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Contribution of Cytochrome P-4502D6 Phenotype to the Neuromodulatory Effects of Dextromethorphan¹

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ABSTRACT

Dextromethorphan (DEM)-mediated *N*-methyl-D-aspartate receptor blockade may result from an action of unchanged DEM or its active metabolite, dextrorphan (DOR). In humans, DEM is metabolized into DOR by the polymorphic enzyme CYP2D6. We therefore investigated the impact of quinidine (Qd), a selective inhibitor of CYP2D6, on DEM disposition and the contribution of CYP2D6 phenotype on DEM antinociceptive and neuromodulatory effects. Using a randomized, double-blind, crossover, placebo-controlled design, healthy volunteers ($n = 7$) received Qd (50 mg Qd sulfate orally) or a placebo and, 12 h later, either DEM (50 mg DEM hydrobromide orally) or a placebo. DEM and DOR pharmacodynamics were assessed for their antinociceptive and neuromodulatory effects. Antinociceptive effects were assessed over 4 h by subjective pain threshold and RIII nociceptive reflex (RIII) monitoring. Neuro-

modulatory effects were studied using the primary and secondary hyperalgesia induced by the topical application of capsaicin. Two of seven subjects were genotypic CYP2D6 PM. Pretreatment of EM by Qd suppressed DOR formation and increased the plasma level of DEM to the levels of poor metabolizers. In poor metabolizers, DEM induced a significant increase in objective (+45%) and subjective (+35%) pain thresholds. In extensive metabolizers, only a slight and short-lasting increase in the subjective threshold was observed, whereas no effect was seen on the objective threshold. DEM modulates secondary hyperalgesia compared with DOR. The CYP2D6 phenotype affects the disposition of DEM and the production of the active metabolite DOR. The impact of the CYP2D6 phenotype is of major importance for the spinal antinociceptive and neuromodulatory effects of DEM.

Dextromethorphan (DEM), a synthetic dextrorotatory analog of codeine, is a non-narcotic morphinan derivative widely used as an antitussive for the past 40 years. Pain is a complex phenomenon involving not only the opioid system but also other neuromediators. The implication of *N*-methyl-D-aspartate (NMDA) receptor modulation of the nociceptive activity in the spinal cord has been extensively documented (Besson and Chaouch, 1987; Dickenson and Sullivan, 1987; Woolf and Thompson, 1991). Experimental data suggest that DEM is devoid of opioid activity and acts in vivo as a functional noncompetitive NMDA receptor antagonist; this could contribute to its documented anticonvulsant, antinociceptive, and neuroprotective activity in various experimental models.

In humans, DEM is metabolized to dextrorphan (DOR) by the polymorphic CYP2D6. The neuromodulatory effect suggested by in vitro data and by animal and experimental human data may result from either an action of DEM or its active metabolite DOR. Indeed, both are NMDA antagonists, bind to σ -1 sites, inhibit calcium flux channels, and

interact with high-voltage-gated sodium channels (Dickenson and Sullivan, 1987; Carpenter et al., 1988; Wong et al., 1988; Netzer et al., 1993). Quinidine has been shown to effectively block the cytochrome P-4502D6 enzyme in humans and to inhibit the *O*-demethylation of DEM into DOR (Leemann et al., 1986; Broly et al., 1989). We therefore investigated the impact of quinidine (Qd) on DEM disposition and the contribution of CYP2D6 phenotype on the antinociceptive and neuromodulatory effects of DEM.

Materials and Methods

Protocol

The experimental protocol was approved by the institutional review board (Department of Anesthesiology, University of Geneva) and conducted in accordance with the Good Clinical Practice Guidelines (Idanpaan-Heikkilä, 1994). Seven healthy volunteers (mean $\pm$ S.D. age, 28 ± 5.9 years; mean body weight, 60 ± 5.3 kg) took part in the study. No subject had clinically abnormal findings on history and physical examination, and none had taken any drugs within the past month. They were phenotyped as extensive metabolizers (EM) or poor metabolizers (PM) for the CYP2D6 (also called sparteine/debrisoquine-type) polymorphism by determination of the DEM/*O*-

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ABBREVIATIONS: DEM, dextromethorphan; NMDA, *N*-methyl-D-aspartate; DOR, dextrorphan; PINS, pain intensity numerical scale; PID, pain intensity difference; SPID, sum of pain intensity difference; PM, poor metabolizer(s); EM, extensive metabolizer(s); Qd, quinidine sulfate.

demethylated DEM metabolic urinary ratio (Küpfer et al., 1986; Dayer et al., 1989).

