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Opponent-Process Theory Predicts Environmental Cues Influence Drug Responses, Pain, and Opioid Abuse

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Abstract

Opponent-process theory describes the responses to drugs during exposure. It defines the processes that can contribute to addiction, and predicts the time course of drug responses, tolerance, withdrawal symptoms, and accidental overdose. Moreover, Siegel and many others have provided considerable evidence showing the influence of environmental cues in such effects. Cues present at the time of drug intake can become associated with the drug through Pavlovian conditioning. If narcotic pain relievers are administered in a consistent environment (e.g., at home or in a hospital room), then those cues can become associated with the drug. When opioid administration is discontinued, the conditioned location cues are predicted to induce hyperalgesia, leading to discomfort and pain. Patients may think they need to continue opioid usage when the pain they are experiencing is not due to their injuries (which are long healed); instead, the pain is due to these associative effects. These processes likely contribute to the widespread and tragic problem of opioid addiction, and provide implications for treatment of acute and chronic pain.

Despite their discovery decades ago, there are well-established, yet often unknown, psychological processes that have important implications for addiction to opioids and other drugs of abuse [1,2]. Nearly fifty years ago, Richard Solomon at the University of Pennsylvania first described how "opponent processes" are capable of exerting an influence on responses during drug exposure [1]. While opponent-process theory (OPT) predicts many human and nonhuman affective responses to a wide variety of experiences, the hundreds of articles on OPT have largely focused on drug processes. OPT has been used to define the processes that can contribute to addiction, and predicts the time course of, for example, drug responses, context-dependent tolerance, withdrawal symptoms, and accidental overdose. While these behavioral and physiological effects have been confirmed experimentally, few practitioners are aware of opponent-processes in response to drug exposure, and how they may contribute to addiction. The closing segment of this report will point out an important new application of this theory to drug addiction involving pain relieving drugs.

Space will not allow a detailed description of OPT, but the foundation can be provided (For a complete description of opponent-process theory, including discussion of A states and B states, see Solomon articles in the references). The initial administration of a drug produces a drug-specific effect on the body or behavior: the "*a-process*" (e.g., euphoria, analgesia, and hypothermia for an opioid, euphoria and increased heart rate for amphetamine, euphoria and sedation for alcohol). These *a-processes* occur quickly after each drug administration, and do not change in magnitude or duration during the lifetime of experience with the drug. In addition to the a-process, drug administration produces an "opponent *b-process*" that acts to counteract the *a-process* (e.g., dysphoria, hyperthermia and hypergesia for an opioid; dysphoria and decreased heart rate for amphetamine; dysphoria and hyperactivity for alcohol). While initially weak in intensity, repeated drug administration increases the *b-process*, the development which nearly always represents adaptive, compensatory responses that serve to maintain the organism at homeostasis, since the *a-processes* move the organism away from equilibrium. For example, the *a process* for a drug may serve to increase heart rate, whereas the *b process* for this drug would decrease the heart rate (a return towards resting rate).

If the a-process is larger than the b-process, the organism will experience symptoms in the direction of the a-process. The opposite is true if the *b-process grows to be* larger than the *a-process*. Early in the organism's experience with the drug, the *a-process* is stronger than the *b-process*, however, after much experience with the drug, *b-processes* will have grown a great deal in magnitude; along with its ability to counteract the *a-process*, and the drug no longer produces many effects on the body, behavior and affective responses. The buildup of the *b-process* with repeated drug exposure thereby promotes tolerance to the acute *a-process* symptoms. There are times when only symptoms produced by the *b-process* are experienced by the individual, since the *b-process* had grown so large that it is much larger than the *a-process*. This is especially notable as the drug is eliminated from the body since the *a-process* will immediately end, and only the *b-process* remains. That is, withdrawal symptoms (*b process*) occur.

