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European Journal of Pharmacology 457 (2002) 99–106
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Different strains of rats show different sensitivity to block of long-term potentiation by nitric oxide synthase inhibitors

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Received 25 April 2002; received in revised form 16 October 2002; accepted 22 October 2002

Abstract

Nitric oxide is presumed to play important roles in the induction of synaptic plasticity and learning. Previous publications, however, reported contradictory results. Block of nitric oxide synthase (NOS) has been shown to impair the induction of long-term potentiation of synaptic transmission in some studies. Other studies observed a partial block of long-term potentiation depending on experimental conditions, while yet other studies did not find an effect of NOS inhibitors under any conditions tested. Some reasons for these differences had been identified, e.g. the temperature of the slice buffer, the age of the animals, and the specific stimulation protocols used. Still, even when taking these parameters into account, not all results can be explained. The present study compares three strains of rats and observes large differences in sensitivity to nitric oxide synthase (NOS) blockers on the induction of long-term potentiation. While Wistar rats showed an almost complete block of long-term potentiation when using the NOS inhibitors 7-nitro-indazole (30 mg/kg ip) or 1-(2-trifluoromethylphenyl) imidazole (TRIM; 150 nmol/5 μl icv), 117 ± 5 S.E.M. of % of baseline slope values of excitatory postsynaptic potentials. Sprague–Dawley and Long–Evans rats showed no or only weak effects of drugs on the induction of long-term potentiation (166 ± 17 S.E.M. of % of baseline slopes in Sprague–Dawley rats, 173 ± 24 S.E.M. of % of baseline values in Long–Evans rats). The results could explain at least some of the discrepancies of the efficacy of NOS inhibitors on synaptic plasticity that is found in the literature. Such large strain differences suggest that results from studies that use laboratory rats could have strain-dependent components and should be generalised cautiously.
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Keywords: CA1 area; Hippocampus; Nitric oxide (NO); Learning; Long-term potentiation; (Rat)

1. Introduction

Nitric oxide is a neuronal transmitter that has been implicated to play a role in the induction of long-term potentiation of synaptic plasticity (Bredt and Snyder, 1992; Garthwaite, 1991). Results from a number of experiments that tried to investigate this theory, however, have been very contradictory. While some studies showed a complete block of long-term potentiation in the hippocampal after application of nitric oxide synthase (NOS) inhibitors (Böhme et al., 1991; Bon et al., 1992; Doyle et al., 1996; O'Dell et al., 1991; Schuman and Madison, 1991), others found only a partial block of long-term potentiation (Boulton and Garthwaite, 1995; Chetkovich et al., 1993; Gribkoff and Lum-Ragan, 1992; Haley et al., 1993; Iga et al., 1993; Musleh et al., 1993; Southam et al., 1996) while yet others did not find any effects using NOS inhibitors (Bannerman et al., 1994a; Cummings et al., 1994; Murphy et al., 1994; Williams et al., 1993). Publications that used 'knock-out' gene deletion mice showed that the neuronal and also endothelial isoforms of NOS are expressed in CA1 pyramidal cells and deletion of both endothelial and neuronal NOS results in loss of long-term potentiation (Son et al., 1996). In some studies that investigated the effects of NOS inhibitors on long-term potentiation in vivo, it was found that long-term potentiation can be blocked almost completely (Doyle et al., 1996; Hölscher, 1999b) yet under very similar experimental conditions there was no visible effect of these drugs in other studies (Bannerman et al., 1994a; Hölscher, 1999a). In behavioural studies that tried to elucidate the effects of NOS inhibitors on learning and memory formation, block of NOS has been shown to impair learning in a number of studies (Bernabeu et al., 1995; Böhme et al., 1993; Chapman et al., 1992; Hölscher, 1994; Hölscher et al.,

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PII: S0014-2999(02)02641-9

1996; Hölscher and Rose, 1992; Prendergast et al., 1997) yet again not all studies showed an effect of such drugs on learning (Bannerman et al., 1994b; see Hölscher, 1997, for a review).

The discrepancies in experimental results found in in vitro slice preparations cannot be easily explained. One finding that explains the observed contradictions to some degree is that a NO-independent component of long-term potentiation in the subarea stratum radiatum of area CA1 in the hippocampus had been identified, while long-term potentiation in stratum oriens is largely NO synthase independent (Haley and Madison, 1995; Kantor et al., 1996; Son et al., 1996). Hence, one could imagine that stimulation of pathways in the stratum oriens might lead to a negative result when trying to block long-term potentiation with NOS inhibitors, while stimulation in subarea stratum radiatum does show an effect. Not all studies differentiate between these subareas when stimulating the hippocampus.

