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Role of Opioid Receptors in Incentive Contrast

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A downshift from a more preferred to a less preferred incentive leads to a transient rejection of the lower incentive. This phenomenon, known as successive negative contrast (SNC), has been reported in studies with mammals, but not with fish, amphibians, or reptiles, all showing gradual adjustments to the new incentive conditions. It is assumed that an understanding of the brain systems involved in the onset of SNC in mammals will suggest likely brain areas for a comparative analysis in nonmammalian vertebrates. Studies reviewed in this article show that opioid receptors are normally engaged during SNC, participate in the detection of the incentive downshift, play a role in SNC onset (delta receptors), and modulate recovery from SNC (kappa receptors). However, opioid receptors do not seem to be involved in the consolidation of the downshift memory. These results suggest a relationship between the evolution of the opioid system and the evolution of learning mechanisms involved in the adjustment to incentive downshifts in vertebrates.

Most animals can be viewed as open systems in behavioral interaction with the environment to obtain resources important for their survival and reproductive success (sessile animals may be cited as exceptions, e.g., sponges). Such resources are called incentives and include food, fluids, shelter, nesting locations and materials, social companions, and others. Incentives have both absolute and relative value. The absolute value of incentives is demonstrated by the basic instrumental conditioning procedure, according to which an animal modifies an existing response or acquires a new response when that response is followed by an incentive (Thorndike, 1911). The relative value of incentives is demonstrated when the behavior supported by an actual incentive depends on the value of past incentives experienced under similar conditions (Elliott, 1928).

Incentive relativity is the basis of a wide variety of phenomena grouped together under the name of incentive contrast effects (see Flaherty, 1996). This article is concerned with one such type of incentive contrast effect known as successive negative contrast (SNC). In the classic demonstration of SNC, Elliott (1928) trained two groups of rats in a complex maze to locate an incentive and measured both the time to reach the goal (latency) and the number of entries in blind alleys (errors). One group was rewarded with bran mash, a wet mixture of cereals (the large incentive, L), whereas the other was rewarded with sunflower seeds (the small incentive, S). Rats learned the correct path to the goal faster when rewarded with L than when rewarded with S, but a shift from L to S resulted in a fast-emerging behavioral disruption (Figure 1a). Notice that the incentive conditions during postshift trials were equal for both groups. A generally accepted view of SNC suggests that the behavioral disruption reflects a comparison between the current incentive and the reactivated memory of the incentive previously

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received in that situation (see Papini & Pellegrini, 2006). When the disparity between past and current incentive is sufficiently large, then a variety of behavioral and physiological effects are observed, including changes in aggressive behavior, glucocorticoid levels, vocalizations, and escape behavior (see Papini & Dudley, 1997). Furthermore, treatments known from other experiments to relate to emotional effects, such as administration of anxiolytics or lesions in limbic structures, also modulate SNC (see Flaherty, 1996). Thus, it is widely appreciated that, when the disparity is significant, the comparator mechanism induces a series of effects that may collectively be referred to as emotional (Flaherty, 1996). The emotion in question is frustration, here defined as an aversive internal state induced by the surprising reduction or omission of an expected incentive (see Amsel, 1992). Amsel (1992) distinguished between an unconditioned form (primary frustration, occurring second-to-minutes after a surprising downshift event) and a conditioned form (secondary frustration, occurring in anticipation of a frustrating event).

As mentioned above, comparative studies suggest that SNC may not be a general learning phenomenon, at least among vertebrates. The SNC and similar effects have been reported in honeybees (Bitterman, 1976; Couvillon & Bitterman, 1984) and bumblebees (Waldron, Wiegmann, & Wiegmann, 2005), but the analysis of these effects at a neurobiological level is almost nonexistent in invertebrates. Consequently, this review is restricted to studies involving vertebrates. Experiments with species assigned to conservative vertebrate lineages in terms of brain structure, such as bony fish (e.g., Lowes & Bitterman, 1967), amphibians (e.g., Papini, Muzio, & Segura, 1995), and reptiles (e.g., Papini & Ishida, 1994), suggest that whereas these animals discriminate different incentive magnitudes, incentive downshift leads to, at best, a gradual adjustment of behavior to the new incentive conditions (see two examples in Figure 1b,c). This is referred to as reversed SNC. Although the mechanisms underlying SNC were proposed to be unique to mammals (Papini, 2002, 2003, 2006; see Bentosela, Jakovsevic, Elgier, Mustaca, & Papini, 2009), starlings (Freidin, Cuello, & Kacelnik, 2009; although not pigeons, Papini, 1997) must be added to the list of species exhibiting this effect. Several research strategies may be implemented to determine the source of this apparent species divergence in learning mechanism. The strategy illustrated in this article is based on a levels approach to learning mechanisms designed to capture some of the most traditional approaches to the study of learning, including the behavioral tradition traced back to Thorndike (1911) and the neurobiological tradition represented by Lashley's (1929) work. Figure 2 captures this idea in terms of four levels of mechanistic analysis. At the top, the traditional behavioral analysis of learning processes, as represented by Thorndike, Tolman, Hull, and the traditions that branched from these early contributions. A psychological level of mechanistic analysis refers to such concepts as stimulus-stimulus associations, as illustrated in the figure. These ideas are "modular" in the sense that they can be applied to a variety of learning processes, including appetitive conditioning and fear conditioning. Unlike the concepts used at other levels of analysis, these terms are specific to the analysis of learning mechanisms. The neurobiological level

