

Drug-Set Interaction: Psychological and Physiological Effects of Epinephrine Under Differential Expectations

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To determine whether physiologic responses to a drug could be changed by expectation, and what role placebo effect might play, 14 medical students were given either epinephrine or placebo. Measurements of subjective response and response of plasma free fatty acids, blood glucose, and heart rate were made. Stimulant expectation was engendered by suggestion of epinephrine-like effects, and sedative expectation by suggestion of barbiturate-like effects. Of 8 drug subjects, 8 had a greater FFA response under stimulant expectations, and 7 had greater subjective, blood glucose, and heart rate responses. In 6 placebo subjects, there was no discernible effect of expectation in any measure.

THE QUESTION of how expectations (i.e., set) can influence the action of drugs is one which is currently receiving a great deal of attention on a number of different fronts.¹⁻⁶ One model of drug-set interaction implies that when subjects have well-defined and appropriate expectations concerning intended drug ac-

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tion, the resulting observed drug effect (defined in terms of the superiority of the drug over an inert placebo) will be greater than when Ss are not permitted to have such appropriate expectations. Thus, evidence now exists which suggests that this model holds in such diverse situations as amphetamine and barbiturate administration in normal Ss,⁷ treatment of neurotic patients with meprobamate,⁸ and evaluation of an appetite depressant in normal Ss.⁵ In the latter study, for example, no drug effect on food intake was revealed when the Ss were told nothing about the intended action of the medication; with Ss who were informed that an appetite-depressing drug was being studied, however, food intake was significantly reduced; placebo administration did not reduce food intake under either condition.

All models designed to predict human

drug response must, of necessity, be extremely complex, and variables (drug dose, physician personality, physical setting, and patient or subject population, as well as many others) influence the quality of the response; nevertheless, in most of the studies cited, drug response was to some degree influenced by set, usually to a greater degree than was placebo response. Drug-set interaction is the phrase used in this report to describe such phenomena.

The purpose of the present investigations was to explore the effects of appropriate and inappropriate expectations upon psychological, physiological, and biochemical measures during administration of a relatively potent sympathomimetic amine. Epinephrine was selected because it produces well-known changes in subjective state and also seems sensitive to set factors;⁹ in addition, it reliably raises pulse rate, blood glucose, and plasma free fatty acids (FFA).¹⁰

Basically, the questions being asked here were: (1) Can epinephrine effects be modified by drug expectations? (2) If modifications should be observed, would they be of the same order of magnitude as those observed when placebo Ss are given differential expectations?

Methods

Subjects

The Ss were 14 healthy medical student volunteers. They were screened for obesity, diabetes mellitus, and a history of paroxysmal tachycardia. Ss were asked to participate in 2 experimental sessions, 1 week apart at the same time of day. At the time of volunteering, they were told that moderate doses of 2 different drugs would be administered, and that they would be told more about the particular drugs at each session. They were further informed that the purpose of the experiment was to see how closely psychological and physiological drug effects tend to parallel each other. Ss arrived for each session after a 5-hr. fast; they

had previously been instructed to avoid strenuous exertion on the day of the session and not to smoke for at least 1 hr. prior to the session. These 14 Ss were studied individually in the same physical environment by the same experimenters at each session.

Procedure

Upon the S's arrival at the laboratory, an indwelling 20-gauge needle was placed in an antecubital vein and the first blood sample withdrawn. Additional samples were drawn every 10 min. thereafter. Immediately after each sampling, pulse rate was recorded and each S completed a symptom checklist (Fig. 1) describing his subjective state. After a 10-min. resting (control) period, the medication was administered: In both experimental sessions, 8 Ss received 0.4 mg. of epinephrine HCl intramuscularly, and 6 received an equal volume of intramuscular saline. Administration was single-blind, with the experimenter knowing the actual medication being administered, while the Ss *believed* they knew what was being administered. Ss' expectations about the medication were controlled in the following manner: During the 5 min. preceding the injection, the experimenter engaged the subject in an informally structured discussion of the procedures which were to follow. In a casual manner, the experimenter was able to induce 1 of 2 differential sets.

For 1 of the experimental sessions, the Ss were told that they would be receiving a stimulant drug which might produce such general effects as increased alertness, anxiety, and nervousness, palpitation, pounding pulse, tremor, and pressure or tightness in the chest. For the other experimental session, the Ss were told that they would be receiving a sedative drug which might produce sleepiness, heavy tongue, droopy eyelids, or a "dopey," "washed-out," or slowed-down sensation.

