Chirality, the concept of nonsuperimposable mirror images, is a fundamental property of biological systems and can be observed on a molecular, cellular, or organism level. Stereoisomer compounds possess the same molecular and structural formula, but they differ in their three-dimensional configurations. Chiral compounds have two mirror-image stereoisomer forms called enantiomers. Compounds containing mirror-image enantiomers in equal proportions are referred to as racemic mixtures or racemates. Racemates and their individual enantiomers can have very different pharmacological properties that are relevant in clinical psychopharmacology. Various examples of drug therapies that show the clinical importance of chirality and stereochemistry are described.
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“Now, if you’ll only attend, Kitty, and not talk so much, I’ll tell you all my ideas about Looking-glass House. First, there’s the room you can see through the glass—that’s just the same as our drawing-room, only the things go the other way…. The books are something like our books, only the words go the wrong way…. How would you like to live in the Looking-glass House, Kitty? I wonder if they’d give you milk in there? Perhaps Looking-glass milk isn’t good to drink.” (Carroll, 1897, pp. 20, 22)

Chirality, the concept of nonsuperimposable mirror images, is a fundamental property of biological systems and reflects the underlying asymmetry of matter (Cintas, 2007). Indeed, chirality can be discerned on a molecular, cellular, or organism level (Levin & Mercola, 1998). For example, mirror-image twinning occurs in approximately 10% to 15% of monozygotic (identical) twins (Hall, 2003). These twins exhibit features that are mirror-image opposite each other, such as handedness, hair whorl direction, tooth patterns, and unilateral eye and ear defects. Stereoisomer compounds possess the same molecular and structural formula but have different three-dimensional configurations. Chiral compounds have two mirror-image stereoisomers called enantiomers. Compounds containing mirror-image enantiomers in equal proportions are referred to as racemic mixtures or racemates. Last month, I described the main principles of chirality and stereochemistry, which are essential for understanding the three-dimensional aspects of psychopharmacology. In this article, I will review examples of drug therapies in which chirality and stereochemistry are clinically relevant.

ANTIDEPRESSANT DRUGS

Most antidepressant drugs exist as racemic mixtures and are marketed in this form, but several are sold as specific enantiomers (Baumann & Eap, 2001). For example, the chemical serotonin is a cis-1S,4S enantiomer that was first marketed as the brand-name product Zoloft®. Similarly, the chemical paroxetine is a trans-(-) enantiomer that was first marketed under the brand name Paxil®. Selegiline (l-deprenyl; Eldepryl®), an approved drug for Parkinson’s disease and depression, is a phenylalkylamine compound that structurally resembles amphetamine. The marketed levorotatory enantiomer (l-deprenyl) is much more biologically active as a monoamine oxidase enzyme inhibitor compared with the dextrorotary enantiomer (Yasar et al., 2006).

Citalopram (Celexa®) is a racemic mixture. The pharmacological activity of citalopram (serotonin reuptake inhibition) is mostly attributable to the S-enantiomer, and the R-enantiomer may competitively interfere with this effect (Sánchez, Bøgesø, Ebert, Reines, & Braestrup, 2004). For this reason, the S-enantiomer escitalopram (Lexapro®) was further developed as an antidepressant drug.

Fluoxetine (Prozac®) is a racemate. The R-fluoxetine and S-fluoxetine enantiomers have differential effects on neurotransmitter transporters, liver metabolic enzymes, and cardiac function. The development of R-fluoxetine as a more “pure” antidepressant molecule was halted because of increased adverse cardiac effects (Shah, 2002), whereas further development of S-fluoxetine as a treatment for migraine headaches has had mixed results (Steiner, Ahmed, Findley, MacGregor, & Wilkinson, 1998).

STIMULANT AND SYMPATHOMIMETIC DRUGS

Dexmethylphenidate (Focalin®) is the d-enantiomer of the racemate stimulant drug methylphenidate (Ritalin®). Preclinical studies have shown that the d-enantiomer accounts for most of the biological activity of the racemate methylphenidate (Heal & Pierce, 2006). Clinical studies suggest that dexmethylphenidate has similar or slightly greater efficacy than methylphenidate in attention-deficit/hyperactivity disorder (ADHD), with a lower propensity for adverse effects and can be given in half the dosage of racemic methylphenidate.

