EFFECTS OF EXOGENOUS STIMULI AND CENTRALLY ACTING DRUGS ON GALVANIC SKIN RESPONSES IN RATS

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Accepted August 1, 1980

Abstract—Effects of physical stimulus and psychic stimulus on the galvanic skin response (GSR) in rats were evaluated. A significant change in the GSR was observed after exposing the rat to the noise of hand-clapping, and introducing another rat into the cage. The latter stimulus had a much greater effect than the former. Changes in GSR were measured after various animals were introduced into the test cage. A shift in the GSR in intrusion of guinea pig or rabbit was significantly greater than that in intrusion of Wistar rat, but no difference was observed in intrusion of rat and mouse. Changes in GSR were studied by introducing another animal into the test cage containing a single rat (isolated state) or a pair of rats (grouped state). The change in the GSR in the grouped state was generally smaller than that in the isolated state, but there was no difference in the score between these states when a rabbit was introduced. When the effect of drugs on changing of GSR was investigated, we found that elevation of GSR value, as induced by exogenous stimuli, was inhibited by tranquilizers such as chlorpromazine, carpipramine and diazepam. These tranquilizers in a remarkably small dose had an apparent effect on the psychic, mutual relation in GSR test in rats.

We have been studying the psychic, mutual relationship of animals and the effect of drugs on this relationship. Using a modified method of Tedeschi et al. (1), we found that fighting episodes increased considerably only when a single mouse was around the test cage containing a pair of mice (2). In the seizure test on El mice (3, 4), lowered seizure threshold and synchronization of seizure occurrence (5) were demonstrated when a pair of mice was given a stimulus by shaking. Next, the effect of cohabitation (2 or 3 mice) on spontaneous exploratory behavior and the influence of drugs acting on CNS were investigated (6). The results in these tests were expressed as a total of 2–3 animals or an average value/animal to minimize the individual variation. In the present investigation, attempts were made to clarify the mutual relationship with respect to emotional parameters of animals by using changes in galvanic skin response (GSR) (7) as an index to indicate changes in the behavior of rats by cohabitation. Further, the influence of various drugs on changes in GSR was evaluated.

GSR (7, 8) is an experimental parameter frequently used in the field of human psychology and psychophysiology; however it is infrequently used on experimental animals (9–12). The majority of experimental animals have been cats. In a previous paper (13), we reported the changes in the electrical skin resistance (ESR), and duration of
sustained response following a physical stimulus to normal and SART (13, 14),
specific stress caused by alternation of rhythm in temperature, stressed rats. SART
stressed animal is a model of a pathological diseased animal with experimental partial vagotonia. The effect of some CNS acting agents on these parameters was also reported.

MATERIALS AND METHODS

Animals: Male Wistar rats weighing 300–350 g were used in most cases, and male SD (Sprague-Dawley) rats, male SHR (spontaneously hypertensive rats), ddY mice or DBA/2 mice were used in some of the tests.

Measurement of GSR: GSR in rats was measured according to our method reported previously (13). The procedure is outlined below. Solder electrodes with a diameter of 3 mm were used to record the GSR. One day prior to the test, hair from the middle back (about 2.5 cm in diameter) was removed using a depilatory agent (Shiseido). After the hair remover cream was wiped off with a cotton ball, ether anesthesia was given, and two electrodes were planted on the skin with a quick-hardening dental resin (Nissin Dental Products, Inc., MEND-REX). The animals thus prepared were set free in the test cage (25 x 45 x 20 cm, Almite) and the electrodes were connected to a GSR recording bridge (Nihon Kohden, GSR-2) with EEG recording cords. To protect the cords from damage and to increase the degree of mobility of the animal, the cords were suspended before being connected to the bridge box. A DC current (3V) was allowed to flow into the electrodes from a Wheatstone bridge and the GSR recorded in a multipurpose polygraph (Nihon Kohden, MR-45) after being amplified with a biophysical amplifier.

As shown in Fig. 1, GSR was recorded with a single rat (isolated state) and two rats of the same strain (grouped state) in the test cage.

