# The assay of the agonist activities of *N*-methyl- and *N*-nor-homologues of morphine derivatives by the guinea-pig ileum method

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It has been shown that normorphine and morphine are equiactive in the isolated preparations of the guinea-pig ileum (Kosterlitz, Lord & Watt, 1972) and the mouse vas deferens (Hughes, Kosterlitz & Leslie, 1975). *In vivo*, normorphine is considerably less potent than morphine when injected intravenously into rats but almost equipotent when injected into the cerebral ventricles; this observation is best explained by the fact that normorphine is less lipid soluble than morphine and will therefore pass the blood-brain barrier less readily (Herz & Teschemacher, 1971). For this reason, studies on the structure-activity relations are preferably carried out on isolated preparations where a diffusion barrier is of much less importance.

In investigations on the guinea-pig ileum it has been found (Kosterlitz & Waterfield, 1975) that in phenylpiperidines and benzomorphans the loss of the *N*-methyl group leads to a very considerable decrease (80–100%) in agonist activity. A similar result has been obtained for (−)-3-hydroxymorphinan (loss of 89%; unpublished observation). This is in contrast to the finding that not only normorphine and morphine are equiactive but also codeine and norcodeine.

Recently, we have been able to assay on the guinea-pig ileum by the method previously reported (Kosterlitz & Watt, 1968) *N*-methyl- and *N*-nor-homologues of compounds which are closely related to morphine (Table 1). Dihydromorphine which differs from morphine by saturation of the $C_7$-$C_8$ bond is the only one of the 5 compounds in which loss of the *N*-methyl group reduces the agonist activity by less than 40%. The agonist activity of nordesomorphine is only 20% of that of desomorphine, which differs from dihydromorphine by the absence of the OH- group at $C_6$. The *N*-methyl group is of similar importance for the agonist activity of diamorphine (3,6-diacetylmorphine) and oxymorphone (14-hydroxydihydromorphinone) and to a lesser degree for that of 6-acetylmorphine. The effects of the lack of the methyl group at the N-atom are even more marked *in vivo*. In hot-plate tests on mice, nordesomorphine, nordiamorphine and 6-acetylnormorphine have only 4 to 5% of the agonist activites of the corresponding *N*-methyl homologues (Sargent & May, 1970; Rice & Jacobson, 1975).

Table 1. *Relative agonist potencies of nor-analogues of morphine derivatives in the guinea-pig ileum.*

| Compound | No. of obs. | Relative agonist potency (morphine=1) | Ratio nor-homologue/ *N*-methyl -homologue |
|---|---|---|---|
| Diamorphine (heroin) | 5 | 1·00 ± 0·13 | 0·17 |
| Nordiamorphine | 5 | 0·172 ± 0·006 | |
| Desomorphine | 3 | 4·43 ± 0·16 | 0·22 |
| Nordesomorphine | 3 | 0·97 ± 0·09 | |
| Oxymorphone | 4 | 3·73 ± 0·52 | 0·23 |
| Noroxymorphone | 4 | 0·84 ± 0·07 | |
| 6-Acetylmorphine | 5 | 0·84 ± 0·06 | 0·39 |
| 6-Acetylnormorphine | 5 | 0·33 ± 0·02 | |
| Dihydromorphine | 3 | 2·36 ± 0·27 | 0·61 |
| Dihydronormorphine | 3 | 1·45 ± 0·09 | |
| Codeine | 5 | 0·0091 ± 0·007 | 0·97 |
| Norcodeine | 5 | 0·0088 ± 0·009 | |
| Normorphine | 6 | 1·00 ± 0·10 | 1·0 |

All compounds were assayed against normorphine as internal standard of reference. The values are the means ± s.e.

In conclusion, it has been shown that, while morphine and normorphine are equiactive, the loss of the *N*-methyl group leads to a considerable loss in agonist activity after even minor changes in the nucleus of the morphine molecule. It would therefore appear that, in this respect, morphine is the exception rather than the rule. The fact that codeine and norcodeine are equiactive is perhaps of less significance because their agonist activities are very low.

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