

Health and Disability

Drug effects: Agonistic and antagonistic processes

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The research presented here has shown that tolerance to drugs can be accelerated by conditioning processes. Placebo effects may be considered the opposite of tolerance, and we have shown that placebo effects may be objectively recorded by physiological measures (electromyography, skin conductance responses, and event-related potentials), as well as by behavioral and subjective methods. The placebo response, or more precisely, the expectation of drug effects, can add to the effect of the drug. Drug antagonistic expectations can also reverse the effect of the drug. There is some evidence that placebo effects are strongest when expectations are reinforced by administration of an active drug. Expectations have graded effects and may affect symptoms to a smaller or larger degree. Although drug effects can be considered stimuli, the investigation of the role of classical conditioning in drug use and drug effects involves special issues that must be carefully considered.

Key words: Placebo response, placebo effect, placebo analgesia, startle, classical conditioning, expectancy.

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INTRODUCTION

Pavlov (1927) reported on an experiment where morphine was administered repeatedly to dogs. Morphine has, like all drugs, several effects, including salivation, vomiting, and sleep. This was well known prior to Pavlov's experiment, and his contribution was the observation that the dog started salivating and vomiting at the sight of the experimenter, prior to the injection of morphine. Thus, the drug acted as an unconditioned stimulus, and the experimenter as the conditioned stimulus that reliably signaled the drug effect. Pavlov further observed that the greater the number of injections of morphine, the stronger was the conditioned reaction.

Drugs are stimuli (Catania, 1971) and may enter into associations with other stimuli, according to the principles of classical conditioning. Most cases of administration of drugs can be considered conditioning trials, since distinct signals are present prior to the administration of the drug, and prior to the occurrence of the effect of the drug. There are, however, important differences between classical conditioning with sensory stimuli compared to conditioning with pharmacological stimuli.

First, the unconditioned stimulus is the effect of the drug on the central nervous system (Eikelboom & Stewart, 1982; Ramsay & Woods, 1997). The drug itself is not the unconditioned stimulus, nor are the peripheral effects of the drug the proper unconditioned stimulus. The proper unconditioned stimulus is the effect of the drug in the central nervous system. Secondly, the onset latency, duration, and intensity of drug effects are different from those of unconditioned stimuli more commonly used, e.g., electric shock or aversive noise. Thirdly, drugs are distributed throughout the organism and often elicit many different unconditioned effects.

THE ROLE OF EXPECTATIONS IN PHARMACOLOGICAL TREATMENT

The field of psychopharmacology was introduced to me by Professor K.G. Götestam and his group at the Department of Psychiatry and Behavioural Medicine in Trondheim. For our thesis, Rolf Gråwe, now a senior scientist at SINTEF, and I experimented on changing the effects of an anxiolytic drug (Flaten, Gråwe, Dahl & Haug, 1991). The basic idea was that by injecting the anxiety relieving drug diazepam in rats prior to the presentation of painful electric stimuli, the rats would associate the effects of diazepam with pain. Consequently, the anxiolytic drug should elicit fear. Some patients have been reported to respond paradoxically, with increased unrest, to benzodiazepines. This could be due to the drug administration regime, as some patients take benzodiazepines on demand, i.e., the drug is ingested prior to anxiety-provoking events for these patients, e.g., social events. One of Götestam's tenets was that basic research should be relevant to clinical problems, and the experimental procedures developed by the group in Trondheim were modeled after clinical problems. Flaten *et al.* (1991) was not able to change the unconditioned effects of diazepam, possibly due to a procedure for measurement of fear that was too complex. Other studies, on the other hand, have shown that the drug administration regime may play a role in the effectiveness of the drug (Berntzen & Götestam, 1987).