refers to studies involving such techniques as brain lesion (pioneered by Lashley), stimulation, and recording of neural activity in relatively large cell populations. These studies aim at identifying the circuitry involved by any given learning phenomenon. The neurochemical level refers to traditional studies involving drug manipulations, such as most of the research reviewed in this article. Pavlov (1927) pioneered these studies by assessing, for example, the effects of bromides on experimental neurosis induced by conditioning procedures and even used morphine as an unconditioned stimulus. Drugs are the main factors used to study synaptic properties related to learning mechanisms. Finally, the cell-molecular level involves factors that interfere with cellular processes involved in synaptic plasticity. Some of the earliest examples involve studies on the role of protein synthesis in long-term memory (e.g., Agranoff, Davis, & Brink, 1966; Potts & Bitterman, 1967). Notice, however, that brain areas, neurotransmitters, and cellular processes are not specific to learning mechanisms, but intervene in a wide variety of biological processes (e.g., Kandel & Abel, 1995).

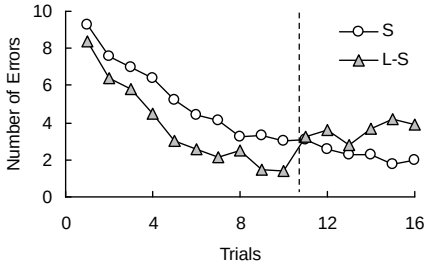
According to the approach illustrated in Figure 2, for learning phenomena in different species to be considered homologous (i.e., based on inheritance from a common ancestor), they must be based on the same mechanisms at the psychological, neurobiological, neurochemical, and cell-molecular levels. Because most progress in the understanding of mammalian SNC has been achieved in the area of neurochemical mechanisms (Flaherty, 1996), the strategy followed in the experiments described in this article aims at discovering the neurochemical systems involved in SNC onset in rats. It is hypothesized that phylogenetic changes in such systems are responsible for the evolution of mechanisms underlying SNC in vertebrates.

Role of Opioid Receptors in SNC

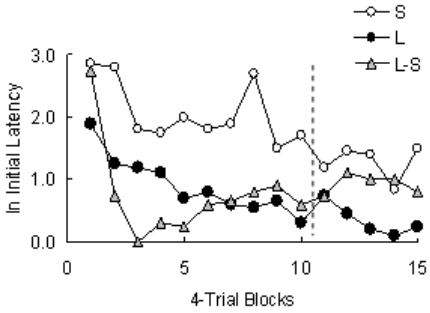
We owe most of our understanding of the neurochemical mechanisms underlying SNC to Flaherty and collaborators (see Flaherty, 1996), who used a consummatory version of this effect (cSNC). In the cSNC situation, two groups of rats receive ten 5-min-long daily trials of access to either 32% or 4% sucrose solutions (the L and S incentives, respectively), followed by five trials in which all rats are exposed to 4% sucrose. Various dependent measures have been used, including the amount of fluid intake, licking responses, and the cumulative time in contact with the sipper tube. Downshifted rats typically reject the 4% sucrose, but their behavior eventually recovers to the level of the unshifted controls only exposed to 4% sucrose. Flaherty (1996) discovered that certain drugs, such as benzodiazepine anxiolytics and ethanol, reduce cSNC on the second postshift trial (usually trial 12), but have no effect when administered before the first postshift trial (usually trial 11). This trial selectivity suggests that the mechanisms that control the triggering of cSNC and those controlling recovery from cSNC are dissociable. If the goal is to understand cSNC onset, then one would have to identify neurochemical systems that are activated selectively on trial 11. Flaherty's research failed to produce unequivocal evidence of this type of trial selectivity, but

he identified several drugs that reduced cSNC when administered before trials 11 and 12, including sodium amytal, cyproheptadine, and morphine (Flaherty, 1996). Of these three, morphine taps on a single neurochemical system, the opioid system, well known because of its role in the modulation of peripheral pain and conditioned fear, among other functions. Because of the known parallels between pain-fear and frustration (e.g., Gray, 1987; Wagner, 1969), it seemed appropriate to concentrate first on opioid receptors.

(a) SNC in Rats



(b) Reversed SNC in Pigeons



(c) Reversed SNC in Toads

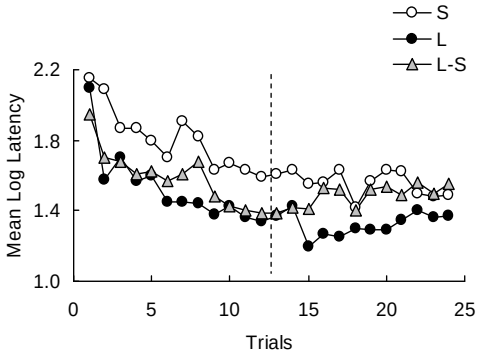


Figure 1. (a) The successive negative contrast (SNC) effect originally reported by Elliott (1928) in rats. ***(b)*** Reversed SNC effect in pigeons (Papini, 1997), and ***(c)*** in terrestrial toads (Papini, Muzio, & Segura, 1995). The dotted line marks the transition from a large (L) to a small (S) incentive. In these experiments, training involved a single trial per day. A runway was used with rats and toads, but the pigeon data were collected in a Skinner box situation. L was bran mash for rats, fifteen 45-mg food

pellets for pigeons, and 1,280 s of access to water for toads. S was sunflower seeds for rats, one 45-mg food pellet for pigeons, and 80 s of access to water for toads.

