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Effects of acute administration of phentermine, alone or in combination with dexfenfluramine, on pain reactivity in the adult rat

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ABSTRACT

In the 1990s, phentermine was combined with either fenfluramine or its active enantiomer dexfenfluramine to promote weight loss. Appetite suppressants are known to alter pain reactivity. The current experiment examined the acute impact of phentermine (0, 2.5, 5, 10, or 20 mg/kg) on paw-lick/jump latencies recorded just before and at 10, 20, and 30 min after phentermine injection. In addition, separate groups of rats were treated with 1, 2, or 4 mg/kg dexfenfluramine or with selected combinations of phentermine with dexfenfluramine. Phentermine induced significant analgesia in rats at a dose of 2.5 mg/kg, whereas only the 4.0 mg/kg dose of dexfenfluramine induced significant analgesia. Combinations of 1 mg/kg dexfenfluramine or 2 mg/kg dexfenfluramine with phentermine were mostly additive in terms of changes in analgesia scores. The present results characterize the analgesic action of phentermine, further confirm the analgesic action of dexfenfluramine and suggest an additive analgesic effect for the combination of dexfenfluramine with phentermine.

Amphetamine and related drugs induce a degree of analgesia in animals and humans (Franklin, 1998). Systemic administration of amphetamine induces analgesia in mice and rats (Goetzl et al., 1943; Drago et al., 1984; Connor et al., 2000), as does administration of related drugs including cathinone (Nencini and Ahmed, 1982), cocaine (Frussa-Filho et al., 1996), and phentermine (Ghelardini et al., 2003). Amphetamine diminishes dental pain in humans (Burrill et al., 1944). These drugs are considered to act through dopaminergic synapses to induce analgesia (Franklin, 1998). Moreover, the amphetamine-like sympathomimetics have the capacity to augment the analgesic properties of opiates an\d opioid-related drugs (Dalal and Melzack, 1998).

Fenfluramine and its active racemate dexfenfluramine are structural analogues of amphetamine that act predominantly through brain serotonergic synapses. The fenfluramines are known to induce analgesia and to potentiate opioid-induced analgesia (Reuter, 1975; Dalal and Melzack, 1998; Wang et al., 1999). In the 1990s, phentermine was combined with either fenfluramine or dexfenfluramine to promote weight loss (Weintraub et al., 1984, Weintraub, 1992). Subsequent studies indicated that the combination of phentermine with a fenfluramine exerts a greater than additive effect on food intake and body weight (Roth and Rowland, 1998, 1999; Wellman and Maher, 1999; Wellman et al., 2003a). Although a single acute icv infusion of phentermine at 3 μg was reported to induce analgesia in mice (Ghelardini et al., 2003), the analgesic effects of acute or chronic systemic administration of phentermine have not been characterized, nor is it known whether combinations of phentermine and dexfenfluramine would induce additive or synergistic effects on pain reactivity in rats.

In this experiment, adult male rats were acutely treated with phentermine (0, 2.5, 5.0, 10.0, or 20.0 mg/kg) or with dexfenfluramine (0, 1, 2, or 4 mg/kg, i.p.) and then tested repeatedly in the hot-plate test (Bardo et al., 1981; Harvey et al., 1975; Ogawa et al., 2007) at −10, 10, 20, and 30 min after drug treatment. In a sub-experiment that examined the additivity of these treatments, adult male rats were injected with combinations of dexfenfluramine (1.0 or 2.0 mg/kg) and phentermine (2.5 or 5.0 mg/kg).

1. Methods

1.1. Animals

The animals were 74 male Sprague–Dawley viral-free albino rats (obtained from Harlan Industries; Houston, TX) weighing approximately 250–300 g at the beginning of the study. The rats were housed individually in standard plastic rodent cages in a colony room maintained at 21.0±1 °C under a 12 h/12 h illumination schedule (lights on at 0800 h). The experimental procedures and treatments of this research were approved by the Texas A&M University Laboratory Animal Care Committee.