Associative tolerance

In Trondheim I was also introduced to the work of Shepard Siegel, and at the time his work on associative tolerance was a hot topic (Siegel, 1976; Siegel, Hinson, Krank & McCully, 1982). Siegel had shown that conditioned stimuli that reliably signaled

the injection of, e.g., morphine, accelerated tolerance development, compared to groups of animals that received morphine injections that were not signaled. This was called associative tolerance, as it could not be explained by physiological processes, and showed that drug effects could be reduced by learning processes. Associative tolerance was observed with different drugs and in different laboratories. Siegel's theory that associative tolerance was due to compensatory conditioned responses was debated. However, Eikelboom and Stewart (1982), in a very influential paper (see also Ramsay & Woods, 1997), argued that the unconditioned effect of a drug is its action on the central nervous system. Many, maybe all drugs, have peripheral actions, e.g., reduced body temperature after morphine. When a drop in temperature is registered in the central nervous system, compensatory mechanisms are activated to restore body temperature to normal values. The input to the central nervous system is the signal to increase temperature, and this is the proper unconditioned stimulus. What seemed to be a compensatory conditioned increase in body temperature, is actually an agonistic conditioned response that mimics the action of morphine, according to this account (Eikelboom & Stewart, 1982).

Siegel's work led to numerous studies in other laboratories, including a few human studies. Flaten, Simonsen, Waterloo, and Olsen (1997) investigated whether associative tolerance could be seen in humans, and if so, could tolerance be related to a conditioned response. The design involved two groups: the conditioned group received administration of the muscle relaxant carisoprodol in the laboratory, and it was hypothesized that the administration procedure in the laboratory would become a conditioned stimulus signaling the effects of carisoprodol (the unconditioned stimulus). The unpaired group ingested the carisoprodol capsules at home, and received capsules containing lactose in the laboratory. Exposure to the conditioned stimulus and the drug were, therefore, the same in both groups, but only the conditioned group received pairings of the conditioned stimulus with the unconditioned stimulus. This procedure was performed three times for each subject, with one week between each procedure. On the fourth day of the experiment the conditions were reversed, so the paired group received lactose in the laboratory, and the unpaired group received carisoprodol.

Carisoprodol decreases blink reflex amplitude as measured by electromyography. My graduate work had been conducted in Kenneth Hugdahl's laboratories at the University of Bergen, and he introduced me to psychophysiological methods, that we used in the study of psychopharmacology. Two main findings emerged from this experiment (Fig. 1): (1) Associative tolerance was evident in the finding that carisoprodol had a stronger inhibitory effect on blink reflexes in the unpaired group compared to the conditioned group, even if both groups received the same amount of drug. The reduced drug effect in the conditioned group was, therefore, evidence of associative tolerance in this group. (2) When the conditioned group received lactose on the fourth and final day of the experiment, blink reflexes were increased compared to the unpaired group. Increased reflex amplitude after presentation of the conditioned stimulus was

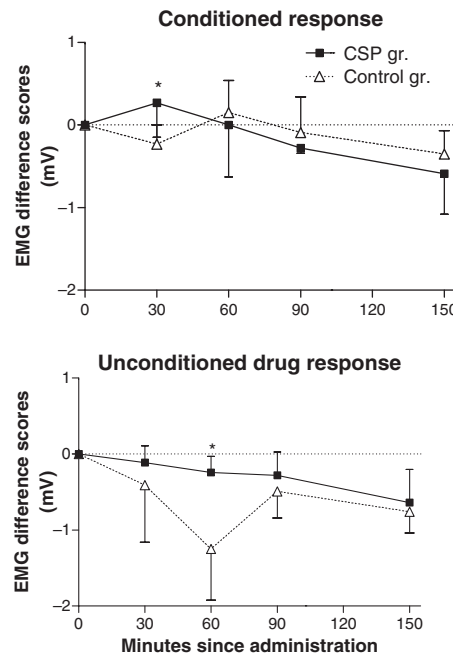


Fig. 1. Top panel: Mean EMG difference scores after administration of lactose. There were increased blink reflexes 30 minutes after administration of the inactive capsules in the group that had received administration of carisoprodol in the laboratory (the CSP group) during acquisition. This is contrary to the inhibitory effect of carisoprodol on blink reflexes. Lower panel: Mean EMG difference scores after administration of carisoprodol. There were increased blink reflexes 60 minutes after carisoprodol administration in the CSP group compared to the Control group, indicating that carisoprodol had less of an effect in the CSP group, probably due to associative tolerance. Source: From Flaten, Simonsen, Waterloo and Olsen (1997). Reprinted with kind permission of Wiley.

opposite to the unconditioned drug effect, and we interpreted these as conditioned antagonistic responses. To our knowledge, this was the first demonstration that drug antagonistic responses could be conditioned in humans and inhibited the drug effect, i.e., tolerance (Flaten *et al.*, 1997).