Medications

The study design was randomized, double-blind, crossover, and placebo controlled. On four occasions (at least 1 week apart), each volunteer received either a placebo or Qd sulfate 50 mg. Twelve hours later, 50 mg of DEM hydrobromide syrup or placebo was given orally.

Elicitation of the Experimental Pain Sensation

Pain was assessed both subjectively and objectively by means of validated techniques (Willer, 1977, 1990; Porchet et al., 1990; Desmeules et al., 1991, 1996). Thus, during the 4 h after the intake of DEM, a pain intensity numerical scale (PINS) and the RIII reflex were used to evaluate the pain thresholds.

Briefly, subjects rested comfortably in a supine position to obtain muscular relaxation. Orange juice was administered every hour to prevent blood glucose and pain threshold variation (Porchet et al., 1990). Cutaneous temperature was maintained at a constant level by using thermal insulation. Cutaneous electrodes were applied, and the sural nerve was stimulated in its retromaleolar track. The electrical stimulus consisted of single rectangular impulses (0.5 ms) delivered by a constant current stimulator at variable intensities (1–100 mA) (Neuroport; Biotron, Miehlen, Germany). Electromyographic responses were recorded using a pair of surface electrodes placed over the tendon of the ipsilateral biceps femoris. The RIII reflex (objective threshold) was identified as a multiphasic signal appearing >90 ms after each stimulation and considered present when the corrected computed surface was >0.5 mV*ms (positive response). Because this type of stimulus is applied directly to the nerve, it circumvents the peripheral nociceptors. The nociceptive flexion reflex is considered a specific and objective physiological correlate of a pain sensation; it is a validated tool for investigating the central effect of analgesic drugs in humans (Willer, 1977, 1990; Porchet et al., 1990; Desmeules et al., 1991, 1996).

Pain Threshold Determination. After electric stimulation of the sural nerve, the subjective sensation was described by means of a 0 to 10 numerical scale. Subjective (PINS) and objective pain thresholds are defined as the intensity of current inducing 50% of positive responses to a series of 30 stimulations and were obtained by fitting the percentage of positive responses to the Hill equation. Subjective and objective pain thresholds were measured during the 4 h after drug intake ($t = 0, 1, 2, 3$, and 4 h).

Experimental Hyperalgesia. To evaluate the neuromodulatory effect of DEM, hyperalgesia was induced by topical application (3 cm²) of capsaicin 0.1% in the sural nerve territory of the ipsilateral leg 1 h after DEM or placebo intake. The selective activation of nociceptive primary afferent fibers of the skin by capsaicin produces a central facilitation of the nociceptive flexion reflex in humans (Grönroos et al., 1993). This facilitation is selective on the nociceptive reflex and depends, at least partly, on the ongoing afferent barrage in C-fibers (Grönroos et al., 1993; Andersen et al., 1995). The intensity of the ensuing pain was measured by a numerical scale during the following 3 h ($t = 2, 3$, and 4 h).

At each time point, a nonpainful electrical stimulation of A-beta fibers (40 Hz) was performed in the area of secondary hyperalgesia surrounding the site where capsaicin had been applied. Simultaneously the sural nerve was stimulated, and the subjective pain threshold was measured (PINS).

After this, at each time point, kinetic mechanical stimulations (12 g) were applied, with a wooden rolling pin fitted with small, soft, rounded spurs, on the exact same spot of secondary hyperalgesia. Simultaneously, the subjective pain was measured (PINS).

These electric and mechanical conditioning stimulations were applied to modulate the central nociceptive excitability surrounding the site of topical application of capsaicin.

Calculation of SPID. PINS scores then are converted into "pain intensity difference" (PID) scores by subtracting the pain score at baseline from the PINS measured at different time points. In this experiment, there is no pain at baseline (time 60 min). Positive scores therefore indicate an increasing pain. The SPID score is the sum of the PID scores obtained at 120, 180, and 240 min.

Antinociceptive Effect. To account for any antinociceptive effect, kinetics of the pain thresholds were also obtained on the contralateral leg that had no capsaicin ("control site").

Data Analysis. Differences between treatments were analyzed by two-factor analysis of variance for time and treatment and one-factor analysis of variance followed by multiple comparisons of the mean values (Bonferroni test analysis). Values of peak effect (mA) and time to peak (h) were determined directly from the data and expressed as the maximal or minimal difference between the control threshold and the peak value.