Stimuli: A simple physical stimulus of a single hand-clap from behind the animal, and a psychic stimulus by introducing another animal into the test cage for 60 sec, were used. The second animals introduced into the cage were the same strain of male Wistar rat, different strain—male SD rat, male SHR, a rodent family but smaller—ddY mouse, chocolate colored DBA/2 mouse, comparable body size but different family—guinea pig, and a much larger animal of a different order—rabbit (white, weighing about 2 kg).

Indicator of changes in GSR: The rate of change of GSR and duration of sustained

Fig. 1. Newly designed procedure using galvanic skin response for testing psychic, mutual relationship.
response were used as a parameter to indicate the degree of response. A stable GSR curve obtained after connecting the electrodes to a GSR recording bridge box was designated as spontaneous reflex (mm). Following the control, the GSR curve shifted widely with a stimulus such as noise from hand-clapping. The amplitude between the peak and the trough of the GSR curve was designated as stimulus reflex (mm) to indicate the intensity of the reflex response. Both spontaneous and stimulus reflex are associated with changes in the skin electrical resistance and expressed in mm, but they may be converted into units of resistance (Ω). The percentage change of the stimulus reflex against the spontaneous reflex is designated as the rate of change in the GSR. The duration of sustained response is the time during which changes in the GSR curve persisted.

Test agents and doses: (a) Major tranquilizers—chlorpromazine hydrochloride (Shionogi, 1 and 5 mg/kg), (b) thymoleptica—carpipramine (Yoshitomi, Defecton®, 5 and 10 mg/kg), (c) minor tranquilizer—diazepam (Takeda, Cercine®, 3 and 5 mg/kg), (d) central inhibitory chemical transmitter and brain metabolic activator—γ-amino-butyric acid (GABA, Daiichi, Gammaron®, 300 and 500 mg/kg), (e) its derivate—L-γ-amino-β-hydroxybutyric acid (L-GABOB, Ono, Gambetal® L-form, 100 and 500 mg/kg), and (f) a neurodepressant extracted from rabbit skin infected with cow pox virus—Neurotropin® (Nippon Zoki, 1.5 and 3.0 ml/kg). These water-soluble drugs were dissolved in saline and water-insoluble or poorly soluble materials were suspended in gum arabic and the concentration adjusted so that the volume for administration was 1 ml/kg. All test agents were given i.p. GSR was measured 60 min after drug administration, and the ratio of GSR before and after treatment was calculated.

RESULTS

1. Changes in GSR under isolated state: Changes in GSR caused by the stimulus of hand-clapping or invasion-retreat by a rat of the same strain, were investigated under an isolated condition. The rate of change in GSR and duration of response are shown in Fig. 2.

From Fig. 2, the rate of change in GSR caused by stimulation by hand-clapping and

![Fig. 2. Influences of stimuli on galvanic skin response of rats. Asterisks show significant differences from the value in "sounds caused by clapping of hands". **: p<0.01, ***: p<0.001. No. of experimental rats: 8 male Wistar rats/group.](image-url)
invasion by another rat was 326±42% (mean ±S.E.) and 557±38%, respectively. Apparently, the latter stimulus caused a more profound change in the GSR. The duration of response caused by invasion of another rat was more prolonged than that by hand-clapping.

In the next experiment, changes in GSR caused by invasion by various animals were estimated. The GSR score obtained by introduction of the same strain (Wistar) of rat was used as a control. The GSR scores obtained after the invasion-retreat stimulus of other animal are illustrated in Figs. 3 and 4.

From Fig. 3, the GSR did not deviate much from the control when SD, SHR or a mouse invaded the cage; however, invasion by a guinea pig or rabbit caused a considerable elevation in the GSR to 728% and 785%, respectively, such being significantly different from the control (553%).

As can be seen in Fig. 4, only in the rabbit there was a significant prolongation of the duration of sustained response.

