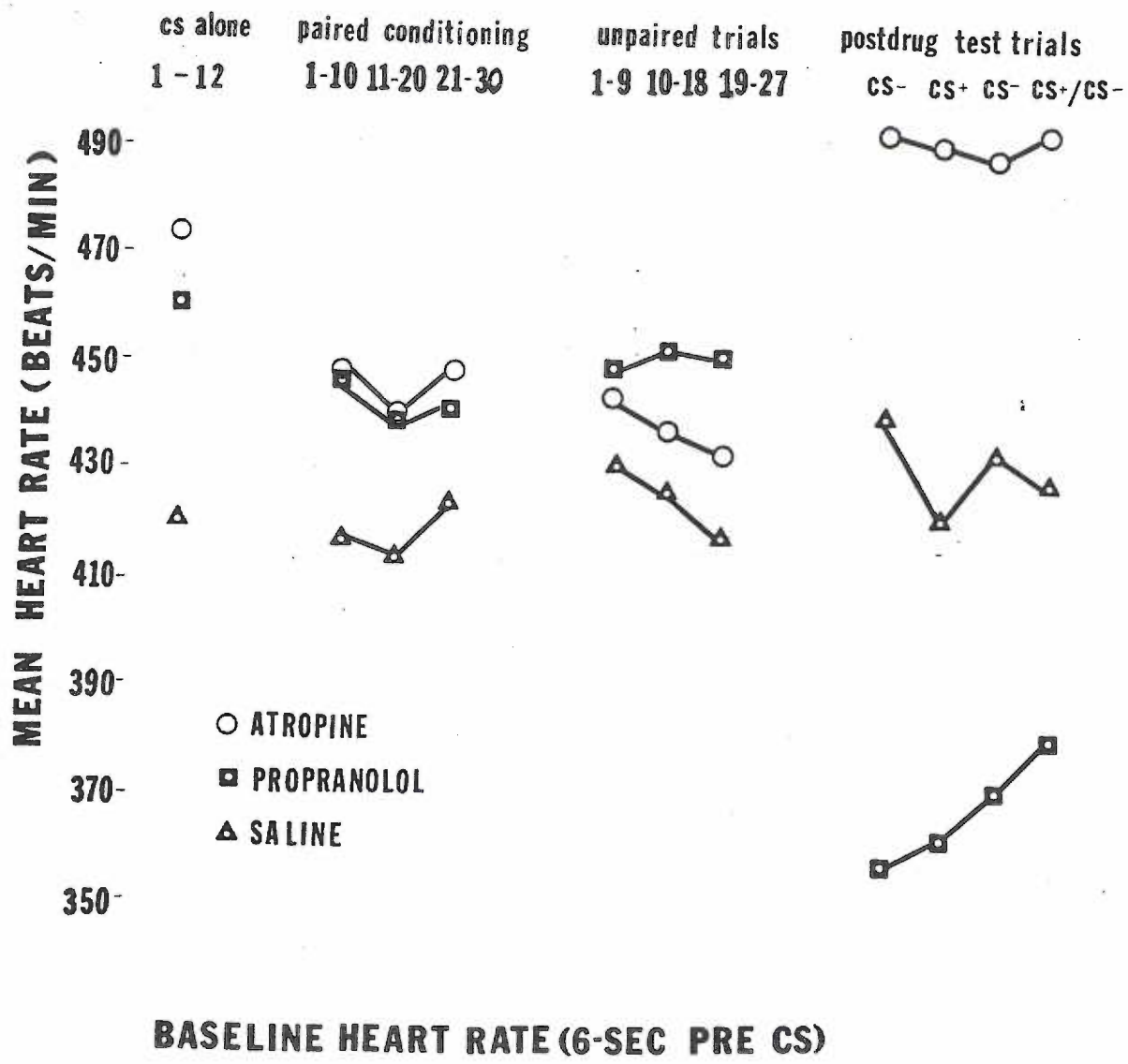

cs alone
1 - 12
paired conditioning
1-10 11-20 21-30
unpaired trials
1-9 10-18 19-27
postdrug test trials
cs- cs+ cs- cs+/cs-
MEAN HEART RATE (BEATS/MIN)
490
470
450
430
410
390
370
350
ATROPINE
PROPRANOLOL
SALINE
BASELINE HEART RATE (6-SEC PRE CS)

Table 1. Baseline heart rate (6-sec pre-CS) during all phases of the study.