The placebo effect

The finding in Flaten *et al.* (1997) showed that environmental contingencies could reduce the drug effect. Finding a way to avoid tolerance, or even increase the effect of a drug would be beneficial for pharmacological treatment, and other forms of treatment. The placebo response may be seen as the opposite of tolerance, and is an example of a drug agonistic response. However, there was little systematic research of placebo effects in the mid-1990s, and one important issue was whether the placebo effect could be observed in physiological and/or health relevant processes. Alternatively, the placebo effect could be a response bias, affecting only the reporting of symptoms. Psychophysiological methods were well suited to study physiological reactions related to placebo effects. Another issue was the definition of placebo effects. What psychological processes

were involved? Research by Don Price (Price, Milling, Kirsch, Duff, Montgomery & Nicholls, 1999) showed a high correlation of an expectation of a drug having a specific effect, and the resultant effect of a placebo. Thus, the induction of an expectation, via verbal information or via conditioning procedures, was the main contributor to placebo effects.

In our first studies of placebo effects, information about drug effects were provided verbally. This procedure had been used successfully by Dinnerstein and Halm (1966) and Brodeur (1965), and in a pilot study of our own (Flaten, 1998). Our aim was to investigate whether a placebo response could be objectively measured, how it compared to the response to the drug, and how the placebo response interacted with the drug response. Carisoprodol was again the drug used in the study, and subjects received information that was either agonistic with the drug effect, i.e., that they would feel relaxed and sleepy, or information that was antagonistic to the drug effect, i.e., that they would feel energetic and alert. Half of the participants received lactose in the capsules, so the placebo response could be seen in these subjects. The other half received carisoprodol, and provided information on the interaction of the drug with drug-related information.

Blink reflexes were decreased by the relaxant information, which was evidence that the expectations reduced not only the subjective reporting of symptoms, but had physiological effects as well. Furthermore, the results showed an increase in reported tension in the subjects who received lactose and had been told they received a stimulating drug, i.e., a placebo response was observed in this group (Fig. 2). The most interesting finding, however, was that the information overrode the drug effect: subjects who received the relaxant carisoprodol with information that it acted as a stimulant, reported being tenser than subjects

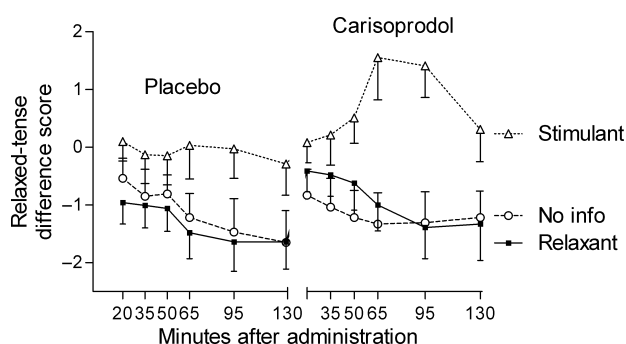


Fig. 2. Increased tension is indicated by higher scores. The left part of the figure displays responses to drug-related information. All participants received placebo, and increased tension in the Stimulant group is a placebo response. The right part displays responses to the same information, but after administration of the muscle relaxant carisoprodol. Note the larger increase in reported tension in the Stimulant group as increasing amounts of the drug were absorbed. The data are expressed as the difference from pretest, performed before administration of the capsules.

Source: From Flaten, Simonsen and Olsen (1999). Reprinted with kind permission of Wolters Kluwer.

who received the same information together with lactose (Fig. 2). Thus, carisoprodol seem to have produced an unspecific internal stimulus complex that was interpreted by the participants in accordance with the drug-related information. The term “active placebo” refers to a control condition in clinical drug trials where instead of lactose, a drug is administered that has no effect on the symptom under investigation, but has side effects similar to those of the drug tested. Carisoprodol has subjective effects, and this could have increased confidence that a drug had been administered, with resultant larger expectations of drug effects. This is, to our knowledge, the first demonstration of an active placebo effect, i.e., that administration of a drug increased the placebo response (Flaten, Simonsen & Olsen, 1999).

The “active placebo” paradigm, where information about the drug is paired with administration of an actual drug with subjective effects, is probably more relevant in the understanding of placebo effects in the ordinary use of drugs than is administration of an inactive agent together with drug-related information. Drug and placebo effects work together in ordinary drug administration, and administration of drugs and placebos, separately and together, allows the investigation of interactions of expectations and drugs.