Amphetamine products are available as dextroamphetamine (Dexedrine®), amphetamine/dextroamphetamine (Adderall®), and lisdexamfetamine (Vyvanse®). Dextroamphetamine is the d-enantiomer of the racemate drug amphetamine (Patrick & Markowitz, 1997). Dextroamphetamine and levoamphetamine have differential effects on the neurotransmitters dopamine and norepinephrine and on the metabolic enzyme monoamine oxidase, and their pharmacokinetic profiles are somewhat different. Early studies suggested that both drugs were effective overall for treating ADHD, but they appeared to have differential effects on attention and hyperactivity. Levoamphetamine is not marketed separately but is present in small amounts in the amphetamine/dextroamphetamine combination products.

Prodrugs are pharmacologically inactive compounds that are...
converted to biologically active metabolites. Lisdexamfetamine is an inactive prodrug in which the enantiomer dextroamphetamine is chemically bonded to the amino acid enantiomer L-lysine (Howland, 2008). After oral ingestion, the bond is metabolically cleaved in the gut, and lisdexamfetamine is converted to L-lysine and to the pharmacologically active drug dextroamphetamine. Compared with regular orally ingested dextroamphetamine, exposure to dextroamphetamine that is released from lisdexamfetamine is decreased and delayed in an extended-release pattern.

Pseudoephedrine (Sudafed®), approved for nasal sinus congestion, is the dextro-enantiomer form of the racemate ephedrine (Mistole®), which is approved for nasal congestion and acute bronchospasm. It is approximately one fourth as potent as ephedrine as a sympathomimetic agent, with much fewer adverse cardiovascular effects (Drew, Knight, Hughes, & Bush, 1978).

Modafinil (Provigil®) is a racemic stimulant-like drug (unrelated to methylphenidate or amphetamine). It is approved for the treatment of excessive daytime sleepiness associated with narcolepsy, sleep apnea, and shift work sleep disorder. The R-modafinil enantiomer has a half-life that is significantly longer than that of S-modafinil, and the elimination of S-modafinil is about three times faster than R-modafinil (Wisor, Dement, Aimone, Williams, & Bozyczko-Coyne, 2006). Because R-modafinil is expected to have a longer daytime therapeutic effect than racemic modafinil, the R-modafinil enantiomer (Nuvigil®) has been approved for the same indications as racemic modafinil.

**OTHER DRUGS**

Thalidomide (Thalomid®) was originally developed and marketed in the 1950s as a sedative medication for treating morning sickness during pregnancy. It was subsequently withdrawn when found to be associated with significant birth defects but was later reintroduced for treating other medical conditions. Thalidomide exists as a racemic mixture of R- and S-enantiomers. Studies have shown that the S-thalidomide enantiomer may have been selectively responsible for the birth defects associated with use of thalidomide (Waldeck, 2003).

The thyroid hormone thyroxine exists as a racemic mixture of levothyroxine (L-thyroxine) and dextrothyroxine (D-thyroxine). Levothyroxine (Levoxyl®, Synthroid®) is used as replacement therapy for hypothyroidism. Dextrothyroxine (Choloxin®) is much less potent than levothyroxine. It is approved for the treatment of hypercholesterolemia but is no longer commercially available. The drug was associated with a significantly higher rate of cardiovascular mortality in clinical trials, and the manufacturer ceased production (Denke, 2003).

Dopa is an amino acid precursor of the neurotransmitter dopamine, and it exists as a racemic mixture of the enantiomers levodopa (L-dopa) and dextro-dopa (D-dopa). Levodopa is used for the treatment of Parkinson’s disease. The early studies of dopa in Parkinson’s disease found that the most significant side effects of the drug were attributable to the D-dopa enantiomer (Coult & Baker, 1989).

Esomeprazole (Nexium®), a proton pump inhibitor used to suppress gastric acid secretion, is the S-enantiomer of the racemate omeprazole (Prilosec®). The drugs have different pharmacokinetic properties: Esomeprazole has less first-pass hepatic metabolism, a lower plasma clearance, and greater oral bioavailability compared with omeprazole (Dent, 2003).