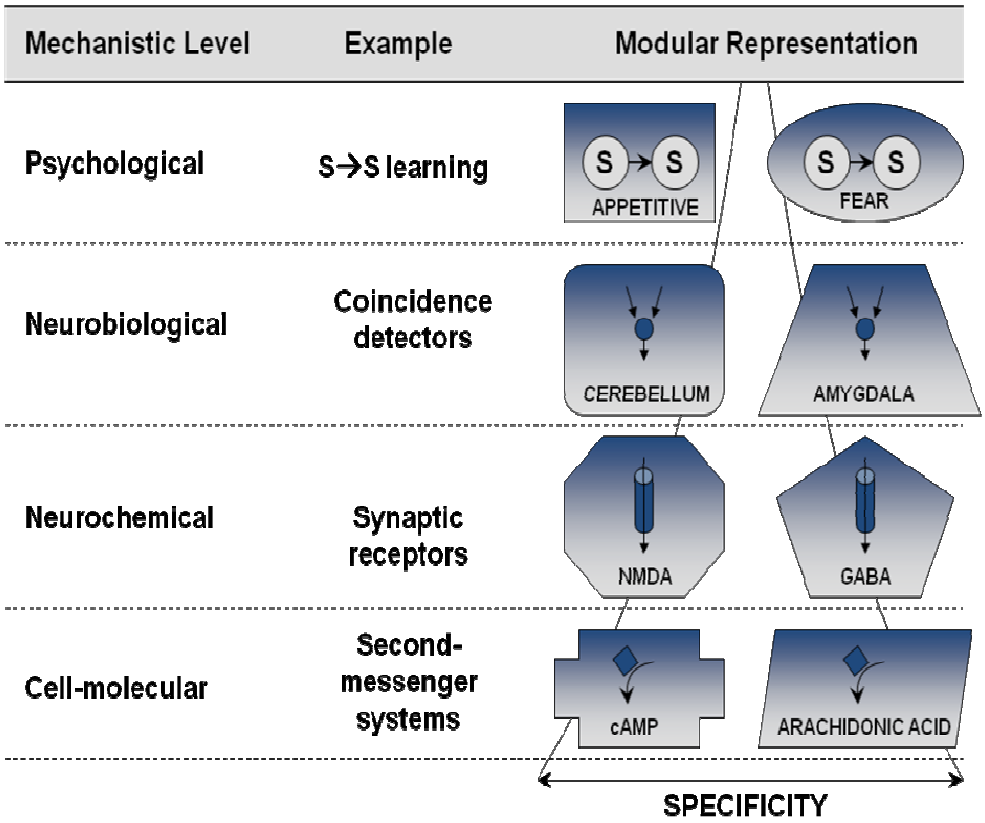


Figure 2. Four mechanistic levels of analysis of learning phenomena such as SNC (Papini, 2008). The modular representation column depicts alternative implementations of these mechanisms at each level. Modularity is implied in the possibility that any specific mechanism at one level may play a role in more than one mechanism at a higher level (e.g., NMDA receptors may be implicated in different types of learning, in different brain areas). Specificity refers to the fact that only psychological concepts are restricted in their application to explain learning phenomena. For example, cAMP is found in bacteria; being unicellular organisms, there is no synaptic plasticity in which cAMP could play a role similar to that which has been identified in animals.

The opioid system is relatively well characterized, from the genes coding for receptors and the precursors of their endogenous ligands, to the distribution and mRNA expression patterns in the rat brain (see Dreborg, Sundström, Larsson, & Larhammar, 2008; Ikeda et al., 2005; Mansour, Fox, Akil, & Watson, 1995; McNally & Akil, 2002; Sim-Selley, Vogt, Childers, & Vogt, 2003). Solutions derived from the poppy seed have been used for millennia to reduce pain induced by physical injury (Brownstein, 1993). Their active ingredient was isolated in 1806

and named morphine by Friedrich Sertürner. Of the four recognized opioid receptors, morphine has greater affinity for the mu receptor (MOR), but it also binds to the delta (DOR) and kappa (KOR) receptors, although not to the opioid receptor-like (ORL) receptor (also known as nociceptin opioid peptide receptor). Morphine is, thus, the starting point for an analysis of the role of opioid receptors in cSNC.

Rowan and Flaherty (1987) first reported that the pretrial systemic administration of morphine (4 and 8 mg/kg), whether before trial 11 or trial 12, attenuated cSNC without completely eliminating the effect. These doses had no detectable effect on consummatory behavior in rats exposed only to 4% sucrose (unshifted controls), but increased consummatory behavior in rats exposed to the 32-to-4% sucrose downshift. A higher dose of morphine (16 mg/kg) also disrupted the consummatory behavior of unshifted controls, thus making it difficult to interpret the effects of morphine on the consummatory behavior of downshifted rats. Rowan and Flaherty also reported that naloxone, a nonselective OR antagonist with greater affinity for the MOR, failed to disrupt cSNC (0.25, 0.5, and 1.0 mg/kg) when administered by itself. However, naloxone (0.5 mg/kg) eliminated the attenuating effects of morphine (4 mg/kg) when both were coadministered.