Placebo effects to caffeine-associated stimuli

Pharmacological treatment is provided to treat illness or reduce symptoms, and this important aspect was not part of our initial experimental model, since we looked at whether expectations could induce psychophysiological processes, or could change the drug response (Flaten, Simonsen, Zahlsen, Sager, Aamo & Olsen, 2004). Placebo effects are stronger when treatment, in some form, is administered to correct a deviation from a set point (Flaten, in press; Siegel, 2008). It is common to ingest a drug, caffeine, in the morning to increase arousal and alertness to optimal levels. In most users, the effects of caffeine had been paired thousands of times with the ingestion of coffee, making coffee a conditioned stimulus signaling increased arousal. Caffeine-deprived subjects should be lower on arousal, and administration of coffee should increase arousal in these subjects.

This hypothesis received support, as we found increased skin conductance responses, an index of sympathetic function, eye-blink reflexes, and subjective arousal after administration of decaffeinated coffee (Flaten & Blumenthal, 1999; Mikalsen, Borgersen & Flaten, 2001) (Fig. 3). Caffeine administered in orange juice increased arousal more than did caffeine administered in coffee. Thus, caffeine-associated stimuli, i.e., the taste and smell of coffee, elicited physiological and subjective reactions that added to the effect of caffeine.

Placebo analgesia

The caffeine model showed that placebo effects could be elicited in individuals expecting a drug to reduce a deviation from a desired state. However, the model of placebo analgesia has

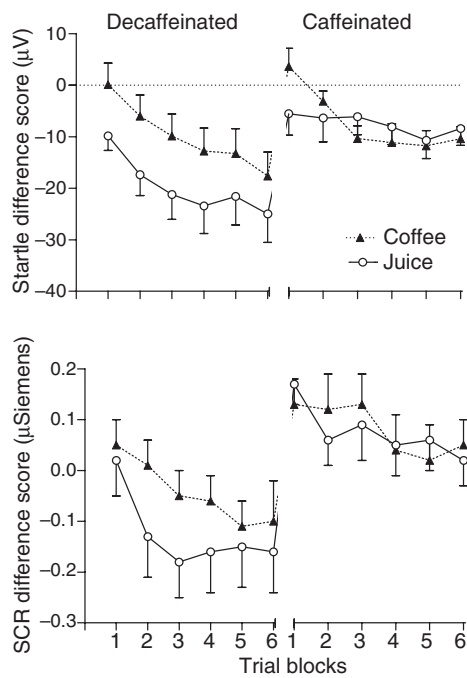


Fig. 3. Mean scores in each trial block for the blink reflex and skin conductance response (SCR) data, for each of the four conditions. The data are expressed as difference from pretest scores.

Source: Reproduced from Flaten and Blumenthal (1999) with kind permission of Springer Verlag.

advantages over the caffeine model. The onset, duration, and intensity of pain can be controlled experimentally. Pain had also been shown to be modified by expectations, and the clinical relevance was obvious. In Johansen, Brox and Flaten (2003) ischemic pain was induced by a tourniquet that occluded circulation in the lower arm. This procedure leads to a linear increase in pain across a period of up to 45 minutes that we used in our studies. When pain reached seven on a ten-point scale, an injection of saline with information that it was a painkiller was administered to some of the subjects, whereas the control group did not receive any injection and information. The main findings were that a small, but significant placebo analgesic response was observed in participants who received the injection.

Another issue that this study addressed was whether the placebo analgesic response was due to some general mechanism such as a reduction in stress. Cortisol levels were not affected by the information that a painkiller had been administered. However, a third group in the study had received information that the injection would increase their pain. In this group a relatively large increase in cortisol was observed, but no further increase in pain, probably due to a ceiling effect. Thus, stress levels during painful stimulation were found to vary depending on the information provided to the participants.