Table 1. Baseline Heart Rate in each Phase of the Study

	CS-alone	Paired Conditioning Trials			Unpaired Conditioning Trials			Post-drug test trials			
	1-12	1-10	11-20	21-30	1-9	10-18	19-27	CS_2	CS_1	CS_2	$CS1-CS_2$
Atropine	474	449	440	448	443	438	433	492	490	488	491
Propranolol	461	445	439	441	439	452	451	357	361	371	380
Saline	421	417	414	424	431	426	418	440	421	433	428

blocks in the different phases of the study are shown in Table 1 and Figure 4. The left side of the table indicates that during the preconditioning CS-alone phase, baseline HR of the saline group was substantially lower than that of the two drug groups, even though the groups were treated identically at that time. A one-way ANOV demonstrated the group differences to be significant, $F(2, 24)= 5.73$, $p < .05$. During the conditioning phase, baseline HR of the two drug groups dropped nearer to the levels of the saline group. A two-way ANOV (groups x trials) indicated that there were no significant effects concerning conditioning baseline HR. Group differences continued to be small and variable on the unpaired conditioning trials. There were no major changes from the levels of the preceding phases. Two of the three groups showed a slight decrease in baseline HR across the unpaired trials whereas for the third group there was a slight increase. A two-way (groups x trials) ANOV gave no significant effects.

The post drug HR listed in the right of Table 1 indicated that relative to the last block of unpaired trials, baseline HR increased to atropine, and decreased to propranolol. Each of these changes was significant according to separate t tests (atropine $t = 7.51$, $df = 9$, $p < .003$; propranolol $t = 10.87$, $df = 9$, $p < .003$). The increase shown by the saline group was not significant. Throughout the postdrug trials, the atropine group had higher baseline HR than the saline group. A three-way ANOV (drug x CS frequency x trials) gave a significant overall drug effect, $F(2, 22)= 46.69$, $p < .001$, establishing that the group differences were reliable. The two saline animals for whom some test trial data was not available were not

included in this analysis. A subsequent Newman-Keuls test showed that each of the drug groups was significantly different from the saline group and from each other, $p < .05$. Although the drug x trial type interaction was not significant, the propranolol group showed a gradual recovery of baseline HR over trials whereas in the other groups HR changed very little. A separate analysis on just the propranolol group showed that the change in HR over the post drug test trials was reliable, $F(3,20)= 8.59$, $p <.01$.

Discussion

The principal findings of the present study were that a) the HR CR to CS+ during acquisition was observed to be a deceleration, b) the HR response to the CS- on the explicitly unpaired trials was a cardioacceleration that developed over trials, c) the cardioacceleration to the CS- was attenuated by both atropine and propranolol, d) the decelerative HR CR to CS+ was eliminated by atropine, e) during the combined cue test phase, the saline group exhibited a biphasic reaction conisting of an early decelerative component to the onset of the CS followed later by an accelerative component. The propranolol group displayed some cardiodeceleration and the atropine group a slight acceleration.

Conditioned responses

The cardiodecelerative CR that occurred in the acquisition phase of the study increased in magnitude over trials, suggesting that it was a learned excitatory response. This result is consistent with reports from previous studies using rats in the restrained condition (Cunningham, Fitzgerald, & Francisco, 1977; Holdstock & Schwartzbaum, 1965; Fitzgerald & Teyler, 1970). A difference between measurement intervals was also seen, which appears to reflect the larger cardiodeceleration exhibited in the latter as opposed to the early part of the CS+. Cunningham, et al. noted a similar effect of CS presentation.

In contrast, the HR response to the second CS (CS-) which was explicitly unpaired with the US, was an overall cardioacceleration. This result was observed on the 27 predrug CS alone trials that were

encompassed in the 50 explicitly unpaired trials. The increase in magnitude of this reponse over trial blocks carries the suggestion of a learned response. The decelerative trend seen in the first measurement interval, which changed to an acceleration in the next two intervals, was more than likely due to stimulus generalization between the CS+ and CS-. The results of Cunningham, et al.(1977) were in accordance with these findings. The cardioaccelerative responding exhibited to the CS- in their study was of greater magnitude, however, reaching 16 bpm above prestimulus baseline by the end of the third trial block. It should be noted that in their study, 63 CS alone trials were given (out of 126 explicitly unpaired trials), whereas in the present study, only27 CS alone trials were administered (out of 50 explicitly unpaired trials).