While from the viewpoint of meticulous experimental design, it would clearly have been desirable to balance the sequence of sets (i.e., sedative set followed by stimulant set for half of the Ss, with reverse sequence for the other half), this was not controlled in the present study. Subjects 4, 5, and 6

SYMPTOM INVENTORY									
Name _____					Date _____				
Session: 1 2		Period: 1 2 3 4 5 6							
How do you feel right now?									
	Not at all	A little	Quite a bit	Extremely		Not at all	A little	Quite a bit	Extremely
Energetic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Washed-out	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tremor of hands, arms, or legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Dopey	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lethargic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Palpitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Eyelids heavy or droopy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Trembling inside	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tongue heavy or hard to move	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Rapid breathing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Restless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pounding pulse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sleepy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Slowed-down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Difficulty in concentrating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pressure or tightness in chest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Apprehensive	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alert	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Calm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Has your body felt strange or different in any other way (besides those listed above)? If so, briefly describe your feelings in the space below. If not, simply write "No".

FIG. 1. Checklist used by subjects to indicate symptoms at intervals during tests.

(each of whom received the epinephrine in both sessions) were the only Ss who were given the stimulant set in the first session and the sedative set a week later in the second session. All other Ss (drug and placebo) were given the sedative set first, followed by the stimulant set.

Subjective response was measured by a 20-item symptom checklist. Each item was scored from 0 to 3, with stimulant items scored "plus" and sedative items scored "minus;" a single total score was derived from the algebraic sum of the 20 items. Data are expressed as maximum change following injection from the mean of the 2 baseline scores.

Pulse rate was monitored manually every 10 min. Blood was analyzed for glucose by the Somogyi-Nelson method,^{11, 12} and for FFA by the method of Dole.¹³ For each measure, the data are expressed as maximum change from the mean of the 2 control levels.

Results

Figures 2 and 3 present individual data under the different sets for drug and placebo Ss, respectively. Change from baseline for each subject is shown as a bar graph for each of the 4 dependent variables, measured under both the stimulant set and the sedative set.

Subjective State

Of 8 Ss receiving epinephrine, 7 had a greater "stimulant" response under the stimulant set ($p < .04$ by a one-tail binomial test); 1 drug S had the same response under the 2 sets. In contrast, only 3 of the 6 placebo Ss (obviously nonsignificant) had a greater response under the stimulant set. In general, then, there is no evidence that placebo Ss were in

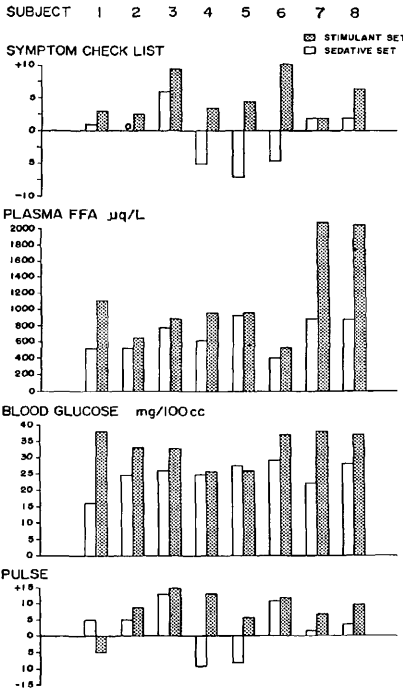


FIG. 2. Results of tests on 8 subjects given epinephrine.

any way subjectively influenced by their expectations, whereas drug Ss showed a consistent tendency to be affected by these same expectations. Of incidental interest is the observation that none of the 3 epinephrine Ss who were given the sedative set on the second session reported subjective sedation during this session (Fig. 2), whereas 3 of the remaining 5 Ss did report subjective sedation consonant with the set.

Sequence had some effect upon drug Ss. It is apparent that the only Ss who responded with predominantly sedative symptoms following a sedative expecta-

tion were those who had been given the sedative expectation on the first occasion. Apparently, the Ss who had been given the appropriate expectation with epinephrine on the first occasion, were not so readily influenced by the inappropriate expectation on the second occasion. Instead of feeling actually sedated, the other Ss simply were less stimulated. The effect of sequence on changes in physiologic variables was not clear.