In Flaten, Aslaksen, Simonsen, Finset, and Johansen (2006), capsules containing a low dose (500 mg) of the painkiller acetaminophen were administered prior to application of the tourniquet, to observe the placebo analgesic response over a longer

time period, up to 45 minutes, compared to Johansen *et al.* (2003). The subjects received either positive information about the capsules, i.e., that they contained a large dose of a very effective drug that acted quickly, or neutral information, that the capsules contained a low dose of a drug that in many individuals had little effect. The results showed reduced pain after positive information about the drug, i.e., an example of a placebo effect. This was the first demonstration of a graded placebo effect, i.e., both groups received information that a painkiller had been administered, but the placebo analgesic response was stronger in the group that had received the positive information.

Flaten *et al.* (2006) showed that the placebo analgesic effect was not related to cortisol (similar to Johansen *et al.*, 2003) or subjective stress, and placebo analgesia could not be explained by decreased stress. One limiting factor was that stress levels were low prior to application of the painful tourniquet, and a further decrease in stress could not be expected.

An unexpected finding emerged, that placebo analgesic responding was seen in males only, and not in female subjects (Fig. 4). The experiment was run by female research nurses at the Department of Clinical Research at the University Hospital of North Norway. The relation of gender to pain and placebo analgesia was investigated by Per Aslaksen in his doctoral thesis. Aslaksen, Myrbakk, Høifødt, and Flaten (2007) showed that males reported less pain when a female acted as the experimenter, compared to males that reported pain to a male experimenter. This finding showed what most researchers know, but occasionally forget about, that subjective report is subject to response bias. Heart rate variability data from Aslaksen *et al.* (2007) showed that pain-induced changes in heart rate variability were similar for males tested by females and males tested by males. Thus, the response to the painful stimulus was the same, but the subjective report was not. This finding was included in a consensus report on the testing and reporting of pain data (Greenspan, Craft, LeResche *et al.*, 2007), and it is now recommended that all publications where pain is reported should provide information on the gender of the experimenters.

A general placebo effect?

The idea that there was a general component that was involved in several or all placebo effects had been difficult to prove, as shown in Johansen *et al.* (2003) and Flaten *et al.* (2006). Aslaksen and Flaten (2008), on the other hand, showed reduced stress after administration of a placebo, and the reduced stress mediated the effect of the placebo on pain. The reason for the discrepant findings is of a methodological character. Aslaksen and Flaten (2008) induced increased stress by applying painful stimulation in a pre-test, thus avoiding the floor effect that seem to have played a role in the findings of Flaten *et al.* (2006).

Reduced stress after administration of treatment is probably a general component in most treatment. In pain, negative emotions, which are an important part of the stress response, have been shown to increase pain (Rhudy, Williams, McKabe, Russell & Maynard, 2008), and positive emotions are associated

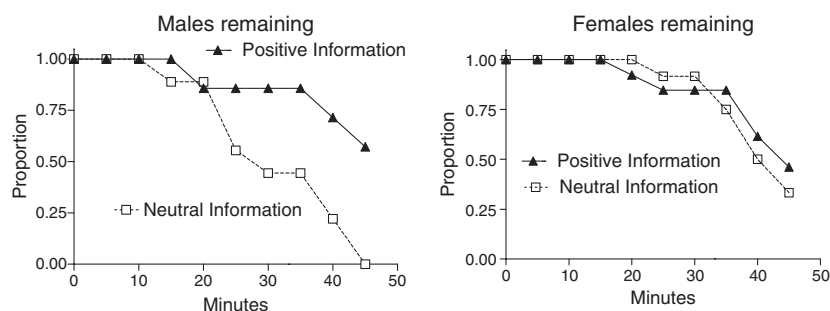


Fig. 4. Pain tolerance to the submaximum tourniquet stimulus. The graphs show the proportion of males and females that have not terminated the painful stimulus at different points in time after stimulus onset. Note that all males in the group that received neutral information about the drug terminated the stimulus before 45 minutes had passed. In the group that received positive information about the drug, 43% of the males terminated the stimulus before 45 minutes.

Source: Adapted from Flaten *et al.* (2006) with kind permission of Elsevier.

with a decrease in pain. The stress response has also been implicated in several other symptoms or processes related to symptoms, e.g., in cardiac heart disease and immunological processes (Pacheco-Lopez, Engler, Niemi & Schedlowski, 2006), that are important for a number of different diseases. Thus, the finding of stress reduction after administration of treatment points to a general component in placebo effects.