ORs are Engaged in cSNC

There were at least two potential problems with the naloxone data reported by Rowan and Flaherty (1987). First, because naloxone is expected to enhance cSNC, a 32-to-4% sucrose downshift could leave little room to detect further suppression of consummatory behavior, especially on trial 11 (i.e., a floor effect). Second, whereas the dose (0.5 mg/kg) used was sufficient to abolish the effects of morphine on cSNC, it may have been insufficient to have effects on its own. With these caveats in mind, Pellegrini, Wood, Daniel, and Papini (2005) exposed rats to a 32-to-6% sucrose downshift while administering a 2 mg/kg dose prior to trials 11 and 12. The treatment successfully enhanced cSNC. As shown in Figure 3, there was evidence of cSNC in both the saline and naloxone pairs of downshifted vs. unshifted groups, but whereas naloxone had no effect on unshifted rats, it significantly reduced consummatory behavior in downshifted rats. Moreover, whereas the cSNC effect (i.e., the difference between downshifted vs. unshifted groups) lasted two trials in the saline comparison (trials 11-12), it lasted at least 5 trials in the naloxone comparison (trials 11-15).

The enhancing effects of naloxone on cSNC were not restricted to these particular conditions. In a second experiment, Pellegrini et al. (2005) reported naloxone-induced consummatory suppression after the more conventional 32-to-4% sucrose downshift (2 mg/kg). This naloxone effect is not an automatic consequence of a downshift experience because a relatively mild reduction in sucrose concentration does not lead to enhanced consummatory suppression. For example, naloxone leads to significant suppression after 32-to-6% or 32-to-12% sucrose downshifts, but not after 16-to-3% or 16-to-6% sucrose downshifts

(Daniel, Ortega, & Papini,2009). Thus, opioid blockage is hypothesized to enhance the frustrative response to incentive loss, which in turn augments the cSNC effect.

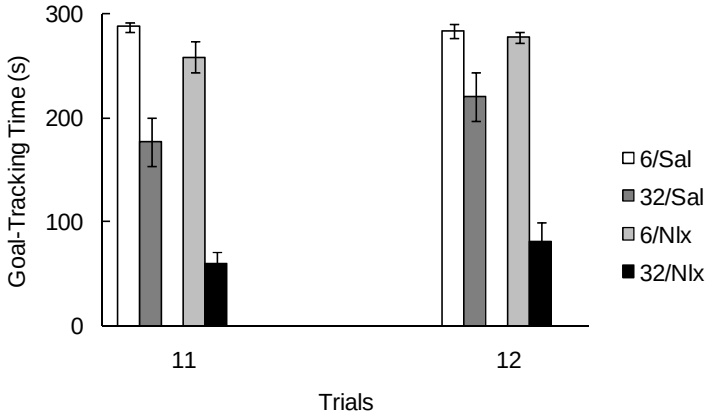


Figure 3. Effects of naloxone on cSNC (Pellegrini et al., 2005). Naloxone is a nonselective opioid receptor antagonist with greater affinity for the MOR. Rats were exposed for 10 trials to either 32% or 6% sucrose. On trial 11, downshifted animals had access to 6% sucrose (rather than the usual 32% sucrose), whereas unshifted controls continue to access the same 6% solution of previous trials. Naloxone (2 mg/kg, ip) was administered 15 min before trials 11 and 12 (shown in this figure). In both trials, there was significantly more suppression of goal-tracking times in the group treated with naloxone (Nlx) than in the saline (Sal) groups. Goal-tracking time is the cumulative time in contact with the sipper tube during the trial.

OR Blockage Alters the Detection of the Incentive Downshift

Detecting a downshift in sucrose concentration is not a purely perceptual problem. The cSNC effect requires a comparison between the sweetness of the current (postshift) solution and the reactivated memory of a previously experienced (preshift) solution. Papini and Pellegrini (2006) showed that, within some limits, equal ratios of postshift/preshift sucrose concentrations yield similar levels of consummatory suppression. For example, a 32-to-4% sucrose downshift leads to similar goal-tracking times as a 16-to-2% sucrose downshift; in both cases, the downshift involves an 8-to-1downshift ratio. In addition, the smaller the ratio, the lesser the consummatory suppression (i.e., an 8-to-1 ratio induces more suppression than a 4-to-1 ratio). This ratio constancy is analogous to Weber's law as applied to comparisons between sensory inputs and it applies to a variety of incentive downshift situations in addition to cSNC (Pellegrini & Papini, 2007; Pellegrini, Lopez-Seal, & Papini, 2008).

