Habituation failure of skin conductance response after intraventricular administration of 6-hydroxydopamine in cats

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Summary. The effects of intraventricular administration of 6-hydroxydopamine on electrodermal activity were studied in cats. The treatment slowed down or eliminated habituation of the skin conductance response to repeated auditory stimuli. However, the impairment of habituation was not accompanied by an increase in the rate of spontaneous skin conductance fluctuation.

A class of psychotropic drugs, called neuroleptics, are blockers of catecholamine receptors[1]. Catecholamine releasers, such as amphetamine and methyl-phenidate, can provoke schizophrenia-like psychosis or exacerbate schizophrenic symptoms[2,3]. These data strongly suggest that some dysfunction of the brain catecholamine system plays a key role in the pathogenesis of schizophrenic symptoms[4]. If this catecholamine theory is correct, a drug that has a more specific action on the catecholamine system should produce some abnormality similar to the disease.

6-Hydroxydopamine (6-OHDA) is a well-known neurotoxin that destroys catecholamine nerve terminals selectively and induces compensatory denervation supersensitivity of the system[5-7]. Various behavioral changes after intraventricular administration of 6-OHDA, such as social withdrawal, loss of initiative, reduction of activity, catalepsy, decrease of self-stimulation rate, and exaggerated aggressiveness when provoked, may have some relationship to schizophrenia[8-10]. However, whether these abnormal patterns of behavior in the animal are equivalent to human psychiatric symptoms is difficult to ascertain.

In the psychophysiology of schizophrenia, the largest amount of data so far collected employs electrodermal measurements (principally skin conductance activity), and this measurement appears to provide the most reliable index to indicate the characteristics of the disorder[11]. Therefore, the present experiment was undertaken to study the changes in the electrodermal activity after 6-OHDA treatment. Part of the work described in this paper has been reported as an abstract[12,13].

Materials and methods. 8 adult housecats were trained to wear a 1-piece leather suit and to be suspended with the suit from the ceiling of an auditory-insulated experimental box (90 × 80 × 110 cm). The skin conductance was measured between the paw pads of both hindlimbs, using silver-silver chloride bioelectrodes (Beckman 650950), sodium chloride paste (Beckman 201210) and adhesive collars (Beckman 650455). The electrodes were connected to a transducer, which had a variable reference resistor and passed a constant voltage (0.5 V) between the 2 electrodes. The transducer indicated the skin conductance as a ratio to the conductance value of the reference resistor (fig. A).

The skin conductance response was evoked by auditory stimuli of 5KHz frequency and 100 dB intensity (C-scale) with a 1-sec duration. They were applied 20 times at irregular intervals of from 10–60 sec about 25 cm obliquely in front of the animal's forehead. The timing of the stimuli and the skin conductance were recorded on a pen recorder (Nihon-Koden, WI-680G) and a magnetic tape (Sony Magnescale, NFR3915) for later analysis. The skin conductance showed some spontaneous fluctuations (F in fig. A). The rate of spontaneous fluctuation was counted from the 2-min recording made just before the first stimulus and calculated as a mean fluctuation number per min. Analysis of the skin conductance response followed the method used by Horvath and Meares[14].

After recording the fluctuation and the response to the stimuli, 5 cats were anesthetized with pentobarbital (26 mg/kg), and 6-OHDA (6 mg dissolved in 300 µl of saline containing 0.1% ascorbic acid) was injected slowly into the lateral ventricle as follows: 1 mg on the first day, followed by 2 mg and 3 mg on the second and third days respectively. The other 3 cats were treated with the vehicle according to the same schedule. On the seventh day after the final injection, the spontaneous fluctuation and the skin conductance response were recorded again. When all the recordings were completed, four 6-OHDA-treated cats and 3 vehicle-treated cats were anesthetized with pentobarbital and decapitated to estimate the catecholamine content in various regions of the brain by a fluorometric method[15]. 5 intact cat brains were used as a control. One 6-OHDA-treated cat was excluded because it died of an illness before the estimation.

