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Rapid communication

Opioid δ receptor subtypes are associated with different potassium channels

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Previous data have indicated that opioid μ and δ receptors may act by opening potassium channels in the central nervous system (North, 1986). A recent report by Ocana et al. (1990) suggests that morphine antinociception may be associated with ATP-sensitive potassium channels. This conclusion was based on the finding that the antinociceptive effect of morphine was antagonized by glyblenclamide, a compound which blocks ATP-sensitive potassium channels (Amoroso et al., 1990), but not by tetraethylammonium bromide (TEA), a compound thought to act on other types of potassium channels (Cook, 1988). This finding raised the question of whether opioid δ receptors are linked with the same potassium channels as morphine, and whether subtypes of opioid δ receptors are linked to the same potassium channels. Evidence suggesting the existence of opioid δ receptor subtypes has now been accumulated, and has demonstrated that these receptors are activated selectively by [D-Pen^2,D-Pen^5]enkephalin (DPDPE) or by [D-Ala^2]deltorphin II (Jiang et al., 1990; Jiang, Mosberg and Porreca, submitted). The purpose of the present experiment was to determine (a) whether the antinociceptive actions of DPDPE could also be linked to a glyblenclamide-sensitive potassium channel (presumably an ATP-sensitive potassium channel) and (b) whether the antinociceptive actions of [D-Ala^2]deltorphin II were associated with potassium channels and if so, whether these channels were also of the glyblenclamide-sensitive type. Additionally, in order to validate the data, an opioid κ receptor agonist was tested as this receptor is thought to be linked to calcium channels in the central nervous system (North, 1986) and responses mediated through this receptor type should be insensitive to potassium channel blockers.

Male, ICR mice (25-30 g, Harlan) were used. Antinociception was determined by recording the latency to a rapid tail-flick using warm water (55 °C) as the nociceptive stimulus with a cut-off time of 15 s. Mice received graded intracerebroventricular (i.c.v.) injections of distilled water or vehicle (0.1% DMSO for [D-Ala^2]deltorphin II only and 2.5% Tween 80 for glyblenclamide only), morphine sulfate (Mallinckrodt), DPDPE, [D-Ala^2]deltorphin II or U69,593 (Sigma) alone, glyblenclamide (40 μg) or TEA (40 μg) alone, or co-administered agonist with glyblenclamide (40 μg) or TEA (40 μg). All compounds were administered in a volume of 5 μl; DPDPE and [D-Ala^2]deltorphin II were synthesized as previously reported. Antinociception was calculated 10 min after i.c.v. injection using the following formula: % antinociception = 100 × (test latency − control latency)/(15 − control latency).

The data from these experiments are shown in table 1. Neither glyblenclamide, TEA or any vehicle produced any measurable antinociception alone (data not shown). In agreement with the results of Ocana et al. (1990), the antinociceptive effects of morphine were antagonized by glyblenclamide, but not by TEA. Similarly, the antinociceptive actions of DPDPE were blocked by glyblenclamide, but not by TEA. As expected, the antinociceptive effects of the κ agonist, U69,593 were insensitive to both glyblenclamide and to TEA. In contrast to the results with morphine and with DPDPE, however, the antinociceptive actions of [D-Ala^2]deltorphin II were blocked by TEA, but not by glyblenclamide.

The present results confirm the previous suggestions that morphine antinociception is sensitive to glyblenclamide, implicating ATP-sensitive potassium channels in this effect. Additionally, these data show that the antinociception produced by the opioid δ agonist, DPDPE, is also sensitive to glyblenclamide, implying that this type of δ receptor is also linked to an ATP-sensitive potassium channel. In contrast to this result, however, the data indicate that the effects of another highly selective δ agonist, [D-Ala^2]deltorphin II (Jiang et al., 1990), are mediated through a glyblenclamide-insensitive potassium channel. That this δ receptor subtype is also linked to potassium channels is supported

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TABLE 1

Antinociceptive A_{50} values (and 95% confidence intervals) for agonists acting at opioid receptor subtypes in the mouse tail-flick test.

Agonist	Glyblenclimide (GLYB)			Tetraethylammonium (TEA)		
	Alone	+40 μg Glyb	Shift ratio	Alone	+40 μg TEA	Shift ratio
Morphine	1.462 (0.81-2.11)	7.18 (3.77-10.59)	4.9	1.462 (0.81-2.11)	1.373 (0.65-2.09)	0.9
DPDPE	21.319 (15.52-27.12)	192.93 (9.94-375.91)	9.1	6.2616 (4.72-7.80)	6.313 (4.24-8.39)	1.0
Deltorphin II	12.235 (9.11-15.36)	10.664 (8.30-13.03)	0.9	4.275 (2.97-5.58)	16.945 (5.89-28.00)	4.0
U69,593	25.477 (17.68-33.28)	26.60 (17.35-35.85)	1.0	16.512 (9.01-24.01)	18.355 (10.23-26.48)	1.1

by the sensitivity of the antinociceptive effect of TEA. Given the previous evidence linking κ receptors to calcium channels, the lack of effect of either glyblenclamide or TEA is not surprising and confirms the validity of the present approach. Thus, it appears that δ receptor subtypes may be linked to different types of potassium channels which can be discriminated on the basis of sensitivity to glyblenclamide or TEA. These glyblenclamide-sensitive potassium channels (i.e., presumably ATP-sensitive potassium channels) appear to be activated by μ opioids such as morphine as well as by the classical δ agonist, DPDPE. Additionally, the present study reveals that a δ receptor subtype, selectively acted upon by [D-Ala^2]deltorphin II, produces an antinociceptive effect via TEA-sensitive potassium channels. The data confirm the existence of δ receptor subtypes and offer novel insights into the mechanism by which these receptors may mediate their antinociceptive effects.

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