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Modulation of Neuronal Transmission and Function by Nitric Oxide in the Brain

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It has been postulated that nitric oxide (NO) is a universal modulator of neurotransmitter release in the brain. This NO function was first shown by investigating in vivo the effects of NO donors and NO synthesis inhibitors on the release of acetylcholine (1,2).

Most of the experiments were carried out on anaesthetized or conscious rats using the push-pull superfusion technique for in vivo access of transmitter release and local administration of drugs in distinct brain areas. This approach was chosen because the push-pull superfusion has some advantageous characteristics such as (a) gliosis is not developed even after long-lasting superfusion, (b) recoveries are good, (c) metabolic rate during transport of the superfusate from the brain to the collecting microvials is low: good recoveries and low metabolic rate contribute to the (d) good time resolution of the technique, (e) microelectrodes can be inserted into the cannula for recordings of extracellular potentials or NO determination in the same brain area in which neurotransmitter outflow is monitored (see below).

The main observation concerning the modulatory function of NO was that, in the ventral striatum, local superfusion with the nitric oxide synthase (NOS) inhibitor L-NAME or the selective neuronal NOS (nNOS) inhibitor 7-NINA decreases the outflow of acetylcholine, while the NO donors linsidomine, DEA/NO and SNAP exert the opposite effect. The release of acetylcholine is also enhanced by the excitatory amino acid NMDA. Since the releasing effect of NMDA is independent of endogenous NO, it was assumed that NO liberates an endogenous excitatory amino acid which in turn increases cholinergic transmission thus enhancing acetylcholine outflow. Indeed NO inhibitors reduce, while NO donors promote glutamate release in the striatum. Moreover electrical stimulation of a glutamatergic pathway within the hippocampus increases the outflow of acetylcholine in the nucleus accumbens. Superfusion of the nucleus accumbens with the NO donor PAPANO releases acetylcholine and potentiates the stimulation induced release of the transmitter, while superfusion of the nucleus accumbens with the selective nNOS inhibitors NS 2028 or 7-NINA decreases the acetylcholine release induced by electrical stimulation of the hippocampus.

Furthermore NO influences histamine release. Superfusion of the anterior hypothalamus with linsidomine reduces, while L-NAME increases the outflow of histamine from histaminergic neurons. Since the muscarinic receptor agonists carbachol and oxotremorine decrease, while the muscarinic receptor blockers atropine, pirenzepine (M_1 blocker) and 4-DAMP (M_1, M_3 blocker) increase the histamine outflow but methoctramine (M_2>M_3 blocker) and p-f-HHSiD (M_3 blocker) are ineffective, it seems that acetylcholine released from cholinergic neurons stimulates M_1 receptors located on histaminergic neurons and in this way histaminergic transmission and histamine release are suppressed. Interestingly, in the presence of atropine the inhibition of histamine release by linsidomine is reversed to an enhanced release pointing to the involvement of a second transmitter in the modulation of histaminergic transmission. This second modulator may be glutamate because the excitatory amino acids kainate,

NMDA, glutamate elicit a very pronounced release of histamine. Thus NO releases glutamate, which stimulates NMDA receptors, located on histaminergic neurons and histamine release is enhanced. Under basal conditions the inhibitory effect of the cholinergic neurons pre-dominates. Blockade of M_1 receptors by atropine unmasks the effect of glutamatergic neurons and release of histamine is augmented.

NO also modulates serotonergic transmission. In the hypothalamus, the release of serotonin is influenced by NO in a dual way. Low concentrations of DEA/NO, SNOG, SNAP, SNP reduce the release of serotonin which is enhanced during superfusion with high concentrations of the NO donors. Moreover low concentrations of L-NAME or 7-NINA increase the release of the transmitter, while a high concentration of L-NAME displays the opposite effect. Hence low endogenous NO suppresses but high NO promotes serotonergic transmission in the hypothalamus (2).

Since NO modulates neuronal transmission, it must also modulate neuronal function. This is indeed the case. Behavioural experiments revealed that, in the locus coeruleus, NO is implicated in the excitation of serotonergic neurons elicited by emotional stimuli like exposure to noise or tail pinch. Furthermore i.c.v. administration of the PDE5 inhibitor UK 114,542 which, by inhibiting phosphodiesterase promotes NO transduction, improves memory and object discrimination performance.

These results demonstrate the involvement of endogenous NO in neuronal transmission and function. This conclusion, however, is based on findings obtained indirectly by using NO inhibitors and NO donors so as to diminish and to increase the tissue level of NO, respectively. Recently, the possibility of in vivo determination of NO release has been addressed. A microelectrode for electrochemical NO detection was inserted into a modified push-pull cannula. This novel technique makes it possible to determine continuously the extracellular NO concentration under *in vivo* conditions. Furthermore NO determination may be combined with monitoring of neurotransmitter release in the same distinct brain area. First findings show that superfusion of the nucleus accumbens with 7-NINA leads to an inhibition of extracellular NO concentration, which is developed gradually within ten minutes. Hence NO is released from nitrergic neurons. The *in vivo* NO determination also demonstrates in a direct way that this molecule is the initiator of neuronal transmission and function in the brain.

REFERENCES

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