Interaction of injectable progestin contraceptives with steroid receptors.

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The injectable progestin-only contraceptives, medroxyprogesterone actetate (MPA) and norethindrone enanthate (NET-EN) are the most widely used contraceptives in Southern Africa. To date, the precise molecular mechanisms of action of these contraceptives are not known. As both compounds are progestins, it is assumed that the mechanisms of action of MPA and NET-EN would be elicited by their ability to interact with the progesterone receptor (PR). However, MPA has been demonstrated to have high affinity for, and is an agonist not only for the PR, but also the glucocorticoid receptor (GR), and androgen receptor (AR). This indicates that MPA, and possibly NET, may exert side-effects via any of these receptors, thus highlighting the importance of understanding the interactions of these compounds with steroid receptors. Whether it also interacts with the mineralocorticoid receptor (MR), is not well-documented. We investigated the relative binding affinity and agonist potency of MPA versus norethindrone acetate (NET) (the active metabolite of NET-EN) for the above-mentioned receptors. Receptor binding experiments show that MPA and NET bind with a high apparent affinity to the GR and AR. We also determined the Kd and Ki values for the test compounds in our COS-1 cell system. We show that these compounds have similar, and relatively strong agonist potency for the AR, while MPA is a much more potent GR agonist than NET. Interestingly, MPA and NET bind to the MR with the same relative affinity, but with much lower affinity than the natural ligand, aldosterone. Our results provide insights into the mechanism of known and potential side effects of MPA and NET.