Recent data suggest that OR blockage alters the downshift detection rule from a ratio to an absolute difference rule (Daniel et al.,2009). Saline treated rats exhibited similar suppression of consummatory behavior when given a 16-to-6% vs. 32-to-12% sucrose downshift (post/pre ratio = 0.38), or 16-to-3% vs.32-to-6% sucrose downshift (post/pre ratio = 0.19). Interestingly, rats treated with naloxone (2 mg/kg) exhibited a level of consummatory suppression on trial 11 that was more

in synchrony with the absolute difference between the pre- and postshift sucrose concentrations, rather than with their ratio. The consummatory behavior of these animals on the first downshift trial (trial 11) yielded a coefficient of determination $r^2 = 0.77$, whereas the same data for the saline controls yielded $r^2 = 0.42$. The difference indicates that a linear function relating consummatory behavior to the absolute difference in concentrations provides a better fit for naloxone-treated animals than for saline-treated animals. Linearity is distorted in saline animals because of ratio constancy. These results suggest that OR blockage distorts the comparison between the current solution and the reactivated memory of the preshift solution, biasing it in the direction of the absolute difference between the two solutions, rather than of their ratio.

DORs Selectively Modulate cSNC Onset

Flaherty (1996) reviewed data showing that benzodiazepine anxiolytics displayed trial selectivity, reducing contrast when administered before trial 12, but not before trial 11. Based on such evidence, Flaherty suggested that recovery from cSNC involved a conflict between the rejection of the downshifted solution and the need to consume sucrose given that animals are usually food deprived in these experiments. In fact, recovery from cSNC is retarded when rats are not food deprived, suggesting that satiety reduces the approach component of the conflict (Dachowski & Brazier, 1991). But none of the extensive series of pharmacological experiments summarized by Flaherty (1996) proved to selectively modulate cSNC on trial 11, during the very first exposure to the downshifted solution.

To test for selective modulation of cSNC on trial 11 vs. 12, Wood, Daniel, and Papini (2005) gave three downshifted-unshifted pairs of groups injections before each of these two trials. One pair received DPDPE (24 μg/kg) before trial 11, but the vehicle before trial 12; a second pair received the vehicle before trial 11, but DPDPE before trial 12; and the third pair of groups received the vehicle before both trials. DPDPE is a selective DOR agonist and, thus, it was expected to reduce cSNC much as morphine did in prior experiments (Rowan & Flaherty, 1987). Surprisingly, however, the attenuating effect of DPDPE was restricted to trial 11, as shown in Figure 4. Although DPDPE-treated downshifted rats showed somewhat lower consummatory behavior on trial 11, the difference with DPDPE-treated unshifted rats was not significant. In addition, DPDPE had no effect when administered before trial 12 or in unshifted controls. Another experiment (Pellegrini et al., 2005) showed that administration of the DOR antagonist naltrindole (1 mg/kg) before trials 11 and 12 enhanced cSNC on trial 11, but had no effect on trial 12. Based on these results, it was hypothesized that DORs play an important and selective role in the onset of the cSNC effect, modulating the intensity of primary frustration, that is, an unconditioned state peaking immediately after a surprising incentive downshift and hypothesized to play a major role in consummatory suppression during trial 11.

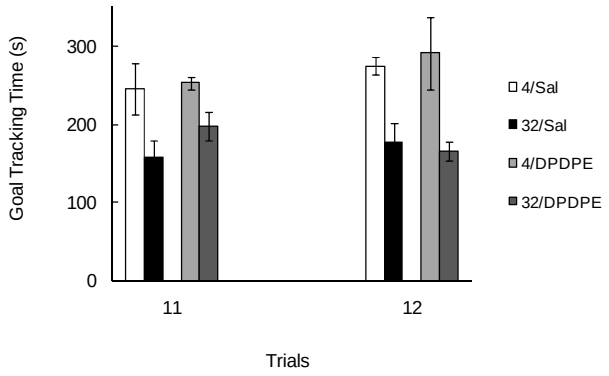


Figure 4. Effects of DPDPE on cSNC (Wood et al., 2005). DPDPE is a selective DOR agonist. Groups of rats received DPDPE (24 μg/kg, ip) administration either before trial 11 or before trial 12. Whereas DPDPE significantly reduced cSNC when administered before trial 11, it had no effect when administered before trial 12. A control group received saline (Sal) administration before both trials.

KORs Selectively Modulate Recovery from cSNC

Another recent series of experiments with the KOR agonist U50,488H provided additional evidence for trial selectivity (Wood, Norris, Daniel, & Papini, 2008). In this case, U50,488H administered before trial 11 had no detectable effect on cSNC, but before trial 12 led to either attenuation (1 mg/kg) or enhancement (3 and 10 mg/kg) of cSNC. Subsequent experiments showed that the attenuating effect of the 1 mg/kg dose failed to occur when U50,488H was administered immediately after trial 11, whereas the enhancing effect of the 3 mg/kg occurred also when it was administered immediately after trial 11. Additional data suggested that the enhancing effect of the 3 mg/kg dose was probably due to the development of a conditioned taste aversion (CTA), as animals given 4% sucrose (i.e., without a downshift) and injected immediately after the trial exhibited less consummatory behavior than animals injected 3 h after the trial (i.e., paired vs. unpaired sucrose-U50,488H trials). Therefore, the enhancing effect of the high dose of U50,488H was tentatively dismissed as due to CTA, whereas the effect of a low dose of U50,488H on cSNC was hypothesized to be similar to that of benzodiazepine anxiolytics in that it is selective for trial 12. Thus, KORs are hypothesized to modulate the intensity of secondary frustration, that is, a conditioned state induced by anticipated frustration, assumed to play a major role in consummatory suppression during trial 12.

