Evidence of a specific role for 5-HT2A and 5-HT7 receptors in hindlimb stepping generation induced pharmacologically in paraplegic mice.

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Serotonin (5-HT) receptor agonists such as quipazine and 8-OH-DPAT can induce 'automatic' locomotor movements in the hindlimbs of completely spinal cord transected animals. This study aimed at identifying, with additional pharmacological and complementary receptor labelling approaches, candidate receptor subtypes involved in the induced locomotor rhythmogenesis. In contrast to the pro-locomotor effect of quipazine (5-$HT_{2A/2C}$ agonist), m-CPP (5-$HT_{2B/2C}$ agonist, 0.5-2 mg/kg, i.p.) or TFMPP (5-$HT_{1B/2C}$ agonist, 0.5-2 mg/kg, i.p.) failed to acutely induce hindlimb locomotor movements suggesting a required activation of 5-HT_{2A} receptors in quipazine-induced stepping. We also found that 8-OH-DPAT (5-$HT_{1A/7}$)-induced stepping remained in mice co-treated or pre-treated with two highly-selective 5-HT_{1A} antagonists (WAY100,135 & WAY100,635) suggesting that 5-HT_7 receptor activation can also induce locomotion. Moreover, in situ hybridization data revealed high expression of 5-HT_{2A} and 5-HT_7 receptor subtypes in the ventral horn and intermediate grey zone of upper lumbar spinal segments. Interestingly, this region is known to contain critical elements of the locomotor network in cats, rats and mice. High 5-HT_7-ir levels were found also in this same area. These results support a role for 5-HT_{2A} and 5-HT_7 receptors in quipazine and 8-OH-DPAT induced hindlimb stepping in paraplegic mice. An identification of the 5-HT receptor subtypes responsible for activation of the locomotor pattern generator may lead to more selective pharmacotherapeutic strategies for spinal locomotor network modulation in the rehabilitation of spinal cord injured patients.