The issue of specificity in placebo effects is still debated. Montgomery and Kirsch (1996) and Benedetti, Arduino, and Amanzio (1999) found evidence of highly specific placebo analgesic responses, as reduced pain after placebo administration was observed on bodily sites where a placebo cream had been applied, but not on sites where the cream had not been applied. Watson, El-Derey, Bentley, Vogt, and Jones (2006) and Watson, El-Derey, Vogt, and Jones (2007) on the other hand, found specific placebo responses only in a subset of subjects, with other subjects showing either a generalized placebo analgesic response (which would be consistent with the notion that placebo effects were due to stress reduction), and some subjects displaying no placebo reaction. Thus, the issue of specificity in placebo reactions is still under debate.

Event-related potentials to painful stimulation

The effect of social context on pain report made it clear that other measures of pain, in addition to subjective report, should be employed. Painful stimulation induces reliable changes in the electroencephalogram and can be observed as event-related potentials (ERPs). The first pain-related ERP component is the N2, that may be observed about 200 ms after stimulus onset, and immediately thereafter the P2 component is observed. These components are often referred to as the N2-P2 complex, and both components are correlated with pain report (Granovsky, Granot, Nir & Yarnitsky, 2007). Both components also vary along with the intensity of the painful stimulation. Thus, more stimuli with higher intensity elicit larger amplitudes in the N2-P2 complex and are correlated with increased reported pain. Only repeated application of stimuli with abrupt onset can be used, i.e., stimuli where the time from onset to peak intensity is

very short. Thus, laser stimuli that activate heat pain receptors are well suited, and contact heat pain where the thermode is rapidly heated can also be used. In our setup the heating rate of the thermode is 70 °C/sec, starting at 32 °C and the maximum is at 52 °C. These parameters produce reliable P2 components, whereas the N2 may not be observed in all subjects.

Aslaksen, Lyby, and Flaten (2009) presented repeated contact heat pain to healthy participants who took part in two conditions. In the natural history condition, painful stimulation was administered in three blocks across a period of about 45 minutes. In the placebo condition, the painful stimulation was the same, but the subjects received capsules, containing lactose, after the first block of stimulation, with information that the capsules contained a powerful painkiller. A significant placebo analgesic response of about 15 mm on a 100 mm scale was observed in the placebo compared to the natural history condition. Interestingly, the P2 component in the ERP was also significantly reduced in the placebo condition. This finding is important for two reasons: The reduced P2 component is an objective measurement of pain-related activity that can validate the subjective pain report. Moreover, the reduced P2 component indicates the biological mechanism underlying placebo analgesia. Since the N2-P2 component is the first cortical response to painful stimulation, the pain signal to the cortex seems to be reduced in the placebo condition. Inhibition of the pain signal could occur in the spinal cord via descending pain inhibitory pathways, as suggested by several authors (Wager, Matre & Casey, 2006; Goffaux, Redmond, Rainville & Marchand, 2007). Alternatively, the pain signal could be reduced in the thalamus, and this would indicate that less attention was paid to the pain stimulus in the placebo condition. The first explanation is the most likely one, as placebo analgesia in several studies has been shown to be reduced by administration of naloxone, and increased levels of β -endorphin have been observed in placebo responders (Lipman, Miller, Mays, Miller, North & Byrne, 1990). Wager, Rilling, Smith *et al.* (2004) showed that placebo analgesia was associated with midbrain, possibly periaqueductal grey activity, which fits well with the notion of placebo analgesia being controlled by a descending, pain inhibitory system.

A general model for the modification of unconditioned reflexes and drug effects?

The idea that drugs are stimuli suggests that the rules of classical conditioning also apply to conditioning with drugs as stimuli. The processes of interest are often drug tolerance or sensitization, and how presentations of the conditioned stimuli, or the context in which the drug has been administered in the past, may affect the development of the unconditioned drug effect (Flaten *et al.*, 1997; Siegel, 1976). In studies of classical conditioning, on the other hand, the conditioned response is the dependent variable of interest. Several authors have suggested that the modification of unconditioned reflexes also follows the laws of classical conditioning, e.g., Pavlov (1927), the opponent process theory of Solomon (1980), and Domjan (2005).

The clinical relevance of studies of associative tolerance in particular cannot be denied; however, such studies are scarce in humans due to the cost of the studies, the unconditioned stimulus can only be administered once per day, and several pairings are needed, making these studies very time consuming. The safety of the volunteers is another issue, in the laboratory and after the session has been run. Thus, if external unconditioned stimuli could be used as models of drug unconditioned responses, then problems related to cost and safety would be greatly reduced.