1.2. Drugs

A vehicle solution was prepared using 0.9% sodium chloride dissolved into sterile distilled water. The dexfenfluramine solutions (1, 2 or 4 mg/ml) were prepared by dissolving dexfenfluramine hydrochloride (Sigma Co., St. Louis, MO) into vehicle. Solutions of phentermine (2.5, 5, 10, or 20 mg/ml) were prepared by dissolving phentermine

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hydrochloride (Sigma Co.) into vehicle. Four combination solutions contained 1 mg/ml dexfenfluramine and either 2.5 or 5.0 mg/ml phentermine or 2 mg/ml dexfenfluramine and either 2.5 or 5.0 mg/ml phentermine. Drug doses were calculated as the salt and all injections were given at a volume of 1 ml/kg (i.p.).

1.3. Apparatus

Assessment of pain perception was conducted using a slide warmer (Clinical Scientific Equipment Company, Melrose Park, IL, Model Number 26020). A transparent Plexiglas enclosure (20×19×32 cm), open at the top and bottom, was positioned on the slide warmer. A digital thermometer (Radio Shack, Ft. Worth, TX) attached to the surface of the hot plate, just outside the enclosure, allowed for continuous measurement of plate surface temperature. Plate temperature was maintained at 50 °C±0.5 °C using a rheostat. A mirror (17×13 cm) was attached to the inside rear wall of the Plexiglas enclosure to improve observation of the rat within the enclosure. A removable wire grid formed the roof of the enclosure. The testing room was illuminated by a 20-Watt halogen light located 50 cm above the hot-plate apparatus.

1.4. Pain perception testing procedures

The pain perception testing procedures were similar to those of Bardo et al. (1981) and Ogawa et al. (2007). At 1600 h, each animal was transported from the colony room to a holding cage located within the testing room. A timer was started when the animal was placed into the Plexiglas enclosure onto the hot plate. When the rat licked one of its paws, the timer was stopped and the rat was immediately removed from the hot plate. Paw-lick latency (0.1 s) was defined as the time difference between the start and stop events. In some instances, the rat jumped from the floor of the hot plate to the ceiling of the enclosure. Such jumps terminated the trial and the latency was recorded as a paw-lick/jump latency. Rats that did not respond within 30 s were removed from the hot plate and a score of 30 s was recorded for that trial. The apparatus was cleaned with a mild ammonia solution and dried between successive trials.

Each rat was randomly assigned to a treatment group (n=5–6 per group) (0, 1, 2, or 4 mg/kg dexfenfluramine or 0, 2.5, 5, 10, or 20 mg/kg phentermine). Each rat was tested in the hot-plate procedure before injection (baseline) and then at 10 min, 20 min and 30 min after drug injection. Paw-lick latencies were recorded to the nearest 0.1 s, with a 30 s maximal trial duration (Ogawa et al., 2007). In a sub-experiment, four additional groups (n=5 each) were tested with combinations of 1.0 mg/kg dexfenfluramine+2.5 mg/kg phentermine, 1.0 mg/kg dexfenfluramine+5.0 mg/kg phentermine, 2.0 mg/kg dexfenfluramine+2.5 mg/kg phentermine, or 2.0 mg/kg dexfenfluramine+5.0 mg/kg phentermine.

1.5. Data analyses

The overall design of the study was a split-plot factorial with dexfenfluramine dose (0, 1, 2 or 4 mg/kg) or phentermine dose (0, 2.5, 5, 10 or 20 mg/kg) as the between-group factor and time (0, 10, 20, and 30 min) as a within-group factor. Separate ANOVAs were computed for paw-lick/jump latencies (0.1 s) for fenfluramine dose (0, 1, 2, or 4 mg/kg) and for phentermine dose (0, 2.5, 5, 10 or 20 mg/kg). The hot-plate scores were converted to percentage of possible maximal effect (MPE %) where %MPE = 100 * [(drug response time − time 0 baseline response time) / (response cutoff score (30) − time 0 baseline response time)] (cf Ogawa et al., 2007). %MPE scores were plotted as a function of phentermine dose or dexfenfluramine dose and were subjected to linear regression (SigmaPlot 9.01) to calculate the dose required to generate a 50% MPE score (i.e. an ED_{50} score). For the combination analyses, the % MPE scores for the 1.0 mg/kg dexfenfluramine+2.5 mg/kg phentermine, and 1.0 mg/kg dexfenfluramine+5.0 mg/kg phentermine groups were combined with the %MPE scores for the 1.0 dexfenfluramine group from the main experiment. Likewise, the data from the 2.0 dexfenfluramine group was combined with the data from the 2.0 mg/kg dexfenfluramine+2.5 mg/kg phentermine, or 2.0 mg/kg dexfenfluramine+5.0 mg/kg phentermine groups. For each dexfenfluramine condition (1.0 or 2.0 mg/kg), the respective %MPE data were plotted against phentermine dose (0, 2.5, or 5.0 mg/kg) and a 50% MPE (ED_{50} value) determined for the combinations. Comparisons between group means were made using Bonferroni contrasts and the level of significance was set at $P<0.05$.