What is the Function of ORs in cSNC?

The enhancing effects of naloxone on cSNC described above can be attributed to at least four mechanisms. First, OR blockage may modulate the

downshift experience, either amplifying the aversive consequences of surprising reward reductions (Papini & Dudley, 1997), reducing the incentive value of the downshifted solution (Norris, Perez-Acosta, Ortega, & Papini, in press), or a combination of both effects. Second, naloxone could exert this effect by affecting the detection of the downshift, as shown above. Additional data are needed to evaluate these possibilities.

Third, naloxone may induce a CTA analogous to that observed with U50,488H. The logic underlying this CTA hypothesis is based on the notion that when 4% sucrose is paired with the aversive state induced by a drug on trial 11, downshifted rats have never tasted 4% sucrose before, whereas unshifted controls have experienced 10 previous trials with 4% sucrose. Thus, since CTA occurs more readily with novel flavors (i.e., latent inhibition; Cannon, Best, & Batson, 1983), downshifted rats would be more likely than unshifted rats to develop an aversion to the 4% sucrose, resulting in an apparent enhancement of the cSNC effect. Despite the potential for CTA, administration of naloxone (2 and 10 mg/kg) immediately after the first experience with 4% sucrose (i.e., in the absence of a downshift experience) failed to support CTA relative to groups receiving either unpaired or backward arrangements between sucrose and naloxone. It should be noted that no information is available on the ability of naltrindole, which also enhances cSNC (see above), to support CTA.

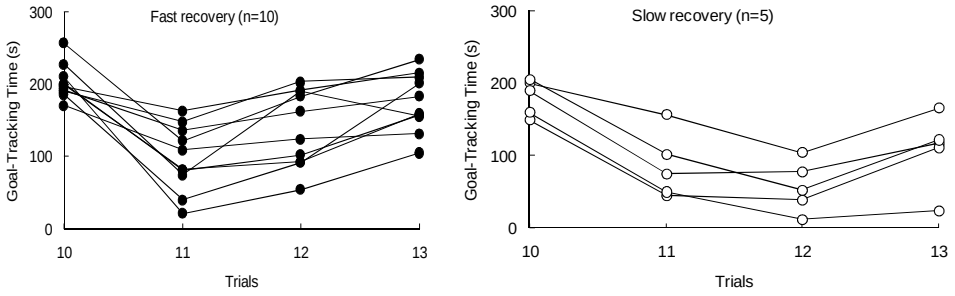
Fourth, OR blockage could enhance cSNC by strengthening the aversive memory of the incentive downshift event first experienced on trial 11. Posttraining naloxone administration is known to enhance the consolidation of fear conditioning (see McGaugh & Roozendaal, 2008). However, the same doses of naloxone (2 mg/kg), naltrindole (1 mg/kg), and DPDPE (24 μg/kg) that were effective when administered before trials 11 and/or 12, had no effect on recovery when administered immediately after trial 11 (Daniel et al., 2009). Therefore, it is hypothesized that ORs are not involved in the encoding of secondary frustration in the cSNC situation.

ORs and Individual Differences in Recovery from cSNC

cSNC is a robust phenomenon, but there are notable differences in the length of the effect across experiments run under the same nominal conditions. Recovery from incentive downshift may take between 1 and 6 postshift trials. In addition, there are substantial individual differences in both the extent of the initial suppression (trial 11) and the speed of the subsequent recovery (trial 12 and beyond), as shown in Figure 5a. Because ORs are implicated in both aspects of the cSNC effect, Pellegrini et al. (2005) hypothesized that individual differences in postshift performance reflect the efficiency of endogenous opioid ligands to their receptors. Rats and humans express several OR isoforms that bind with different effectiveness and play a role in drug addiction (e.g., Ikeda et al., 2005). Thus, an experiment was designed to test the hypothesis that rats that expressed fast vs. slow recovery from cSNC (as measured in terms of the performance on trials 11 and 12) exhibit differential sensitivity to OR blockage in an activity situation.

Activity was measured in a narrow, dark, and walled box designed to minimize anxiety-like responses that rats often exhibit in open, lighted spaces (Pawlak, Ho, & Schwarting, 2008). Groups matched for performance on trial 11 (i.e., equal initial suppression) that exhibited either fast or slow recovery of goal-tracking times on trial 12 received naloxone (2 mg/kg) treatment immediately before a 15-min activity session. As predicted, whereas naloxone had no effect on activity for fast-recovery rats, it significantly reduced activity late in the session for slow-recovery rats (Figure 5b). These results were interpreted as providing support for the hypothesis that the animal's ability to cope with an experience of incentive downshift is directly related to OR effectiveness.

(a) Individual differences in recovery from incentive downshift.



(b) Effects of naloxone on activity in fast-recovery vs. slow-recovery rats.