**2. Changes in GSR under grouped state:** Changes in GSR caused by hand-clapping and invasion-retreat of other animals (same strain of rat, ddY mouse, guinea pig and rabbit) under a grouped state were investi-

| Animals entered cage as a stimulus | % Variation of GSR wave (Mean ± S.E.) |
|-----------------------------------|-------------------------------------|
|                                   | 0  | 200 | 400 | 600 | 800 | 1000 |
| (Spontaneous variations)          |    |     |     |     | 100 |      |
| Rat                               |    |     |     | 553 ± 42 |     |      |
| same strain (control)             |    |     |     |      |     | 497 ± 40 |
| different strain                  |    |     |     |      |     | 497 ± 32 |
| SHR                               |    |     |     |      |     | 497 ± 32 |
| Mouse                             |    |     |     |      |     |      |
| white                             |    |     |     | 509 ± 94 |     | 524 ± 78 |
| chocolate colored                 |    |     |     |      |     |      |
| DBA/2                             |    |     |     |      |     |      |
| Guine pig                         |    | 728 ± 74** |     |     |     |      |
| Rabbit                            |    | 785 ± 61** |     |     |     |      |

**Fig. 3.** Changes of GSR in rats due to an animal entering cage as a stimulus. Asterisks show significant differences from the value in "same strain rat entering". *: p<0.05, **: p<0.01. No. of experimental rats: 7-16 male Wistar rats/group.

| Animals entered cage as a stimulus | Duration of response (sec) (Mean ± S.E.) |
|-----------------------------------|----------------------------------------|
|                                   | 0  | 20 | 40 | 60 | 80 | 100 | 120 |
| Rat                               |    |    |    |    |    | 75.9 ± 2.2 |      |
| same strain Wistar                |    |    |    |    |    |     |      |
| different strain                  |    |    |    |    | 80.8 ± 1.6 |      |
| SHR                               |    |    |    |    | 77.3 ± 2.4 |      |
| Mouse                             |    |    |    |    |    |      |      |
| white                             |    |    |    |    | 77.2 ± 3.3 |      |
| colored                           |    |    |    |    |     |      |      |
| DBA/2                             |    |    |    |    | 75.8 ± 2.7 |      |
| Guine pig                         |    | 82.1 ± 2.4 |     |     |     |      |
| Rabbit                            |    | 103.4 ± 6.7*** |     |     |     |      |

**Fig. 4.** Influence of an entering animal on response time of GSR in rats. Asterisks show the significant difference from the value in "same strain rat entering". ***: p<0.001. No. of experimental rats: 7-16 male Wistar rats/group.
gated and the results compared with findings when the animals were isolated.

As shown in Fig. 5, it was evident that there was no significant difference in the GSR by hand-clapping between the two states.

The percent changes of GSR caused by invasion-retreat of the same strain of Wistar rat in the isolated state and grouped state were 553±42% and 383±52%, respectively, with an apparent reduction in scores in the latter case. Although the stimulus by the ddY mouse caused a slight change in the average percent change of GSR, it was not significant. A guinea pig caused a significant decrease of the score in the grouped state but the rabbit did not produce any difference in either state.

As shown in Fig. 6, there was no significant difference in the duration of sustained response by any of the stimuli in both states.

### Table 1: Variations in GSR wave (Mean ± S.E.)

| Stimulus                  | % Variation in GSR wave (Mean ± S.E.) |
|---------------------------|---------------------------------------|
| (Spontaneous variations)  | 100                                   |
| Sounds caused by clapping of hands | 386±55  |
| Rat (Wistar)              | 553±42  |
| Mouse (ddY)               | 599±84  |
| Guinea pig                | 729±74  |
| Rabbit                    | 785±81  |

**Fig. 5.** GSR of rats at the grouped state with another rat compared with the isolated state. Experimental rats were at the isolated state in a test cage. Experimental rats were at the grouped state with another Wistar rat in a test cage. Asterisks show the significant differences from the value in “isolated state”, respectively. *: p<0.05, **: p<0.01. No. of experimental rats: 7–16 male Wistar rats/group.