Results

Drug Pharmacokinetics. Seven healthy volunteers (four men and three women) were involved in the study. At the end of the study, the urinary metabolic ratio of DEM to DOR recovered in the urine 8 h after DEM intake was >2 for two PM (one man and one woman) versus <0.05 in five EM of CYP2D6.

Pretreatment of EM subjects with 50 mg of Qd significantly increased the mean urinary metabolic ratio of DEM more than 75-fold (range, 10–265). In PM, DEM plasma concentrations reached a peak [$C_{\max} = 233 \pm 0.40$ (S.D.) nmol/ml] at $t_{\max} = 3 \pm 0.7$ h with DOR ($C_{\max} = 3 \pm 1$ nmol/ml). After Qd intake in EM, DEM $C_{\max}$ increased from 65 ± 58 to 244 ± 44 nmol/liter at $t_{\max} = 2.4 \pm 0.9$ h and DOR decreased from 75 ± 30 to 21 ± 11 nmol/ml (see Table 3). Figure 1a depicts the pharmacokinetics of DEM and DOR in EM with and without Qd blockade in comparison to PM (Fig. 1B).

Hyperalgesia. The pretreatment pain thresholds were similar on each separate occasion, and a close interindividual correlation was found between PINS and RIII thresholds (range, 0.8–0.89; $p < .05$).

On the ipsilateral leg, primary and secondary hyperalgesia was observed after 0.1% of capsaicin was applied on the sural nerve territory. A burning sensation appeared 20 to 45 min after application, and this pain lasted approximately 1 h. Although a trend toward pain relief was observed, DEM did not significantly modify pain induced by capsaicin in either EM or PM ($p = .08$). Dextromethorphan did, however, result in a significant decrease in response to mechanical stimulations (allodynia) in both PM phenotype (genotypic PM and EM + Qd) and EM ($p < .01$). This result has been expressed as the SPID (120–240 min) in Table 1.

During nonpainful A β stimulation of the site of secondary hyperalgesia, the subjective pain threshold (PINS) in EM as well as in PM decreased significantly when placebo or Qd was administered without DEM. Under these conditions, a decrease was also observed in EM after DEM intake. This is in sharp contrast to the PM phenotype (PM and EM + Qd), in which the pain threshold remained positive (Table 2).

Antinociception. In PM, testing of the contralateral leg revealed that DEM induced a significant increase in both subjective and objective pain thresholds. The peak of the analgesic effect was significantly superior to placebo for the objective and subjective thresholds [peak effect RIII = $45 \pm$

24% (S.E.M.) and PINS = $35 \pm 7\%$, $p < .015$ and $p < .01$, respectively, versus RIII = $9 \pm 1\%$ and PINS = $13 \pm 2\%$ during placebo or RIII = $3 \pm 2\%$ and PINS = $5 \pm 2\%$ during Qd sessions). In PM, the analgesia outlasted the experimen-

tal time by >4 h. In EM, a slight and short-lasting increase in PINS was observed (peak effect PINS = $23 \pm 2\%$, $p < .01$), whereas no significant effect could be observed on the RIII objective reflex (peak effect RIII = $13 \pm 3\%$). The time course of subjective and objective pain threshold measurements after DEM intake and after subtraction of the values at time 0 is presented in Fig. 2.

The concentration-effect relationship disclosed a parallel increase in DEM plasma levels and antinociceptive effect, in sharp contrast to DOR, which produced an opposite relation between the concentration and effect (Fig. 3).