Results. The average skin conductance level of the 8 intact cats just before the stimulation was 12.4 ± 2.6 (SE) µmho. When the novel auditory stimulus (S in fig. A) was given to the cat, the skin conductance increased temporarily after a latency of 1.5 ± 0.1 sec, reaching its peak within 2.4–5 sec and then declining gradually (R in fig. A). Following repetition of the stimulation, the amplitude of the response became smaller, eventually disappearing. This phenomenon is 'habituation' of the responses. Figure B(a) shows an example of the response in an intact cat at the first (S-1) and the 20th (S-20) stimulus. The habituation process of the responses is indicated more quantitatively by figure C(a). Each point in this figure represents the mean amplitude of the responses of the 8 intact cats (the response amplitude was expressed by 'change in log conductance' from the prestimulus level to its peak value, see fig. A). A regression was carried out for each cat on each recording. The 'log habituation point' was determined from the regression line as the log number of the stimuli required for extinction of the response. The average log habituation point of the 8 cats was 1.32 ± 0.15.

In contrast, the 6-OHDA treated cats showed little or no habituation of the response. Figure B(b) shows a specimen recording of the responses of a 6-OHDA-treated cat to the first (S-1) and the 20th (S-20) stimulus. The mean response amplitude of the five 6-OHDA cats to each stimulus is indicated in figure C(b). In one 6-OHDA cat, the regression line sloped upward, and the log habituation points of the other 6-OHDA cats were 8.25, 4.28, 3.54 and 2.46, respectively. These values were significantly higher than those of the intact cats ($p < 0.005$, the number-of-runs test). The 3 vehicle-injected cats showed normal habituation, with the log habituation points being 1.67, 0.97 and 0.74, respectively. These values did not differ significantly from those of the intact cats ($p = 0.79$), but did from those of the 6-OHDA cat ($p < 0.05$).

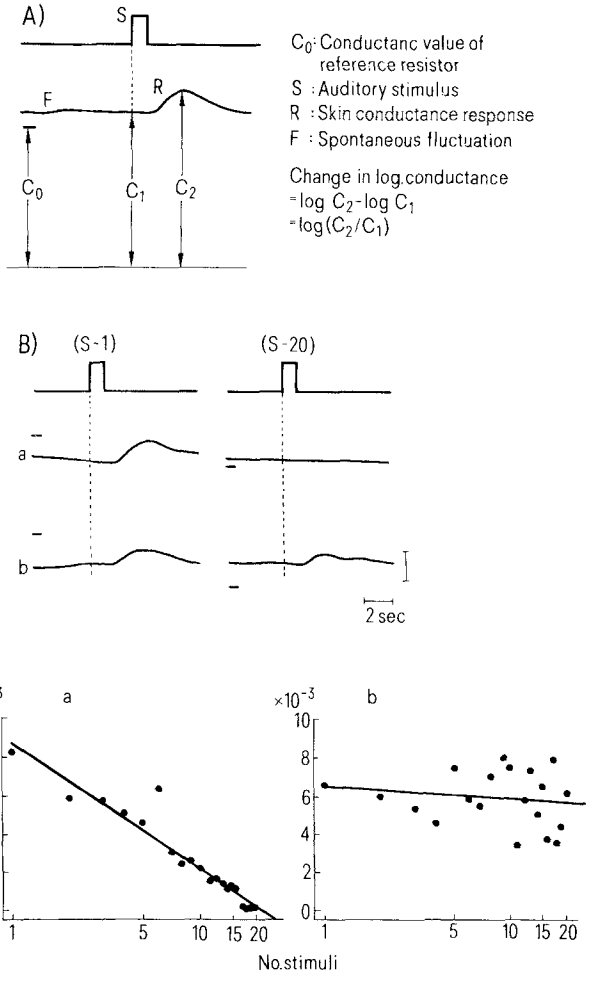
The rate of spontaneous skin conductance fluctuation varied from 3 to 13 per min (mean 5.6 ± 1.2 per min) in the intact cats. As with human electrodermal activity[14], the value of the spontaneous fluctuation showed a correlation with the rate of habituation; the higher the fluctuation frequency, the slower the habituation of the skin conductance response. In the 8 intact cats, the correlation coefficient between the log habituation point and the fluctuation rate was 0.77 ($p < 0.05$). The recorded points obtained from the 3 vehicle-treated cats were within the confidence interval of the regression line of the intact cats ($p > 0.1$). In spite of the extreme slowing of the habituation, the spontaneous fluctuation frequency of the five 6-OHDA cats did not increase, but rather tended to decrease (mean 3.3 ± 0.3 per min). 4 points obtained from the five 6-