### Table 2: Duration of response (sec) (Mean ± S.E.)

| Stimulus                  | Duration of response (sec) (Mean ± S.E.) |
|---------------------------|-----------------------------------------|
| Sounds caused by clapping of hands | 9.1±1.5 |
| Rat (Wistar)              | 7.3±2.2  |
| Mouse (ddY)               | 7.7±3.3  |
| Guinea pig                | 8.2±2.4  |
| Rabbit                    | 10.3±6.7 |

**Fig. 6.** Response time of GSR in rats at the grouped state with another rat compared with the isolated state. Experimental rats were at the isolated state in a test cage. Experimental rats were at the grouped state with another Wistar rat in a test cage. No. of experimental rats: 7–16 male Wistar rats/group.
strain of rat were investigated in the isolated state, and the results are presented in Table 1. From Table 1, chlorpromazine at 1 mg/kg caused only a slight decrease in the GSR in response to hand-clapping, and at 5 mg/kg produced a significant reduction in the GSR. A dose-dependent fall in the GSR score by hand-clapping was also demonstrated with carpipramine, diazepam, and Neurotropin®. L-GABOB showed a tendency to lower the

Table 1. Influences of several drugs on change of GSR in rats due to sounds caused by clapping of hands or other rat entering cage.

| Treatment          | Dose (mg/kg) | Rate\(^a\) of response | Other rat |
|--------------------|--------------|-------------------------|-----------|
| Before administration | 1.00         | 1.00                    |           |
| Chlorpromazine     | 1            | 0.89±0.17               | 0.78±0.31 |
|                    | 5            | 0.61±0.09**             | 0.44±0.07*** |
| Carpipramine      | 5            | 0.79±0.19               | 0.84±0.19 |
|                    | 10           | 0.46±0.04***            | 0.44±0.03*** |
| Diazepam           | 3            | 1.14±0.13               | 1.18±0.16 |
|                    | 5            | 0.70±0.12*              | 0.67±0.07*** |
| GABA               | 300          | 1.05±0.24               | 0.79±0.06** |
|                    | 500          | 1.60±0.11**             | 1.27±0.07*** |
| L-GABOB            | 100          | 0.80±0.14               | 0.73±0.11* |
|                    | 500          | 0.77±0.17               | 1.24±0.15 |
| Neurotropin        | 1.5\(^b\)    | 0.44±0.02***            | 0.57±0.02*** |
|                    | 3            | 0.28±0.19*              | 0.61±0.02*** |

GSR was measured before and 60 min after the i.p. administration of drugs. Data show the mean value±S.E.. Asterisks show significant differences from the value before administration. \(^*\): \(p<0.05\), \(^{**}\): \(p<0.01\), \(^{***}\): \(p<0.001\). No. of experimental rats: 4–13 male Wistar rats/group. \(^a\): The value obtained by dividing GSR value after a drug by that before the drug. \(^b\): ml/kg.

Table 2. Influences of several drugs on the duration of response to stimuli in GSR of rats.

| Treatment          | Dose (mg/kg) | Rate of response time |
|--------------------|--------------|-----------------------|
|                    |              | Sounds                | Other rat  |
| Control            | 1.00\(^a\)   | 1.00\(^a\)            |           |
| Chlorpromazine     | 1            | 0.82                  | 0.99      |
|                    | 5            | 0.86                  | 0.84      |
| Carpipramine      | 5            | 0.87                  | 0.99      |
|                    | 10           | 1.11                  | 0.99      |
| Diazepam           | 3            | 0.92                  | 1.03      |
|                    | 5            | 1.00                  | 1.11      |
| GABA               | 300          | 1.02                  | 0.93      |
|                    | 500          | 0.87                  | 0.87      |
| L-GABOB            | 100          | 1.09                  | 0.89      |
|                    | 500          | 0.99                  | 0.95      |
| Neurotropin        | 1.5\(^c\)    | 1.11                  | 1.02      |
|                    | 3            | 1.20                  | 0.96      |