As noted, the process of reflex modification is conceptually similar to drug conditioning processes. Reflex modification procedures involved the presentation of a weak stimulus, e.g., a tone, prior to the presentation of a reflex-eliciting stimulus, e.g., a loud noise. As in drug conditioning studies, the dependent variable is the magnitude of the unconditioned response, which in most cases is inhibited by the presentation of the weak first stimulus (Hoffman & Ison, 1980). To investigate the role of associative factors in reflex modification, a series of studies were performed with skin conductance responses (Flaten & Hugdahl, 1990a) and subsequently the startle blink reflex as the unconditioned response (Flaten, 1993; Flaten & Hugdahl, 1990b). The results were clear, as they showed that inhibition of the unconditioned response was not due to learning, and reflex modification could not be used as a model to investigate how the conditioned response could modulate the unconditioned response (Flaten & Hugdahl, 1990b). However, there are claims that the inhibition of unconditioned responses can be due to learning (Solomon, 1980; Domjan, 2005). The published data suggest that conditioned fear induced by the CS may enhance unconditioned responses (e.g., Nees, Hahn, Schulz, Blumenthal & Schächinger, 2009), but there is little evidence suggesting that other learning processes may inhibit startle below baseline levels.

Emotional modulation of reflexes

Peter Lang's group developed reflex modification into a model for the study of emotional valence (Lang, Bradley & Cuthbert, 1990; Lang, Davis & Öhman, 2000). The startle eyeblink reflex

was reliably increased when elicited in the presence of a stimulus that induced negative emotions, and some studies showed a decrease in reflex magnitude when elicited in the presence of positive emotions. Among the advantages of the startle reflex is the short latency, about 50 ms for acoustic stimuli, from stimulus onset to a response can be recorded. Ole Åsli and I used this feature of the startle reflex to investigate the minimum latency of conditioned fear. The general procedure involved a first phase of aversive classical conditioning where the conditioned stimulus, a tone, was paired with an aversive unconditioned stimulus, e.g., loud noise or electrical stimuli. In a second phase, startle eyeblink reflexes were elicited at different points in time shortly after onset of the conditioned stimulus. It was hypothesized that the tone would induce conditioned fear, and the negative emotion of conditioned fear should increase startle reflexes. The variable of interest was the minimum stimulus onset asynchrony between the conditioned stimulus and the reflex eliciting stimulus at which reflexes were increased, compared to a control group that did not receive paired presentations of the tone with an aversive stimulus. Some theories state that cognitive appraisal of the stimulus would be necessary for the conditioned stimulus to evoke fear. Other theories state that fear is detected by a mechanism that extracts simple features from a stimulus, with a resultant fast elicitation of conditioned fear (Öhman & Mineka, 2001).

The results favored the last theory. Conditioned increases in startle reflexes were seen already at 30 ms after onset of the conditioned stimulus (Åsli, Kulvedrøsten, Solbakken & Flaten, 2009). However, this was seen only in participants who were exposed to a delay conditioning procedure, where the conditioned stimulus is present till the unconditioned stimulus, aversive noise in this experiment, is administered. In subjects exposed to a trace conditioning procedure, where there is a temporal gap between offset of the conditioned stimulus and the onset of the unconditioned stimulus, no conditioned fear could be observed. These findings have been replicated with electric shock as the unconditioned stimulus (Åsli & Flaten, submitted).

The implications of these findings are that fear is elicited rapidly, and consequently requires relatively little processing. Fear reactions may, therefore, be elicited by cues that are outside the subject's attention. These speculations are supported by the finding of fast fear reactions after delay classical conditioning, but not after trace conditioning procedures, where working memory is involved.

CONCLUSION

Drugs are stimuli, and may enter into associations with other stimuli. A signal that a specific drug will be administered, may generate subjective and physiological responses that are agonistic, or antagonistic, to the drug effect. Drug-anticipatory responses may provide information on how subjective states change bodily processes, may increase or decrease the effect of drugs, and may have consequences for health. Drug agonistic

and antagonistic responses can be understood as activation of homeostatic mechanisms by stimuli associated with drug effects.

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