Pharmacologic Blockade

Finding that the atropine treatment blocked the decelerative HR to CS+ whereas the propranolol treatment did not lends support to the notion that the cardiodecelerative CR to the CS+ was vagally mediated, and that the sympathetics have little if any effect on this response tendency.

It has been suggested that the vagus is responsible for the conditioned bardycardia seen in other species. A decrease in HR has been observed to a CS+ in unrestrained (Hein, 1969) as well as restrained cats (Santibanez, et al, 1963; Santibanez, et al, 1965). As atropine blocked this response in the Hein study, it was assumed that the cadiodeceleration was of vagal origin. Hein also reported that blood pressure did not rise during the deceleration and thus concluded that the

carotid sinus reflex was not implicated. The author reflected that a central mechanism of subcortical location might be the basis of the deceleration. Flynn (1960) also reported a cardiodecelerative CR in cats, which vagotomy attenuated. This further supports the notion that this response is under vagal control.

Other findings have been reported, however. Fitzgerald, Martin, and O'Brien (1973) noted a small residual bradycardia after the atropine treatment and attributed it to sympathoinhibition. Though the authors stressed that the response was primarily controlled by the vagus, they noted that the sympathetic division may have a minor role in its occurrence.

Dual autonomic control has been suggested in the mediation of HR CRs in other species. For instance, Cohen and Pitts (1968) reported that in pigeons, which displayed a cardioaccelerative CR, the principal contribution to the magnitude of the response was by the cardiac sympathetics, while the shortest latency component of the response was mediated by the vagi.

Diaz, et al. (1969) investigated the role of the sympathetics in the HR CR of restrained cats. Subjects received 70 sessions of 15 trials each, consisting of six CS+ (500 hz tone) and the shock US interspersed with six nonreinforced CS- (1000 hz tone) and three combined cue type trials (CS- plus CS+ nonreinforced). The CR to the excitatory CS+ was observed to be a consistent deceleration in normal animals and a smaller deceleration to CS- and to the CS+/CS- compound. Four out of six sympathectomized cats failed to establish a bradycardic CR to the CS+ and instead exhibited a tachycardic response. The brady-

cardia that had been observed to occur in normal animals to CS- and to the CS+/CS- compound also occurred in the sympathectomized group. The authors suggested that there are different mechanisms operating in the bradycardic responses to CS+ and CS-. The decelerative HR CR to the CS+ was believed to be due to tonic sympathetic inhibition (because sympathectomy unmasked an accelerative response), while the cardiodeceleration displayed to the CS- and to the CS+/CS- combination was thought to reflect an increase in vagal tone (because sympathectomy did not change the response).

Sympathetic control of the reactions without a major vagal contribution has been advanced in other studies. Giavelli, et al. (1977) reasoned that if the conditioned bradycardia seen in the cat is a consequence of sympathetic inhibition rather than vagal activation, as Diaz, et al. (1969) suggested, it would follow that bilateral ablation of the vagal innervation at the cardic level should not alter the conditioned bradyacardia. Briefly, 11 restrained cats were assigned to either of two groups; intacts, or bilateral vagotomized. The training procedure was virtually identical to that used by Diaz, et al. (1969). The cariac vagotomized cats were capable of learning a conditioned bradycardic response and were also able to discriminate between the positive and inhibitory stimuli. These results lend support to Diaz's notion that it is the tonic inhibtion of cardiac sympathetic activity that is responsible for the conditioned bradycardia seen in cats.

In the current study, the saline control responded to CS- in the drug test phases with a persistent cardioacceleration. The topography

of the reponse was similar to that occurring on the 10 predrug CS- trials. In the other two groups the accelerative response was blocked by both of the drug treatments for the first set of four CS- trials. No reliable drug effect was detected for the second set of four CS-. Because both drug groups showed a diminished response tendency to CS- in the first set of post drug trials, it can be advanced that the cardio-acceleration normally seen is under dual control by the sympathetic and parasympathetic divisions of the autonomic nervous system. The smaller magnitude response of the drug groups on the second set of CS- test trials may have been due to a decrease in the drugs efficacy with time. Nevertheless, on the following block of CS+/CS- test trials, an effect due to drug was noted in the form of a significant drug x measurement intervals interaction.