Plasma Free Fatty Acids

All 8 Ss who received epinephrine had a greater FFA rise when they were expecting a stimulant ($p < .005$); only 2 of the 6 placebo subjects showed a greater rise under the stimulant set.

Blood Glucose

Of the 8 drug Ss, 7 had a larger glucose increase under the stimulant set

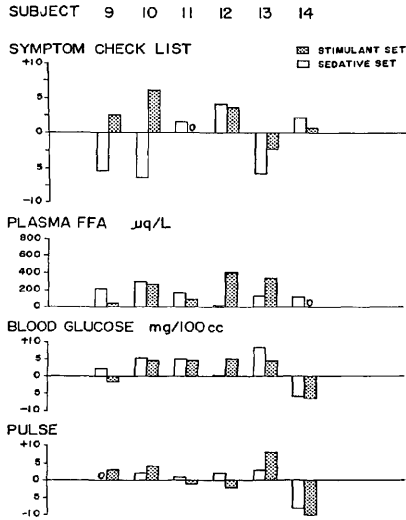


FIG. 3. Results of tests on 6 subjects given placebos only.

($p < .04$). Blood glucose changed very little in placebo Ss, with 5 of the 6 showing in fact a somewhat smaller increase under the stimulant set.

Pulse Rate

Of the 8 drug Ss, 7 had a greater pulse rise with stimulant expectations than with sedative expectations ($p < .04$); and 3 of the 6 placebo Ss responded appropriately to the different sets.

Discussion

Since it is widely accepted that subjective response to drugs can be manipulated by experimenters and clinicians, it is not surprising that the effect of expectations was evident in the subjective response of our subjects to epinephrine. It is of interest that the physiologic variables under observation were equally susceptible to set effects. The lack of appreciable consistent response to placebo suggests that in this particular model, the presence of epinephrine was essential to successful manipulation of response. The population of medical students is relatively sophisticated; they have heard about placebos and have a high index of suspicion. The degree of manipulation used in this experiment was gentle and personal. Subjects had been told that, because a moderate dose of drug was to be used, they might or might not experience symptoms. With less sophisticated Ss, and/or a more vigorous attempt at manipulation, consistent placebo response might have been evoked.⁸ Nevertheless, in the model described, the effect of expectation was seen in the presence of the drug and not seen in its absence.

The lack of consistent physiologic response to placebo, either as a function of expectation or across measures in individual subjects, deserves brief comment. The placebo itself has no effect on plasma

FFA, blood glucose, or pulse rate, whereas epinephrine does. Changes in FFA were much smaller with placebo injection, and probably reflect a response secondary to the anxiety engendered by the injection itself.¹⁴ Changes in blood glucose and in pulse rate were very small, usually not exceeding the inherent error of measurement. Apparently such small changes are not in themselves significant. The major point is that the changes were small and inconsistent and therefore could not explain the large and consistent effect of set upon drug action.

The use of a single-blind must be justified because the possible effect of experimenter bias cannot be denied. In pilot studies, it became quite apparent that the experimenter could readily discern epinephrine effects in Ss 3–10 min. following injection. Since Ss were studied twice, the experimenter would therefore be blind in the first session but not in the second. It seemed preferable therefore not to attempt to have the experiment blind on both occasions.

The consistency of drug Ss' reactions to set influence cannot be overemphasized. The actual amount of consistency across the different measures, however, is more difficult to estimate; of the 8 drug Ss, it was *not* the same individual who deviated from the group mode on the symptom check list, blood sugar, and pulse rate—for each measure, a different subject was involved. This was even more pronounced in the placebo group, where there was no evidence of any relationship across the 4 measures; knowing how a placebo subject responded psychologically told us nothing about what to expect on the physiological measures.

In summary, the subjective and physiologic effects of epinephrine were amenable to manipulation by variation of S expectation. This could not be explained additively by placebo response. If the stimulant set simply added endog-

enous epinephrine to the exogenous epinephrine to produce the results observed in epinephrine Ss, the same amount of endogenous epinephrine should have been observed in placebo Ss, and a systematic difference due to set should have been observed; this was not the case. This model seems to represent an example of interaction between expectation and drug at the subjective and at the physiologic levels.

The mechanism of differential physiologic response to epinephrine as a function of expectation is not clear. Further studies relating higher integrative function to modified physiologic responses to drugs may ultimately explain these findings.

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