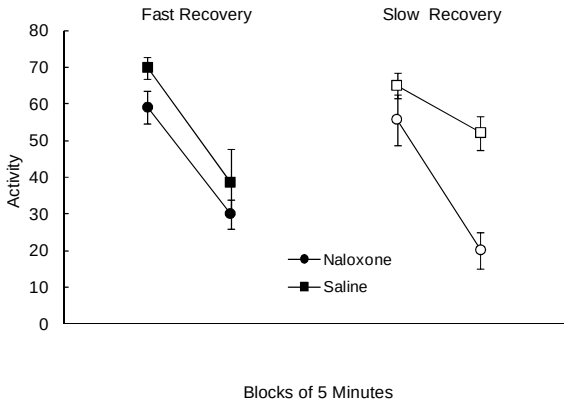


Figure 5. (a) Unpublished data showing individual performance during the last preshift trial (trial 10) of access to 32% sucrose and the initial three postshift trials (trials 11-13) of access to 4% sucrose. Animals differ in terms of their performance on trial 12 relative to trial 11: scores go up for fast recovery rats, but stay the same or go down for slow recovery rats. ***(b)*** Effects of naloxone (2 mg/kg, ip) on activity in groups of rats that exhibited either fast or slow recovery during a 32-to-4% sucrose downshift (Pellegrini et al., 2005).

Evolution of the Opioid System

Using Figure 2 as a guide, one could argue that despite its complexity, SNC is beginning to be understood at the behavioral and neurochemical levels. Whereas nothing much can be said about the neural circuit and the cell-molecular processes underlying SNC, the behavioral and neurochemical research described in this article offers a general guide to generate some hypotheses about the possible evolutionary history of the mechanisms underlying SNC. It is useful to start by making explicit two assumptions: (1) that the behavioral differences illustrated in Figure 1 reflect a divergence in learning mechanisms underlying adjustments to incentive downshifts, rather than the effect of some contextual variable unrelated to learning (e.g., perceptual, motivational, or motor differences across species; Bitterman, 1975); and (2) that the set of mechanisms underlying SNC evolved in Mesozoic mammals (or their ancestors) by means of co-option of brain mechanisms originally involved in fear conditioning (Papini, 2003, 2006). Some set of fear conditioning mechanisms appears to be general to most, if not all, vertebrates, as shown by research on avoidance learning in teleost fish (*Carassius auratus*; Portavella, Salas, Vargas, & Papini, 2003; Portavella, Torres, Salas, & Papini, 2004). Based on these assumptions and on the results reviewed above, it is hypothesized that evolutionary changes in the functions of ORs made SNC possible in mammals.

The evolution of the opioid system is beginning to be understood by recent work with a variety of vertebrates, thanks to the involvement of ORs in nociception (Sneddon, 2004). The four recognized ORs (delta, mu, kappa, and ORL), whose genes share a similar sequential structure, have been identified in mammals, birds, reptiles, amphibians, and teleost fish, but not in chondrychthyes (sharks), cephalochordates (lancelets), urochordates (tunicates), or arthropods (fruit flies; Dreborg et al., 2008; Stevens, 2009). There is some indication that endogenous ligands may bind with less specificity in nonmammalian ORs than in their mammalian homologues (Stevens, Brasel, & Mohan, 2007), but the status of this claim is uncertain. ORs may be equally selective across vertebrates, but their selectivity may relate to different endogenous ligands (Dreborg et al., 2008). Studies using selective radioligands for the DOR, MOR, and KOR in the amphibian *Rana pipiens* show that binding to these ORs is just as specific as it is for mammals (Newman, Sands, Wallace, & Stevens, 2002). Interestingly, although the amino acid sequences in these ORs are very similar both across species and within species, nonmammalian ORs are more similar to each other than mammalian ORs (Stevens et al., 2007). This suggests greater divergence in OR structure in the mammalian lineage compared to nonmammalian vertebrates. The extent to which this divergence allowed the mammalian opioid system to extend its influence to situations involving incentive loss remains to be determined. However, a tentative evolutionary hypothesis is presented in Figure 6.