2. Results

Fig. 1A depicts the impact of systemic injections of phentermine on paw-lick/jump latencies at four different time points. ANOVA of the paw-lick/jump latencies prior to drug injection revealed no significant between-group differences. Split-plot ANOVA of the paw-lick/jump latencies over the 4 time points revealed a significant effect of phentermine dose ($F(4,24)=5.45$, $P<0.0001$) and of time ($F(3,72)=37.9$,

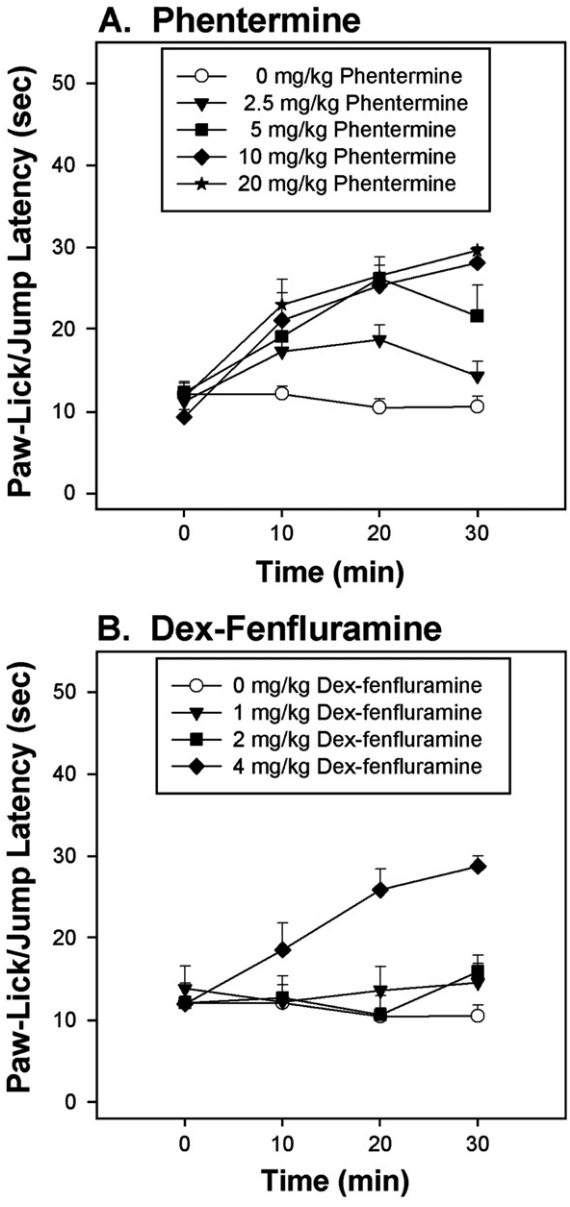

Fig. 1. Mean group paw-lick/jump latencies recorded in a hot-plate test prior to and at 10, 20, and 30 min after i.p. administration of 0, 2.5, 5.0, 10.0 or 20.0 mg/kg phentermine (panel A) or 0, 1, 2 or 4 mg/kg dexfenfluramine (panel B). The vertical lines above each symbol represent the standard error of the mean.

$P<0.0001$), and a significant interaction between phentermine dose and time ($F(12,72)=4.5$, $P<0.0001$). Subsequent contrasts indicated that all doses of phentermine above 2.5 mg/kg significantly increased paw-lick/jump latencies, relative to vehicle. The calculated %MPE (ED_{50}) value for phentermine analgesia was 6.8 mg/kg.