OHDA cats were out of the confidence intervals of $p = 0.001$, the remaining one being out of the $p = 0.025$ criterion.

The fluorometric estimation revealed that the concentrations of noradrenaline and dopamine in the brain were decreased in the 6-OHDA-treated cats. The noradrenaline content was markedly decreased in the frontal cortex (to 15% of control), the hippocampus (18%), the n. accumbens (21%), the hypothalamus (25%), the amygdala (28%) and the n. caudatus (32%). A significant decrease of dopamine was noted only in the n. caudatus (28%) and the n. accumbens (48%). The content of catecholamine was not found to decrease significantly in the vehicle-treated cats.

Discussion. Studies of human electrodermal activity in normal subjects have disclosed that both the habituation rate of the skin conductance response and the spontaneous fluctuation rate reflect the vigilance level of the central nervous system, and the value of the former correlates highly with that of the latter[16]. In various neurotic or agitated depressive patients, relatively slow habituation and high spontaneous fluctuation are observed, suggesting a high level of arousal in these conditions[17]. On the other hand, there is general agreement that extremely slow habituation of the skin conductance response tends to be observed in schizophrenia[11]. Recently, Hovarth and Meares have noticed that the habituation failure in schizophrenia is not accompanied by elevation of the spontaneous fluctuation rate[14]. This finding may suggest that, in schizophrenia, the arousal system is neither in a simply overactive state nor in an underactive state, but has some dysfunction in itself. A good correlation between the habituation rate and the spontaneous fluctuation rate was also observed in intact and vehicle-treated cats in this experiment. However, in the 6-OHDA cats, the habituation was significantly slowed down, but the spontaneous fluctuation rate did not increase. This observation is consistent with the above-described characteristics of schizophrenia. Therefore, 6-OHDA-treated animals may be a useful animal model of the disease for elucidation of its pathogenesis.

At present, many investigators assume that overactivity of the dopamine system, especially the mesolimbic dopamine system, might be implicated in the pathogenesis of schizophrenia[18]. However, our neurochemical study on the 6-OHDA-treated cat brain revealed significant reductions in the noradrenaline concentration, but relatively less marked reductions in the dopamine concentration. The enhancement of noradrenaline depletion in this experiment may be a consequence of the multiple doses of 6-OHDA[19]. Studies with anesthetized cats have demonstrated that the central noradrenaline system is indispensable for the generation of electrodermal responses[20]. There is also evidence that the brain noradrenaline system has a strong relationship to the arousal function[21]. These findings suggest that some disturbance such as denervation or supersensitivity in the noradrenaline system, rather than in the dopamine system, may play an important role in the development of the electrodermal changes. Further studies will be necessary to elucidate this mechanism.



A Illustration of the skin conductance response and the measurement of its amplitude (change in log. conductance). F shows an example of the spontaneous fluctuation.

B Specimen recording of the skin conductance response to the first (S-1) and the 20th (S-20) stimulus from a cat before (a) and after (b) the 6-OHDA treatment. The horizontal bar at the beginning of each trace indicates the conductance level of the reference resistor. It was 25 µmho in (a) and 30 µmho in (b). The vertical calibration indicates 5% of the reference conductance, that is, 1.25 µmho in (a) and 1.5 µmho in (b).

C The mean response amplitude of the intact (a) and the 6-OHDA-treated cats (b) to each stimulus.

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