One important issue for the present discussion is that Siegel [2,3] has provided much evidence showing the influence of environmental cues in such effects. Cues present at the time of drug intake can become associated with the drug through Pavlovian conditioning. According to this widely-accepted conditioning component of OPT, the learned response to these cues is responsible for producing the *b-process*. The cues elicit this "compensatory response" to prepare the person for the drug that is about to be experienced. Much experimental evidence confirms these predictions. These effects may even be responsible for changes in physiological mechanisms of tolerance. By giving drug administrations in the presence of cues (to build up the learned

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response to the cues), and then (in order to test the learned response in the presence of cues), one can compare the drug effect with the cues present to the effect of the drug with the cues absent. These studies show a significantly smaller response to the drug when the cue is present, supporting the prediction of OPT [4].

In addition, OPT predicts that a cue repeatedly paired with a drug would produce a measurable "anti-drug response" (the *b-process*), if the cue alone is presented in the absence of the drug. The drug does not have to be given in order to see an explicit response to the cue. Dr. Chris Cunningham and his colleague [5] repeatedly administered ethanol to rats in the presence of distinctive environmental cues of the experimental chamber. According to OPT, these environmental cues would come to produce a conditioned response (CR) when the organism encounters the cues, and this CR will be the opposite of the (*a-process*) effect of ethanol. Because an ethanol injection produces a hypothermia response (*a-process*), the cues associated with ethanol would be expected to produce a hyperthermia response; leading to an attenuated overall drug effect when the drug and cues are presented together (the cue reduces the response to the drug). This presentation of drug with and without the cues is a very respectable test of the theory, and the empirical effect (reduction in hypothermia) is solidly confirmed. However, regarding the critical issue discussed below involving opioid addiction, it is important to note that one particular test used by Mansfield and Cunningham was even more important. They tested the effect of the environmental cue when no ethanol was given, and the cue produced hyperthermia. Siegel's [4] rats were given repeated pairings of environmental cues with morphine, and were measured for pain tolerance (hyperalgesia/hypoalgesia). After many pairings, the analgesic response to the morphine was lower when the cues were presented along with the morphine. Again, this is an effect predicted by the opponent-process theory and shown by many laboratories. However, Siegel also tested the direct effects of the environmental cues in the absence of morphine, and the rats exhibited evidence of low tolerance to pain- hyperalgesia to these cues.

How might these processes affect a person in their environment? What does this mean for opioid addiction? Some cases of addiction arise for patients given pain relievers for a medical condition, and they become addicted to the drug, and strive to continue usage even after the pain from the original injury has subsided. Opioids produce analgesia (pain relief as the *a-process*). If opioids (e.g., hydrocordone, oxycontin) are consumed often at home or the hospital during a stay, then those cues can become associated with the opioid. Cues associated with opioid, because of the learned association, can cause the opposite response from that of the a process (i.e., pain induction). Sustained opioid use in a particular location will cause the *b-process* to grow, thereby diminishing the analgesic effect (cue-induced tolerance). When opioid administration is discontinued, those location cues will lead to discomfort from the *b-process*. This can cause the person to experience pain as a result of these conditioning cues triggering hyperalgesia. People may think they need to continue opioid usage when the pain they are experiencing is not due to their injuries (which are long healed); instead, the pain is due to these associative effects. These processes likely contribute to the widespread and tragic problem of opioid addiction as usage is prolonged. The solution to the conditioned pain response is, rather than more opioids (more conditioning trials if given with the cue), is to experience the cues without the drug. This process is called extinction. Cue-alone exposure will cause the conditioned pain response to decrease over many drug exposures. The notion that conditioned responses to cues associated with narcotics can induce pain themselves has not received any attention, and its potential to prolong the apparent need for such drugs mandates that its effects be recognized. This recognition may lead to clinical strategies that discourage the acquisition of such associations (e.g., by varying the locations where the drug is administered) or may encourage additional cue exposure (in the absence of the drug) as an extinction treatment.

Significance Statement

Opponent-process theory describes the responses to drugs during drug exposure, and the influence of environmental cues in such effects. These processes likely contribute to the widespread and tragic problem of opioid addiction, and the end of the review of this topic provides new perspectives on cues and addiction as well as treatment of acute and chronic pain.

Conflict of Interest Statement

- Both authors state no conflicts of interest regarding this manuscript.
- Both authors had a role in writing this manuscript.
- As a theoretical short report, there are no data to make available.

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