Fig. 1B depicts the changes in paw-lick/jump latencies induced by systemic injection of dexfenfluramine. ANOVA of the paw-lick/jump latencies prior to drug injection was not significant. ANOVA of the 4 time points revealed significant effects of dexfenfluramine treatment ($F(3,22)=13.8$, $P<0.0001$), and of time ($F(3,66)=6.5$, $P<0.001$), and a significant interaction between dexfenfluramine and time ($F(9,66)=5.2$, $P<0.0001$). Only the 4 mg/kg dexfenfluramine dose induced a significant change in paw-lick/jump latencies, relative to the saline control group. The calculated %MPE (ED_{50}) value for analgesia for dexfenfluramine was 2.8 mg/kg.

To evaluate the additivity of the combinations of dexfenfluramine and phentermine on pain reactivity, an isobologram (Berenbaum, 1989; Wellman et al., 1995) was prepared using the data for phentermine alone and for dexfenfluramine alone (see Fig. 2). Points lying along the isobologram line are considered to represent dose additivity. In this sub-experiment, rats were treated with 1.0 mg/kg dexfenfluramine and either 0, 2.5 or 5.0 mg/kg phentermine or with 2.0 mg/kg dexfenfluramine and either 0, 2.5 or 5.0 mg/kg phentermine. Estimated %MPE (ED_{50}) values were calculated for dexfenfluramine alone and for phentermine alone and plotted on the isobologram. For the lower dexfenfluramine dose (1.0 mg/kg), the predicted phentermine dose required to generate an ED_{50} analgesic response was 4.4 mg/kg, while the actual dose was 3.65 mg/kg. For the 2.0 dexfenfluramine dose, the predicted phentermine dose required to generate an ED_{50} analgesic response was about 2.0 mg/kg, a value quite close to the actual dose. Although this analysis was limited in terms of number of doses chosen for testing, it appears that the overall pattern represents additivity between phentermine dose and dexfenfluramine dose on pain reactivity in the adult male rat.

3. Discussion

In the present experiment, acute systemic injections of phentermine were noted to induce a degree of analgesia. Acute administration of 2.5–20 mg/kg phentermine significantly increased pain reactivity scores and these effects persisted for at least 30 min after injection. These results confirm and extend the observation by Ghelardini et al. (2003) in which an acute icv infusion of phentermine increased hot-plate pain reactivity scores in mice and strengthen the conclusion that phentermine, like other sympathomimetic drugs, induces analgesia. Moreover, the present results confirm that fenfluramine can alter pain reactivity (Reuter, 1975; Rochat et al., 1982; Wang et al., 1999).

With regard to neurochemical mechanism of action, phentermine interacts with each of the monoamine transporters so as to alter the release of dopamine, norepinephrine, and of serotonin. An in vitro study (Rothman et al., 2001) using rat brain indicates that phentermine exerts the greatest releasing action at the norepinephrine transporter (39.4±6.6 nM), followed by the dopamine transporter (262±21 nM), with the least activity at the serotonin transporter (3511±6.6 nM). In terms of reuptake inhibition, phentermine is less potent than is amphetamine and exerts minimal action at the serotonin transporter (John and Jones, 2007). In vivo microdialysis studies generally confirm the capacity of phentermine to augment brain extracellular levels of dopamine (Balcioglu and Wurtman, 1998; Baumann et al., 2000; Rowley et al., 2000) and, to a lesser degree, that of serotonin (Prow et al., 2001; Tao et al., 2002). As might be expected for an older appetite suppressant, the impact of phentermine on extracellular levels of norepinephrine in brain has not been explored using the microdialysis technique.

The behavioral actions of phentermine have been related to changes in dopamine neurotransmission. The hypophagic action of phentermine, for example, is noted at dose levels that augment brain dopamine levels (Roth and Rowland, 1998; Rowley et al., 2000; Wellman et al., 2003a) and phentermine hypophagia is antagonized by the receptor antagonist pimozide (Dobrzanski and Doggett, 1979). With regard to reinforcement, phentermine stimulates locomotion (Baumann et al., 2000; Rowley et al., 2000), and is self-administered in rats as well as primates (Griffiths et al., 1978; Papasava et al., 1985). A study by Jain et al. (1979), in which phentermine was noted to routinely appear in urine screens of drug abusers, provides indirect support for the proposition that phentermine has abuse potential in humans. Although no studies could be identified that have examined the neuropharmacology of phentermine-induced analgesia, a body of research