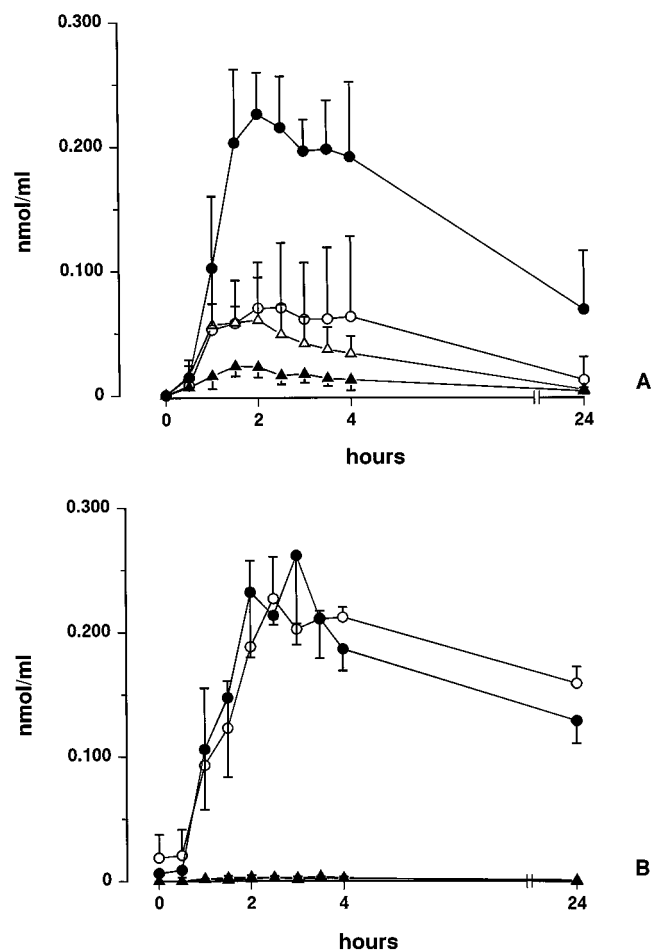


Fig. 1. A, time course of mean $\pm$ S.D. plasma concentration expressed in nmol/liter after DEM intake in EM ($n = 5$) pretreated by Qd (DEM, ●; DOR, ▲) or placebo (DEM, ○; DOR, △). B, time course of mean $\pm$ S.D. plasma concentration expressed in nmol/ml after DEM intake in PM ($n = 2$) pretreated by Qd (DEM, ●; DOR, ▲) or placebo (DEM, ○; DOR, △).

TABLE 1
Spontaneous pain and mechanical allodynia

Capsaicin	Mean Peak Effect (PINS)	S.D.	Mechanical Allodynia Mean (SPID 2-4 h)	S.D.
Placebo	5.3	1.6	10.1	4.2
Qd + placebo	5.5	1.9	10.1	2.4
DEM in EM	4.5	1.5	6.4	2.3
DEM + Qd in PM + EM	4.5	1.2	5.7	3.0

TABLE 2
Nadir subjective pain threshold during A-beta stimulation of the secondary hyperalgesia area

	Subjective Pain Threshold during A-beta Stimulation	S.D.
	% change from time 0	
Placebo	-21	22
Qd + placebo	-19	20
DEM in EM	-16	5
DEM + Qd in PM + EM	+4	19