Pregabalin (Lyrica®) is a chemical analog of the inhibitory amino acid gamma-aminobutyric acid (GABA). It is approved for the treatment of diabetic neuropathy and fibromyalgia. Pregabalin is the pharmacologically active S-enantiomer of racemic 3-isobutyl GABA (Frampton & Foster, 2006). Compared with the racemate, pregabalin binds with higher affinity to a particular site of the GABA receptor complex in the central nervous system.

Eszopiclone (S-zopiclone) is a marketed hypnotic agent (Lunesta®) for insomnia. It is the S-enantiomer of racemic zopiclone (Imovane®), which is not available in the United States but is marketed elsewhere for the treatment of insomnia. Preclinical trials demonstrated that the S-enantiomer was more active at the benzodiazepine receptor complex than the R-enantiomer and contributed to most of the

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Profound differences can sometimes be demonstrated between different chemical enantiomers.

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hypoactive activity of racemic zopiclone (Lane & Baker, 1999). Ketamine (Ketolar®), an anesthetic agent derived from the hallucinogenic drug phencyclidine (PCP), is a racemate that has been investigated for treatment-resistant depression. Compared with racemate ketamine, the S-ketamine enantiomer is less likely to cause perceptual disturbances and confusion, while preserving its anesthetic effects (Uehlinger et al., 2007).

Methadone (Dolophine®), a synthetic opioid analgesic, is a racemate. The R-methadone enantiomer is more pharmacologically active and potent than S-methadone. The metabolism of racemate methadone in the liver is stereospecific, which means that each enantiomer is metabolized differently by various hepatic enzymes. Taking medications that selectively inhibit the metabolic enzyme that stereospecifically metabolizes the R-methadone enantiomer may increase R-methadone concentrations, potentially resulting in greater analgesic and adverse effects (Uehlinger et al., 2007).

Propoxyphene, an opioid analgesic structurally related to methadone, exists as a racemate. The dextropropoxyphene enantiomer is marketed as an analgesic (Darvon®) because the levopropoxyphene enantiomer has little or no analgesic activity (Burke & Kratochvil, 2002). Although no longer manufactured, the levopropoxyphene enantiomer was once marketed as a centrally acting cough suppressant with the trade name Novrad® (Darvon spelled backward).

CONCLUSION

Alice wondered whether Looking-glass milk might not

and potential antidepressant effects (Burke & Henderson, 2002; Paul, Schaaff, Padberg, Moller, & Frodl, 2007).

Methadone (Dolophine®), a synthetic opioid analgesic, is a racemate. The R-methadone enantiomer is more pharmacologically active and potent than S-methadone. The metabolism of racemate methadone in the liver is stereospecific, which means that each enantiomer is metabolized differently by various hepatic enzymes. Taking medications that selectively inhibit the metabolic enzyme that stereospecifically metabolizes the R-methadone enantiomer may increase R-methadone concentrations, potentially resulting in greater analgesic and adverse effects (Uehlinger et al., 2007).

Propoxyphene, an opioid analgesic structurally related to methadone, exists as a racemate. The dextropropoxyphene enantiomer is marketed as an analgesic (Darvon®) because the levopropoxyphene enantiomer be good to drink. If one considers the chemical constituents of milk, it would certainly be reasonable to speculate about the possible physiological differences in mirror-image milk. Odors and tastes are chemically mediated, and profound differences can sometimes be demonstrated between different chemical enantiomers (Sell, 2004; Temussi, 2009). For example, the dipeptide combination of the amino acids L-aspartic acid and L-phenylalanine methyl ester (L-Asp-L-PheOMe) is manufactured as the artificial sweetener aspartame. However, this dipeptide combination can exist in four stereoisomer forms. The stereoisomers D-Asp-D-PheOMe, D-Asp-L-PheOMe, and L-Asp-D-PheOMe are bitter. Because the introduction of stereochemically pure drugs is expected to increase, nurses should understand the rationale for their development and how they may improve the pharmacotherapy of patient care.

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