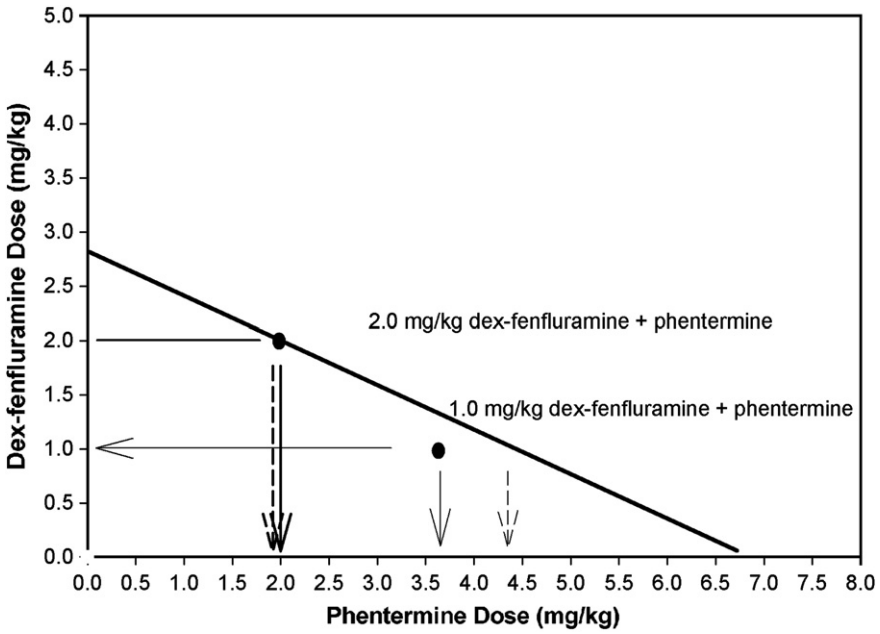

Fig. 2. An isobologram based on the ED_{50} values for phentermine and for dexfenfluramine. Values along the line represent dose additivity. The solid arrows reflect the actual dose of phentermine required to generate an ED_{50} effect when given in combination with 1.0 mg/kg dexfenfluramine or 2.0 mg/kg dexfenfluramine. The dashed arrows reflect the predicted ED_{50} dose of phentermine determined from the dose-additive line.

indicates that dopamine neurotransmission can modulate the analgesia induced by amphetamine. Antagonists of D1 receptors and of D2 receptors diminish amphetamine analgesia (Morgan and Franklin, 1991), whereas depletion of dopamine induced by infusion of the dopamine neurotoxin 6-OHDA into the nucleus accumbens (Clarke and Franklin, 1992), the ventral tegmental area (Morgan and Franklin, 1990) or the ventral striatum (Morgan and Franklin, 1990) can diminish amphetamine analgesia (Franklin, 1998).

On the other hand, the view that phentermine's behavioral actions, including analgesia, reflect altered dopamine neurotransmission is challenged by several observations. The first is that pimozide has affinity for noradrenergic receptors as well as dopaminergic receptors (Wellman et al., 2003b). Thus, a pimozide reversal effect may reflect either an action on noradrenergic or dopaminergic receptors. Additionally, a recent in vivo study suggests that phentermine may not release DA in brain at clinical doses (Alexander et al., 2005).

Early in vitro studies noted the capacity of phentermine to release norepinephrine from rabbit atria (Paton, 1975). In terms of peripheral activity, phentermine increases plasma norepinephrine levels (Alexander et al., 2005) and urinary epinephrine/norepinephrine/dopamine levels (Hirsch et al., 2000). As noted above, in vitro studies suggest that phentermine exerts a greater action at the release of norepinephrine than it does for the release of dopamine or serotonin (Rothman et al., 2001), although whether phentermine alters in vivo release of norepinephrine in brain has not been studied using the microdialysis technique.