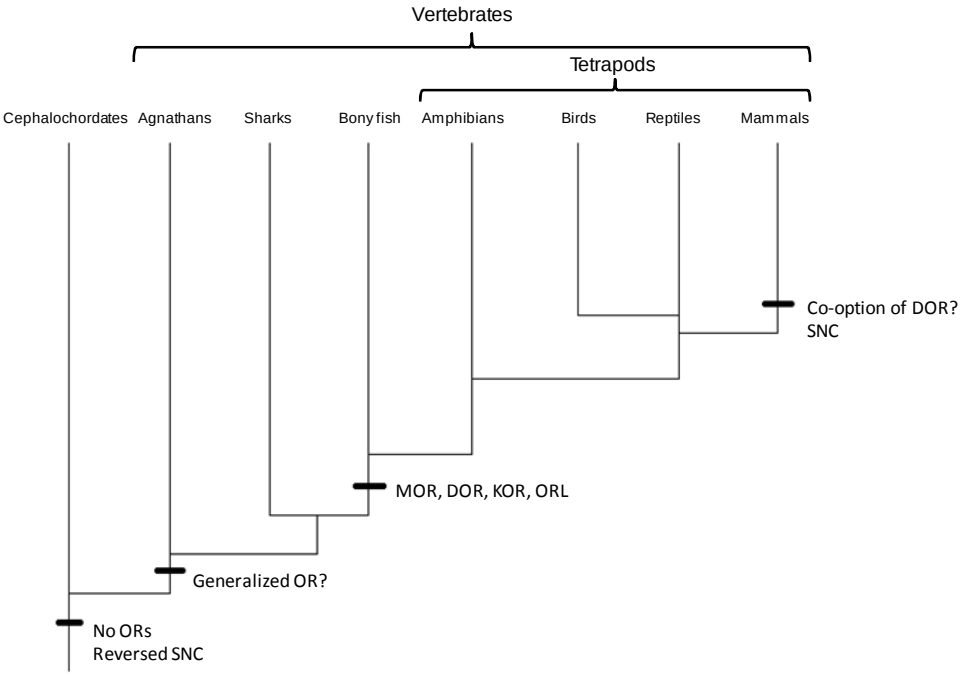


Figure 6. A phylogenetic tree showing the main vertebrate lineages and the hypothesized events in the evolution of opioid receptors. The four described opioid receptors, MOR, DOR, KOR, and ORL, have been found in bony fish and tetrapods. Because these proteins are characterized by a high degree of sequence similarity, they have been hypothesized to have evolved in two events of gene duplication from a generalized ancestral protein. Here it is also hypothesized that the DOR underwent co-option from playing a role in the pain-fear domain to playing a role in the onset of incentive contrast situations.

The evolutionary hypothesis based on the functional co-option of fear conditioning mechanisms into those subserving adjustment to incentive loss (Papini, 2003) requires some specificity as to the nature of those functions for the opioid system. In relation to fear conditioning, the opioid system has been suggested to play a role in modulating (1) the intensity of the shock-induced pain and signal-induced fear (Fanselow & Bolles, 1979), (2) the magnitude of the error-correction mechanism involved in fear acquisition and extinction (McNally, in press), and (3) the consolidation of the fear memory (McGaugh & Roozendaal, 2008). As reviewed in this article, the functional role of the opioid system suggested by research on incentive downshift would be consistent with (1), uncertain about (2), and inconsistent with (3). But the task of comparing the function of the same neurochemical system on different behavioral functions is rather complex. Consider the opposite effects of opioid blockage on extinction. Naloxone treatment retards fear extinction (McNally & Westbrook, 2003), but it facilitates appetitive extinction (Norris et al., in press). Different behavioral effects may reflect either the same or different opioid function. For example, if opioid

blockage enhances aversive emotional states, then a signal for pain should cause more intense fear (thus retarding fear extinction) and more intense frustration (thus enhancing appetitive extinction). On the other hand, opposite effects may reflect different functions. For example, opioid blockage may interfere with error correction in fear extinction (McNally, 2009), but have a different function in the case of appetitive extinction. Clearly, the evidence is presently insufficient to determine whether evolutionary changes in the opioid system can be meaningfully related to opioid function in the pain-fear and frustration domains.

Conclusions

Based on a level's view of the mechanisms underlying SNC, the research described here was designed to build on the extensive work on the neurochemical basis of cSNC published by Flaherty and collaborators. Systemic administration of opioid peptides was selected as an initial manipulation because a series of experiments indicated that morphine reduced the initial impact of incentive downshift in the consummatory situation (Rowan & Flaherty, 1987). Systemic drug administration is a relatively practical approach to determine some general effects and identify ORs involved in cSNC, but it has at least two disadvantages related to the widespread distribution of ORs in the mammalian brain. First, it does not tell us where in the brain a given opioid peptide is causing the observed behavioral effects. Second, the same compound acting in different brain sites may affect behavior in opposite ways, thus obscuring the outcome of some experiments. Nonetheless, systemic administration provides a rough roadmap to target specific brain sites. Lesion studies implicate several brain nuclei in the development of cSNC, including the parabrachial nucleus (Grigson, Spector, & Norgren, 1994), gustatory thalamus (Sastre & Reilly, 2006), medial amygdala (Becker, Jarvis, Wagner, & Flaherty, 1984), and medial prefrontal cortex (Pecoraro, De Jong, Ginsberg, & Dallman, 2008). A study using c-Fos-like immunoreactivity identified the medial amygdala and a variety of brain areas activated selectively on trial 11, during initial exposure to incentive downshift (Pecoraro & Dallman, 2005). Such studies provide a guide to explore the role of ORs in specific brain locations on cSNC onset using microinjection procedures (e.g., Liao & Chuang, 2003).

Once the minimum circuitry for cSNC is known, it would be possible to approach the homologous brain areas in other vertebrates to determine similarities and differences across species. Potential nonmamalian models include the goldfish (*Carassius auratus*), terrestrial toad (*Bufo arenarum*), and pigeon (*Columba livia*). These species have been extensively studied in incentive downshift situations and the behavioral effects are strikingly different from those observed in mammals. Recent research with pigeons shows, for example, that their adjustment to a downshift in incentive is regulated primarily by the magnitude of the preshift incentive, rather than the ratio of post-to-preshift magnitudes, as described above for rats (Pellegrini et al., 2008). Such systematic study of key model species will open the way to a deeper understanding of the evolution of learning mechanisms in vertebrates.

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