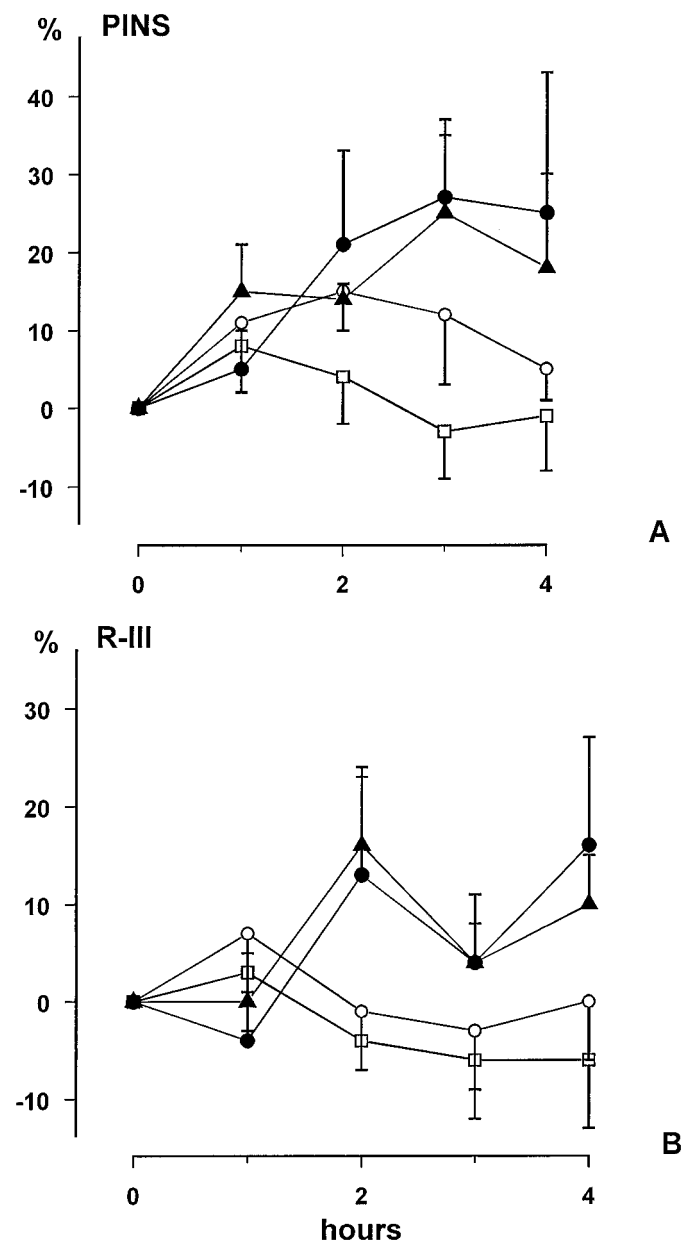


Fig. 2. A, time course of mean $\pm$ S.E.M subjective pain threshold (PINS; pain intensity expressed by means of a numerical scale) on the side without capsaicin expressed in percentage change from pretreatment values after DEM in PM ▲ ($n = 2$) and EM ○ ($n = 5$), after DEM + Qd in EM ● and after placebo □. B, time course of mean $\pm$ S.E.M objective pain threshold (RIII) on the side without capsaicin expressed in percentage change from pretreatment values after DEM in PM ▲ ($n = 2$) and EM ○ ($n = 5$), after DEM + Qd in EM ● and after placebo □.

TABLE 3
Plasma pharmacokinetic parameters for the parent compound DEM and its metabolite, DOR, in EM and PM subjects

	DEM + Placebo		DEM + Qd	
	EM	PM	EM	PM
DEM				
C _{max} (nmol/ml)	65 ± 58	233 ± 40	244 ± 44	270 ± 90
T _{max} (h)	2.2 ± 0.8	3 ± 0.7	2.4 ± 1.1	2.8 ± 0.4
AUC (0,24 h) (h/nmol·ml ⁻¹)	0.7 ± 0.9	4.3 ± 0.1	3 ± 1	3.8 ± 0.7
DOR				
C _{max} (nmol/ml)	75 ± 3	3 ± 1	21 ± 1	3.4 ± 2
T _{max} (h)	1.5 ± 0.5	2.5 ± 0.7	1.5 ± 0.0	2.3 ± 0.3
AUC (0,24 h) (h/nmol·ml ⁻¹)	0.52 ± 0.2	0.03 ± 0.02	0.2 ± 0.1	0.03 ± 0.02

AUC, area under the curve.

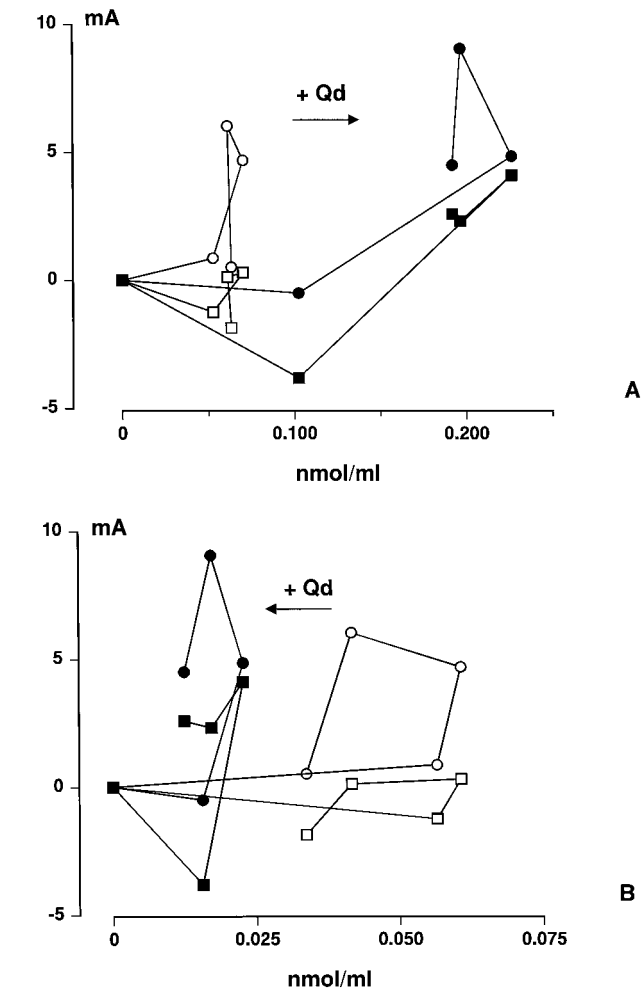


Fig. 3. A, mean DEM plasma concentrations (nmol/ml) versus mean pain thresholds expressed in mA changes from pretreatment values after DEM intake in EM pretreated by Qd (PINS, ●; RIII, ■) or placebo (PINS, ○; RIII, □). B, mean DOR plasma concentrations (nmol/ml) versus mean pain thresholds expressed in mA changes from pretreatment values after DEM intake in EM pretreated by Qd (PINS, ●; RIII, ■) or placebo (PINS, ○; RIII, □).