Several lines of evidence indicate that norepinephrine is a key component of the endogenous pain inhibition systems. Antidepressant drugs that act by altering norepinephrine neurotransmission also induce analgesia (Jasmin et al., 2003). Descending noradrenergic fibers can hyperpolarize neurons in the substantia gelatinosa, and increase the release of GABA or glycine from spinal cord interneurons (Yoshimura and Furue, 2006). Jasmin et al. (2002) studied pain reactivity in mice lacking the gene that codes for the enzyme dopamine β-hydroxylase, the enzyme required to form NE from DA. Mice lacking norepinephrine were hyperreactive to thermal pain stimuli and were refractory to the analgesic action of morphine. However, pain reactivity was restored in mice for which CNS norepinephrine was rescued by infusion with a synthetic precursor for norepinephrine. These studies demonstrate that norepinephrine has the capacity to inhibit ascending pain information and are consistent with the view that phentermine may interact with brain norepinephrine neurons to induce analgesia.

Fenfluramine activates central serotonin neurons to reduce meal size and eating rate (Simansky, 1996; Bray, 2005). Fenfluramine increases extraneuronal levels of serotonin via stimulation of serotonin release and secondarily via inhibition of serotonin reuptake (Garratini et al., 1975; Gobbi et al., 1992). The capacity of fenfluramine to induce analgesia has long been known (Reuter, 1975). Acute administration of fenfluramine or its active enantiomer dexfenfluramine decreases sensitivity to painful stimuli in rats and mice (Rochat et al., 1982; Wang et al., 1999; Ghelardini et al., 2003). Serotonin plays a key role in the modulation of pain perception. Activation of descending serotonin neurons engages anti-nociceptive circuits, resulting in analgesia (Basbaum and Fields, 1984). Destruction of ascending serotonergic fibers in brain results in a depletion of forebrain serotonin and increases sensitivity to painful stimuli (Harvey et al., 1975). Although some doses of phentermine can increase extracellular levels of serotonin (Prow et al., 2001), antagonism of serotonin receptors does not attenuate phentermine anorexia (Mitchell et al., 1998). Given that relatively high doses of phentermine are required to engage brain serotonin systems, it is unlikely that phentermine acts through serotonergic neurotransmission to induce analgesia.

The aforementioned studies suggest that phentermine predominantly acts through noradrenergic synapses to alter eating and to induce analgesia, whereas fenfluramines act through serotonergic synapses. Studies using sub-chronic administration of phentermine and fenfluramine have observed additive as well as synergistic interactions between fenfluramine and phentermine. Roth and Rowland (1998) used osmotic mini-pumps to deliver vehicle, 5 mg/kg phentermine, 2 mg/kg dexfenfluramine or a combination of 5 mg/kg phentermine plus 2 mg/kg dexfenfluramine over an 11 day period. Daily measures of intake of a sweetened condensed milk diet were recorded for an hour per day. Phentermine alone, at 5 mg/kg had no effect on milk intake. The combination of dexfenfluramine and phentermine exerted a significantly greater reduction of milk intake than did dexfenfluramine alone. Halladay et al. (2000) reported similar synergistic interactions between phentermine and fenfluramine in rats fed a control diet. In a follow-up study, Roth and Rowland (1999) used an isobolographic analysis to demonstrate that the interaction between phentermine and dexfenfluramine was predominantly synergistic. Wellman et al. (2003) reported a greater than additive effect of dexfenfluramine and of phentermine on food intake and body weight in rats. One explanation for these effects is that fenfluramine may diminish the clearance of phentermine from the brain (Kaddoumi et al., 2003).

The present experiment sought to determine the degree to which combinations of phentermine and of dexfenfluramine would induce greater enhancements of analgesia than either drug alone. In this study, a full dose range of each drug was employed and there was no evidence of a potentiation of the analgesic effect of phentermine by dexfenfluramine or vice versa, rather phentermine and dexfenfluramine exerted mostly additive effects on pain reactivity. These results would suggest that supra-additive interactions between phentermine and dexfenfluramine are peculiar to eating and body weight but not analgesia. In other end-points, fenfluramine can antagonize the conditioned place preference induced by phentermine (Rea et al., 1998) and reverse the locomotor stimulation induced by phentermine (Baumann et al., 2000). These interaction patterns would argue against a general pharmacokinetic effect of fenfluramine altering the clearance of phentermine, as suggested by Kaddoumi et al. (2003).

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