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Autonomic Neuroscience: Basic and Clinical 125 (2006) 34 – 41

AUTONOMIC NEUROSCIENCE: Basic & Clinical

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Review

The role of nausea in taste avoidance learning in rats and shrews

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Received 10 January 2006; received in revised form 10 January 2006; accepted 10 January 2006

Abstract

When paired with a novel flavoured solution, the injection of an emetic drug, such as lithium chloride, produces avoidance of that solution in both non-emetic rats and in emetic shrews. On the other hand, the pairing of a novel flavour with a drug with rewarding properties results in conditioned taste avoidance in rats, but in conditioned taste preference in shrews. It, therefore, appears that nausea may be necessary for the establishment of conditioned taste avoidance in the emetic shrew, but not in the non-emetic rat. Indeed, pre-treatment with the anti-emetic agents, ondansetron or Δ^9-tetrahydrocannabinol, interferes with the establishment of lithium-induced conditioned taste avoidance in the shrew, but does not even attenuate the establishment of lithium-induced conditioned taste avoidance in the rat. The results of a number of studies suggest that the nature of flavour–drug associations varies on the basis of the emetic capacity of the species.

Keywords: Shrew; Rat; *Suncus murinus*; Insectivore; Omnivore; Learning; Taste avoidance; Taste aversion; Δ^9-tetrahydrocannabinol; Cannabinoids; Ondansetron; Serotonin; Lithium

Contents

1. Introduction

Emetic drugs have been shown to produce taste avoidance in diverse species (e.g., Garcia et al., 1977); however, the predominant species of investigation has been the laboratory rat. This is somewhat surprising, because

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doi:10.1016/j.autneu.2006.01.010

rodents are incapable of vomiting. In fact, there have been very few investigations of taste avoidance learning in species capable of vomiting (e.g., Rabin and Hunt, 1983). Recently, Smith et al. (2001) reported that the house musk shrew (*Suncus murinus)*, an insectivore that vomits when injected with a toxin, avoids a flavour paired with the emetic drug, lithium chloride. Lithium chloride is the standard emetic agent used in hundreds of studies of conditioned taste avoidance learning in rats (see Riley and Freeman, 2004). In this paper we compare the nature of flavour–drug associations produced in the rat and the *S. murinus.*

1.1. Conditioned taste avoidance learning in rats

Although rats are incapable of vomiting, they readily learn to avoid a taste previously paired with toxins that produce nausea by acting on the emetic system of the midbrain and brainstem (Garcia et al., 1974). Garcia et al. argued that the avoidance of the taste is mediated by a conditioned shift in the palatability of the taste revealed as conditioned disgust. More recently, Grill and Norgren (1978) using a more systematic test for the assessment of palatability of fluids, showed that rats, indeed, demonstrate disgust reactions during an intraoral infusion of lithium-paired sucrose. The taste reactivity (TR) test has revealed that rats display conditioned disgust reactions (predominantly gaping) when infused with flavoured solutions that have been paired with low to high doses of lithium chloride (Berridge et al., 1981; Grill and Norgren, 1978; Parker, 1982), cyclophosphamide (Parker, 1998; Limebeer and Parker, 1999), high doses of nicotine (Parker, 1993) and apomorphine (Parker and Brosseau, 1990), naloxone-precipitated morphine withdrawal (Mc Donald et al., 1997), and full body rotation (Cordick et al., 1999; Ossenkopp et al., 2003). Each of these agents produces vomiting in species that are capable of vomiting.

1.2. Rewarding drugs produce taste avoidance, but not taste aversion in rats

Rats not only avoid flavours paired with emetic drugs but they also learn to avoid flavours that have been paired with drugs that are not readily characterized as aversive, such as amphetamine. Rats will simultaneously avoid an amphetamine-paired flavour while demonstrating that the drug is rewarding. They prefer the amphetamine-paired place in a place-preference assessment (Reicher and Holman, 1977) and self-administer the drug (Wise et al., 1976). Because Garcia et al. (1974) had developed a model to account for taste aversion produced by emetic agents, early investigators assumed that the reason rewarding drugs also produce taste avoidance in rats is that they produce the side effect of nausea, which becomes selectively associated with flavours (Reicher and Holman, 1977). Recent findings, however, suggest that this is not the case (e.g., Parker, 1995).

According to the model of Garcia et al. (1974; refined Garcia, 1989), feedback from nausea produces conditioned disgust, reflecting an aversion to the taste; therefore, a manipulation that produces nausea should establish conditioned disgust reactions. However, taste avoidance produced by rewarding drugs is not accompanied by conditioned disgust (Parker, 1982, 1988, 1991, 1993, 1995), indicating that rats do not develop an *aversion* to a taste paired with a rewarding drug. We (for review see Parker, 1995) have evaluated the potential of a range of doses of a number of drugs with rewarding properties to produce place preference learning and conditioned disgust reactions. At doses that produce a place preference and taste avoidance, none of the following drugs produce conditioned disgust reactions: Amphetamine (Parker, 1982, 1984, 1988, 1991), apomorphine (Parker and Brosseau, 1990), cocaine (Mayer and Parker, 1993; Parker, 1993), lysergic acid diethylamide (LSD, Parker, 1996), methamphetamine (Parker, 1993), methylphenidate (Parker, 1991), morphine (Parker, 1991), nicotine (Parker and Carvell, 1986) and phencyclidine (Parker, 1993).

Of course, one might argue that the failure to detect disgust reactions in the TR test with corresponding taste avoidance simply reflects differential sensitivity of the measures. That is, if reinforcing drugs simply produce weaker taste–drug associations, then this association may be detected in a sensitive intake test, but may not be detected in a less sensitive TR test. We specifically addressed this issue in our early work. When evaluated over 9 conditioning/testing trials, rats displayed equivalent taste avoidance produced by lithium (50 mg/kg, i.p.) and amphetamine (3 mg/kg, i.p.), but dramatically displayed disgust reactions only to the lithium-paired taste (Parker, 1984). Furthermore, Zalaquett and Parker (1989) demonstrated that when the doses of amphetamine and lithium were adjusted to produce weaker taste avoidance with lithium (12 mg/kg) than with amphetamine (3 mg/kg), only the lithium-paired flavour elicited disgust reactions. The fact that drugs usually characterized as rewarding motivate flavour avoidance in rats has been an enduring enigma and has given rise to considerable theoretical analysis (e.g., Gamzu, 1977; Grigson, 1997; Hunt and Amit, 1987; Parker, 1982).

1.3. Effects of anti-emetic agents on the establishment and/or the expression of taste avoidance and conditioned disgust

Garcia's claim that nausea is a necessary stimulus for taste aversion learning has been evaluated using anti-nausea treatments. Considerable evidence indicates that such treatments do not interfere with conditioned taste avoidance in rats. Although Coil et al. (1978) reported that various anti-nausea agents interfered with the *expression* of previously established taste avoidance produced by lithium chloride, others have not replicated this finding using similar anti-nausea treatments (Goudie et al., 1982; Parker and Mc