The response in the saline group to the combined cue presentations was a biphasic cardiodeceleration-acceleration. A possible explanation for the form of the response may be that the initial decelerative component was evoked as a response to the CS+ part of the two stimulus complex. The cardioacceleration that appeared in the second and third measurement intervals may have reflected a separate response to the CS- component of the complex.

Responding to a combined cue, in the past, has been discussed in terms of algebraic summation (Rescorala,1969b). If an inhibitory conditioning paradigm (conditioned inhibition proper or discrimination conditioning) the excitatory and inhibitory stimuli are considered parallel events, it would be expected that when combined, the responses to these two stimuli would summate algebraically and no change from

baseline level responding would be displayed. This largely theoretical notion was not supported in the present study. It appears from the present results that at the beginning of the combined cue presentation the response to the CS+ predominated, while later the response to CS- became the stronger behavior.

It is also possible to invoke an attention theory to explain the findings. As excitatory conditioning was the initial training procedure, perhaps the CS+ was stamped in as the most salient cue. Subsequently when the two stimulus events were presented together, the animal responded to the CS+ first and later to the CS-. This notion is opposed to what Rescorla (1969b) wrote on the subject of differential attention to the two stimuli in the combined cue test. He felt that the treatment designed to make the CS- an inhibitor might lead the organism to attend to it to the detriment of attention to CS+. This did not appear to be the case in the present study. However, it can be seen in the combined cue test that CS- reduced the response normally elicited by the excitor CS+. While the response in the saline group for the first measurement interval was decelerative, HR rose well above baseline for the remainder of the CS, obviously indicating a decremental response to that normally seen to CS+.

Cunningham, Fitzgerald, and Francisco (1977) utilized a combined cue test. The response of the explicitly unpaired group appeared depressed compared to the truly random control group, though an analysis of variance did not indicate any differences between groups. Twelve combined cue presentations were given. In the first block of four trials, the subjects responded in the 6-sec of CS onset with

a small cardioacceleration-deceleration. In the succeeding four trials (five through eight) the response was an increasing cardiodeceleration, while in the next four trials (nine through twelve) mean HR change developed from -12 bpm to near zero. Direct comparisons between the results of this study and the present are difficult to make because of differing response topographies. It should be noted that prior training in the way of explicitly unpaired presentations in the Cunningham et al. study exceeded that of the present study.

Hoffman (1981) in a recent work, reported the use of a combined cue test. In this study twelve combined cue trials were presented after 24 paired conditioning and 96 explicitly unpaired trials. Plotted in blocks of four trials, the data reveal that for the first block of four trials, the response developed from zero HR change to an acceleration, then a return to zero by the last two seconds of the CS. For the second set of four trials, the response was a consistent cardioacceleration. Most interesting, is the response in the last four trials. The response grew from a cardiodeceleration in the first two seconds of the CS, to near baseline responding in the third and fourth seconds, and to a cardioacceleration in the fifth and sixth. This biphasic response could almost be superimposed on the response seen in the current study. Form of the response and magnitude are comparable. In both cases the cardiodeceleration consisted of responding -6 to -7 bpm from baseline and an eventual increase to about 7 bpm above zero responding. An anlaysis of variance performed on the combined cue phase of the Hoffman study revealed a groups x trials x measurement intervals interaction, $p < .05$.

In the present study, the atropine group response to the onset of the combined stimuli was a small cardioacceleration which was statistically different from the response seen in the saline group. It appears that the drug blocked the cardiodeceleration seen in the saline group. Responding in the next two measurement intervals was near baseline. In contrast, the propranolol animals displayed a cardiodeceleration to the onset of the stimulus complex. Though smaller in magnitude, the response was of similar direction and topography to that of the saline control group. In the second and third measurement intervals, HR rose to near baseline. These results lend further support to the notion of vagal control of the CR to CS+, if it is to be assumed that the initial cardiodeceleration displayed by the saline group was a response to CS+. The dual control notion of the mediation of the response seen to CS- is also supported, if the cardioacceleration seen to the latter part of CS onset reflected a response to the CS-. Both drugs blocked the cardioacceleration seen in the saline group in the last two measurement intervals.

It has been suggested in an earlier work (Cunningham, et al., 1977) that conditioned inhibition may have been responsible for the HR acceleration produced by the explicitly unpaired procedure. It can similarly be advanced in the present study that the explicitly unpaired method generated inhibtion as the same set of requirements for a conditioned inhibitor (according to Rescorla, 1969b) were met. For instance, the explicitly unpaired CS evoked a response tendency opposite to that seen to the excitatory CS and the same US was used in all phases of the study. Moreover, the responses seen to CS- were in keeping with

the criterion of opposite responding detailed by Gray (1975).