GSR was measured before and 60 min after the i.p. administration of drugs. No. of experimental rats: 4–13 male Wistar rats/group. \(^a\): mean time±S.E. of response to sounds was 8.9±0.8 sec. \(^b\): mean time±S.E. of response to other rats was 81.4±3.7 sec. \(^c\): ml/kg.
DISCUSSION

It is speculated that an emotional change in animals evoked by various stimuli can be elucidated by studying a shift in the GSR. It is conceivable from the nature of the GSR that a psychological stimulus produced a far greater change in the GSR than did a physical stimulus. The psychological stimulus caused by invasion-retreat of other animals all caused a considerable shift in the GSR, especially with the guinea pig and rabbit. It appeared that rats exhibited a greater emotional change, comparable to the state of fear, when exposed to larger and different species of animals.

A psychological state was apparently established among a pair of rats in a cage, and the response to an intruding animal was reflected by a shift of GSR in the grouped state. Namely, when the size of the invading animal is the same as rats such as another rat or guinea pig, the reaction of the host animals in a grouped state will be slight. It is assumed that a mutual reassurance was established among the two rats in the cage. However, no significant difference in the GSR was observed in the grouped state when a mouse or rabbit was introduced, and this seems to suggest the presence of a negative united sense among the host rats. Psychologically, the host rats appeared to ignore an invading mouse which is smaller in size and could be cope with by a rat alone without requiring a united front. A large animal such as a rabbit, on the other hand, appeared to evoke a greater emotional response comparable to the state of fear exceeding the limits of the united front of the host rats.

A report on the mutual psychological relationship of animals, is presented below. Tadokoro (15) conducted a test with a pair of monkeys in a Skinner box in which a lever pressed by a monkey was designed to deliver a painful electrical stimulus to the other monkey. In this study, it was demonstrated that the number of times the lever was pressed to get a reward was less in the presence of a much larger boss monkey, but the frequency was more in the presence of a smaller young monkey. When psychotropic drugs such as diazepam or chlordiazepoxide were administered, the inhibition on lever pressing was removed even in the presence of the boss monkey, due to loss of fear. An interesting phenomenon of labor division in rats has been reported by Mowrer (16) and investigated by Kataoka et al. (17) from a pharmacological standpoint. For this study, rats were trained to press a lever to get a reward. When two trained rats were housed together in a Skinner box, there was one animal who pressed the lever without getting a reward and another animal who was rewarded without pressing the lever. These authors discussed the activities of psychotropic drugs by referring to the loss or inversion of the above relationship by the drugs.

There are only a few papers in pharmacology which deal with the psychic, mutual relationship of animals. As far as the effect of psychotropic drugs is concerned, studies on the psychic, mutual relationship rather than on a single animal provide more valid data.

In the present experiment, psychotropic
drugs were used in much smaller doses than the usual pharmacological doses given experimentally.

The reason is as follows. GSR value is increased by exogenous environmental stimuli. It is thought that the increase may be caused by changes in delicate and psychic conditions of the animal. Psychotropic drugs have well-known pharmacological effects in usual doses. The possibility cannot be denied that a psychotropic drug may have a significant effect on these delicate and psychic conditions of animals, in addition to their ordinary effect. Thus a psychotropic drug may be effective in a much smaller dose than a usual pharmacological dose prescribed.

We clarified that an increase in the GSR value caused by an exogenous stimulus can be significantly inhibited by a small dose of a tranquilizer such as chlorpromazine, carpipramine or diazepam. It is a matter of course that this small dose of the tranquilizer had no influence on the usual common behavior of a rat, and on GSR of a rat in an isolated state. Thus, there is the possibility that an action of tranquilizer can be observed from the viewpoint of the psychic, mutual relationship between animals.

Neurotropin®, a neurosedative is considered to be clinically effective for disturbances related to the autonomic nervous system, and proved to be effective on experimental partial vagotonia in our specific ally-induced stress rats and mice (13, 14). Why Neurotropin® has inhibitory effects on increase of GSR, similar to the effects seen with tranquilizers, remains to be determined.

Our results support past proposals that GSR is related to both psychological and physiological activities.

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