Discussion

The main objective of the study was to evaluate the clinical consequences of CYP2D6 polymorphism on the antinociceptive and neuromodulatory effects of DEM. Our data show that the CYP2D6 phenotype significantly affects the disposition of DEM and the formation of the metabolite DOR. Although poor absorption could explain low plasma concentra-

tions of DEM in some subjects, a number of studies support the idea that extensive first-pass metabolism is the probable explanation (Küpfer et al., 1986; Woodworth et al., 1987). Quinidine has been shown to effectively block the oxidation catalyzed by the cytochrome P-4502D6 enzyme and, notably, the O-demethylation of DEM (Leemann et al., 1986; Broly et al., 1989). Pretreatment of EM subjects with Qd increased the urinary metabolic ratio of DEM, converting all EM into phenotypic PM as depicted in Fig. 1. The clinical significance of the CYP2D6 (also called debrisoquine/sparteine) polymorphism is well established, and there is now convincing evidence that PM are unable to activate the analgesic properties of drugs like codeine (Desmeules et al., 1991; for review, see Sindrup and Brosen, 1995). Moreover, a link may exist between the debrisoquine/sparteine-type polymorphism, endogenous opioid synthesis, differences in pain thresholds, and some neuropsychological traits (Cardinale et al., 1987; Llerena et al., 1993; Sindrup et al., 1993).

DEM exerted a clear and marked antinociceptive effect in PM with raised objective and subjective pain thresholds on the control side that outlasted the experimental time. In contrast, the analgesic effect was short lasting in EM (Fig. 2). In addition, the concentration-effect curve in EM (Fig. 3) disclosed a parallel increase in DEM plasma levels and antinociceptive effect, whereas an opposite relationship between concentration and effect was observed for DOR.

In our study, although a trend was observed, primary hyperalgesia was not statistically modified by DEM itself in either PM or EM. Capsaicin directly activates nociceptive C- and A-delta fibers (Kenins, 1982; Szolcsanyi et al., 1988). Activation of C-polymodal nociceptors seems to be especially effective in producing a central type of sensitization or secondary hyperalgesia, ascribed mainly to central plasticity in this model (Cook et al., 1987; Dickenson and Sullivan, 1987; Torebjörk et al., 1992; Grönroos and Pertovaara, 1993; Kolzenburg et al., 1994; Andersen et al., 1995). It has been shown that stimulus-evoked allodynia in the area surrounding the capsaicin-treated site is mediated by large, rapidly conducting fibers (Koltzenburg et al., 1992, 1994). Mechanical stimulation of these fibers produced a secondary hyperalgesia that was effectively attenuated in phenotypic PM and EM after DEM intake compared with after placebo. This implies that the parent molecule DEM and its metabolite DOR produce neuromodulatory effects in humans, as has already been demonstrated in animal models (Tal and Bennett, 1994; Chaplan et al., 1997).

Although the parent molecule DEM is less potent in vitro as an NMDA antagonist, in these clinical conditions it seemed clearly more active than DOR because the antinoci-

ceptive effect is more pronounced in PM. Nonpainful electrical stimulation of the area of secondary hyperalgesia, resulting in A-beta fibers activation, induced a perceptible sensitization with an unequivocal statistical decline in subjective pain thresholds after sural nerve stimulation during all treatment sessions except when DEM was administered to phenotypic PM (PM and EM + Qd).

These observations may be due to an enhanced distribution of DEM to the central nervous system compared with that of DOR, which could be related to the more lipophilic nature of DEM (Steinberg et al., 1996). Because the brain-to-plasma ratio of DEM extends from 25 to 500, the DEM brain concentration at the highest plasma level achieved in the PM (233 and 244 nmol/ml) of our experiment might have reached 5.82 to 6.1 $\mu\text{mol/liter}$, corresponding to the range of the in vitro ED_{50} level (3–18 μmol) for anticonvulsant or neuroprotective activity (DeCoster et al., 1995; Kazis et al., 1996).

Taken together, these observations suggest that after a single dose, it is mainly the parent moiety DEM that produces the neuromodulatory effect, whereas the metabolite DOR plays a weaker part. This may explain why analgesic properties of DEM have remained dubious until now and why greatly variable and contradictory results have been observed, particularly when low doses were used (McQuay et al., 1994; Price et al., 1994; Kauppila et al., 1995; Nelson et al., 1997).