Hearst (1972) noted some additional conditions for an inhibitor which were met in the current study; decremented behavior (1) occurred as a result of conditioning to the CS-, (2) was produced by a discrete external stimulus, (3) occurred when all the conditions responsible for the initiation and maintenance of baseline performance were held constant and then a stimulus was presented which led to a decrease in performance and (4) the conditioned inhibition developed from a training procedure that involved some negative relationship between the presentation of an external stimulus and subsequent occurrences of another event or outcome.

To return for a moment to attentional explanations of inhibitory-like outcomes, according to Hearst (1972), if an organism is "indifferent" to a particular stimulus, the stimulus should produce no significant decremental effect in either a combined cue or a new-learning situation. It has also been suggested that the behavioral decrements which may occur because of prior "inhibitory" training might lead the subject to be less attentive to the test stimulus (Cunningham, Fitzgerald, & Francisco, 1977) and this could account for a lack of diminution of the response in the combined cue test trial.

It is difficult to apply these notions in the present case, however, because of the nature of the saline groups combined cue response. Neither cardioacceleration nor deceleration was totally eliminated. The biphasic character of the response indicates that the response was not exclusively of the same direction of either of the prior test trials, but rather included the response direction and topography

of both the response to the CS+ and CS-. Broadly speaking, the explicitly unpaired CS- continued to decrement the excitatory response in the combined cue trials as indicated by the cardioacceleration seen in the latter part of the CSs.

Another possible explanation for the cardioacceleration seen to CW- is the idea of reduced excitation. Strictly speaking, this notion can be ruled out as the HR acceleration seen to CS- was not simply due to a reduction in vagal output. Instead it was controlled jointly by an increase in sympathetic activation and a decrease in vagal output.

One view that fits nicely within the present framework has to do with competing reponses. Briefly, the subject is thought to develop a specific form of "active" competing or antagonistic behavior during the acquisition of a response to CS- which interferes with behavior in another direction(Hearst, 1972). As inhibition is often conceptualized as a response tendency opposed to excitation, this notion neatly accounts for the responses observed here. In the present study there were two different responses by two different systems, the response to CS+ being mediated by the vagus, and the response to CS- being under dual vagal and sympathetic control.

Summary and Conclusions

An investigation was made to determine the autonomic correlates of conditioned responses generated by an explicitly unpaired procedure. A 3 x 2x3 x 3 factorial design (drugs x CS frequency x measurement intervals x trial blocks) was used. Thirty rats received 30 pairings of a tone CS (5 or 10 kHz) and a shock US followed by 20 trials on Day 1 and 30 on Day 2 of another tone CS and the US presented in an explicitly unpaired fashion. Animals were then assigned to either of three groups and were administered atropine sulfate, propranolol hydrochloride, or saline. The subjects then received 10 additional explicitly unpaired CSs- and USs (four CS- and six US), four CS-, and four combined cue presentations.

The main findings were that: (1) the cardiac CR during acquisition was a deceleration, (2) the cardiac CRin the predrug explicitly unpaired trials was an acceleration, (3) the cardioacceleration was attenuated by both atropine and propranolol, (4) the cardiodeceleration was eliminated by the atropine treatment and, (5) a biphasic cardiodeceleration-acceleration was seen in the saline group during the combined cue phase while the atropine treatment blocked most decelerative components of the response and the propranolol treatment eliminated above baseline responding.

The results tended to support the view that two different systems were responsible for the differing responses to CS+ and CS-. The parasympathetic branch of the autonomic nervous system was believed to mediate the excitatory CR, while the response to the CS- was under dual

autonomic control from the cardiac sympathetics and the vagus. This notion fits in nicely with a "competing responses" theory, in that the subject apppeared to develop a specific form of "active" competing or antagonistic behavior during acquisition of a response to CS+ which interfered with behavior in another direction (the response to CS-).

It is also possible to suggest that the response to CS-, which was opposite in direction to that elicited by CS+, was due to an inhibitory mechanism. Numerous conditions for inhibition were met. More specifically, opposite responding was noted and the same US was used in the training of responses to both CS+ and CS-.

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