Although our study was not designed to differentiate the mechanisms of the underlying mode of action of DEM, our observations suggest that DEM possesses antinociceptive properties in addition to its neuromodulatory effect. After inducing noncompetitive NMDA receptor antagonism, DEM and its metabolite bind to σ -1 site, inhibit calcium flux channels, and interact with high voltage-gated sodium channels (Carpenter et al., 1988; Wong et al., 1988; Netzer et al., 1993). The phencyclidine-like properties of DOR (Székely et al., 1991), in contrast to DEM, could explain part of its abuse potential. In human subjects, the metabolic conversion of DEM to DOR may thus be an important determinant in the potential for abuse, as has already been suggested for DEM and for codeine (Dayer et al., 1988; Löscher and Hönack, 1993; Wu et al., 1995).

Conclusion

The CYP2D6 (sparteine/debrisoquine) polymorphism significantly affects the disposition of DEM and the formation of its active metabolite DOR. Our observations strongly support the major impact of CYP2D6 phenotype on the magnitude of the antinociceptive and neuromodulatory effect of DEM taken orally. The pharmacodynamic and clinical consequences after repeated administration in PM and EM will require further investigation.

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References

- Andersen OK, Gracely RH and Arendt-Nielsen L (1995) Facilitation of the human nociceptive reflex by stimulation of A β -fibers in a secondary hyperalgesic area sustained by nociceptive input from the primary hyperalgesic area. *Acta Physiol Scand* **155**:87–97.
- Besson J-M and Chaouch A (1987) Peripheral and spinal mechanisms of nociception. *Physiol Rev* **67**:167–186.
- Broly R, Libersa C, Lhermitte M, Bechtel P and Dupuis B (1989) Effect of quinidine

- on the dextromethorphan O-demethylase activity of microsomal fractions from human liver. *Br J Clin Pharmacol* **28**:29–36.
- Cardinale GJ, Donnerer J, Finck AD, Kantrowitz JD, Oka K and Spector S (1987) Morphine and codeine are endogenous components in human cerebrospinal fluid. *Life Sci* **40**:301–306.
- Carpenter CL, Mark SS, Watson DL and Greenberg DA (1988) Dextromethorphan and dextrophan as calcium channel antagonists. *Brain Res* **439**:372–375.
- Chaplan SR, Malmberg AB and Yaksh TL (1997) Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. *J Pharmacol Exp Ther* **280**:829–838.
- Cook AJ, Woolf CJ, Wall PD and McMahon SB (1987) Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent fibre input. *Nature* **325**:185–187.
- Dayer P, Desmeules J, Leemann T and Striberni R (1988) Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome P-450 db1/bufl). *Biochem Biophys Res Commun* **152**:411–416.
- Dayer P, Leemann T and Striberni R (1989) Dextromethorphan O-demethylation in liver microsomes as a prototype reaction to monitor cytochrome P-450DB1 activity. *Clin Pharmacol Ther* **45**:34–40.
- DeCoster MA, Klette KL, Knight ES and Tortella FC (1995) σ Receptor-mediated neuro-protection against glutamate toxicity in primary rat neuronal cultures. *Brain Res* **671**:45–53.
- Desmeules J, Gascon M-P, Dayer P and Magistris M (1991) Impact of environmental and genetic factor on codeine analgesia. *Eur J Clin Pharmacol* **41**:23–26.
- Desmeules J, Piguet V, Collart L and Dayer P (1996) Contribution of monoaminergic modulation in tramadol analgesic effect. *Br J Clin Pharmacol* **41**:7–12.
- Dickenson AH and Sullivan AF (1987) Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C-fibre stimulation. *Neuropharmacology* **26**:1235–1238.
- Grönroos M and Pertovaara A (1993) Capsaicin-induced central facilitation of a nociceptive flexion reflex in human. *Neurosci Lett* **159**:215–218.
- Idanpaan-Heikkilä JE (1994) WHO guidelines for good clinical practice for trials on pharmaceutical products: Responsibilities of investigator. *Ann Med* **26**:89–94.
- Kauppila T, Grönroos M and Pertovaara A (1995) An attempt to attenuate experimental pain in humans by dextromethorphan an NMDA receptor antagonist. *Pharmacol Biochem Behav* **52**:641–644.
- Kazis A, Kimiskidis V and Niopas I (1996) Pharmacokinetics of dextromethorphan and dextrophan in epileptic patients. *Acta Neurol Scand* **93**:94–98.
- Kenins P (1982) Responses of single nerve fibers applied to the skin. *Neurosci Lett* **29**:83–88.
- Koltzenburg M, Lundberg LER and Torebjörk HE (1992) Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain* **51**:207–219.
- Koltzenburg M, Torebjörk HE and Wahren LK (1994) Nociceptor modulated central sensitization causes hyperalgesia in acute chemogenic and chronic neuropathic pain. *Brain* **117**:579–591.
- Küpfer A, Schmid B and Pfaff G (1986) Pharmacogenetics of dextromethorphan O-demethylation in man. *Xenobiotica* **16**:421–433.
- Leemann T, Dayer P and Meyer UA (1986) Single-dose quinidine treatment inhibits metoprolol oxydation in extensive metabolizers. *Eur J Clin Pharmacol* **29**:739–741.
- Llerena A, Edman, G, Cobaleda J, Benitez J, Schalling D and Bertillon L (1993) Relationship between personality and debrisoquine hydroxylation capacity: Suggestion of an endogenous neuroactive substrate or product of cytochrome P-4502D6. *Acta Psychiatr Scand* **87**:23–28.
- Löscher W and Hönack D (1993) Differences in anticonvulsant potency and adverse effects between dextromethorphan and dextrophan in amygdala-kindled and nonkindled rats. *Eur J Pharmacol* **238**:191–200.
- McQuay HJ, Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA and Wiffie PJ (1994) Dextromethorphan for the treatment of neuropathic pain: A double-blind randomised controlled crossover trial with integral n-of-1 design. *Pain* **59**:127–133.
- Nelson KA, Park KM, Robinovitz E, Tsigos C and Max MB (1997) High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* **48**:1212–1218.
- Netzer R, Pfimlin P and Trube G (1993) Dextromethorphan blocks N-methyl D aspartate-induced currents and voltage operated inward currents in cultured cortical neurons. *Eur J Pharmacol* **238**:209–216.
- Porchet HC, Piletta P and Dayer P (1990) Objective assessment of clonidine analgesia in man and influence of naloxone. *Life Sci* **46**:991–998.
- Price DD, Mao J, Frenk H and Mayer DJ (1994) The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* **59**:165–174.
- Sindrup SH and Brosten K (1995) The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* **5**:335–346.
- Sindrup SH, Poulsen L, Brosten K, Arendt-Nielsen L and Gram LF (1993) Are poor metabolisers of sparteine/debrisoquine less pain tolerant than extensive metabolisers? *Pain* **53**:335–349.
- Steinberg GK, Bell TE and Yenari MA (1996) Dose escalation safety and tolerance study of the N-methyl-D-aspartate antagonist dextromethorphan in neurosurgery patients. *J Neurosurg* **84**:860–866.
- Székely JJ, Sharpe LG and Jaffe JH (1991) Induction of phencyclidine-like behaviour in rats by dextrophan but not dextromethorphan. *Pharmacol Biochem Behav* **40**:381–386.
- Szolcsanyi J, Anton F, Reeh PW and Handwerker HO (1988) Selective activation by capsaicin of mechano-heat sensitive nociceptors in rat skin. *Brain Res* **446**:262–268.
- Tal M and Bennett GJ (1994) Neuropathic pain sensations are differentially sensitive to dextrophan. *Neuroreport* **5**:1438–1440.
- Torebjörk HE, Lundberg LER and LaMotte RH (1992) Central changes in processing

- of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol* **448**:765–780.
- Willer JC (1977) Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain* **3**:69–80.
- Willer JC (1990) Exploration clinique de la nociception par des techniques de réflexologie. *Neurophysiol Clin* **20**:335–256.
- Wong BY, Coulter DA, Choi DW and Pince DA (1988) Dextrorphan and dextromethorphan common antitussives are antiepileptic and antagonize N-methyl-D-Aspartate in brain slices. *Neurosci Lett* **85**:261–266.
- Woodworth JR, Dennis SRK, Hinsvark ON, Amsel LP and Rotenberg KS (1987) Bioavailability evaluation of a controlled release dextromethorphan liquid. *J Clin Pharmacol* **27**:133–138.
- Woolf CJ and Thompson SW (1991) The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic receptor activation: Implications for the treatment of postinjury pain hypersensitivity states *Pain* **44**:293–299.
- Wu D, Otton V, Kalow W and Seller EM (1995) Effects of route of administration on dextromethorphan pharmacokinetics and behavioral response in the rat. *J Pharmacol Exp Ther* **274**:1431–1437.

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