A second reason that can explain the contradictory results to some extent is the observation that the stimulation protocol that is used to induce long-term potentiation can be of crucial importance. Some studies observed that high frequency stimulation in the hippocampal slice induced stable long-term potentiation that could not be blocked by NOS inhibitors when using a *weak* stimulation protocol, but it was possible to block long-term potentiation that was induced by using a *strong* stimulation protocol (Gribkoff and Lum-Ragan, 1992; Lum-Ragan and Gribkoff, 1993). The opposite results were described by others, for example it was found that long-term potentiation induced by weak stimulation was blocked by NO synthase inhibitors, but not long-term potentiation induced by strong stimulation (Chetkovich et al., 1993; Haley et al., 1993). It is not possible to directly compare these studies since the actual strength of stimulation was not measured, and a 'strong' stimulation protocol used by one group might be considered 'weak' by others. These differences however cannot explain all contradictions seen in the literature. For example, long-term potentiation was blocked by two types of NOS inhibitors, 7-nitro-indazole and 1-(2-trifluoromethylphenyl) imidazole (TRIM) (Doyle et al., 1996; Hölscher, 1999b) using an in vivo recording set-up that was identical with a set-up in another study where long-term potentiation was not blocked by these agents (Hölscher, 1999a). There was one difference, however. The studies used different strains of rats. Since NOS is a highly regulated enzyme that is expressed at varying rates that depend on several factors (Lam et al., 1996; Minc-Golomb and Schwartz, 1995, 1994), it is possible that the amount of NOS expressed and the actual activity of the enzyme differs between strains. It has been shown that the inducible isoform of NOS is expressed at different levels in different strains (Johannesen et al., 2001). Also, it has been shown that the expression of neuronal NOS can be induced to some extent (Lam et al., 1996). Other strain differences in rats have been described in detail, e.g. differences in the ability to learn (McMillan and Li, 2001), in the sensitivity to benzodiazepines (Bert et al., 2001), in the expression of receptors (Farook et al., 2001), or in the expression of immediate early genes (Arnold et al., 2001).

In order to test the sensitivity of long-term potentiation induced by high-frequency stimulation in different rat strains to NOS inhibitors, two NOS inhibitors were tested. The first drug was 7-nitro-indazole, a NOS inhibitor that is not selective for any isoform of NOS, but does not affect blood pressure at the concentrations used here. This had been shown in an in vivo study where application of this dose of 7-nitro-indazole inhibiting NOS activity by 95% over 1.5 h (Babbedge et al., 1993) and therefore appears to inhibit neuronal NOS in vivo more than other isoforms via an unknown mechanism (Hara et al., 1996; Moore et al., 1993). The second drug was 1-(2-trifluoromethylphenyl) imidazole (TRIM), a drug with similar properties that appears to preferably inhibit neuronal NOS in the in vivo situation (Handy and Moore, 1997; Handy et al., 1995). Three different strains that are most commonly used in electrophysiological investigations were tested, Wistar, Sprague–Dawley and Long–Evans.

2. Materials and methods

2.1. Surgery and recoding procedure

Male Wistar, Sprague–Dawley, or Long–Evans rats weighing 220–280 g were anaesthetised with urethane (ethyl carbamate, 1.8 g/kg, ip) for the duration of all experiments.

A cannula (22 gauge, 0.7 mm outer diameter, 11 mm in length, Bilaney, Kent, UK) was implanted (1.5 mm anterior to bregma, 0.5 mm lateral to the midline and 3.55 mm ventral) into the right hemisphere. Electrodes (tungsten with Teflon coating, Bilaney, Kent, UK) were implanted unilaterally 3.4 mm posterior and 2.5 mm lateral to the midline, and the stimulating electrode 4.2 mm posterior to bregma and 3.8 mm lateral to the midline. The electrodes were slowly lowered through the cortex and the upper layers of the hippocampus and into the CA1 region until the appearance of a negative deflecting excitatory postsynaptic potential (EPSP) that had a latency of ca. 10 ms. Recordings of EPSPs were made from the stratum radiatum in the CA1 region of the right hippocampal hemisphere in response to stimulation of the Schaffer collateral/commissural pathway.

Field EPSPs were recorded on a computerised stimulating and recording unit (PowerLab, ADI Instruments, UK) in which the trigger threshold was adjustable. The triggered unit activated a constant current stimulus isolation unit (Neurolog, UK). The data acquisition system was triggered simultaneously to record all events. Sampling speed was at 20 kHz recording of EPSPs. The standard high-frequency stimulation protocol for inducing long-term potentiation consisted of 10 trains of 20 stimuli, inter-stimulus interval

of 5 ms (200 Hz), inter-train interval of 2 s. Stimulation intensity was 70% of the max. EPSP during high-frequency stimulation and during baseline stimulation. Three sets of this standard high-frequency stimulation (inter-set interval of 30 s) have been shown to induce maximal long-term potentiation under these recording conditions (Hölscher et al., 1997). Long-term potentiation was measured as % of baseline EPSP slope recorded over a 20-min period prior drug injection and 25 min prior to application of high-frequency stimulation. Baseline was recorded for 20 min and averaged to 100%.

All experiments were licensed according to EU regulations.

2.2. Drugs

7-Nitro-indazole was obtained form BIOMOL (USA) and emulsified in sesame oil by sonication for 5 min. Rats were injected ip 9 mg of 7-nitro-indazole emulsified in 0.2 ml oil which results in a concentration of 30 mg/kg. Control animals received 0.2 ml sesame oil only. TRIM was obtained from Lancaster Eastgate (UK) and dissolved in saline. The pH was adapted to 7.4 with NaOH when necessary. A unilateral icv injection of 5 μl containing 150 nmol or vehicle was administered 25 min before high-frequency stimulation.

2.3. Statistics

Unless otherwise stated the values are expressed as the mean ± standard error of the mean EPSP slope. The slopes of the field EPSPs were compared at different time points as stated, using a nonparametric Wilcoxon test when two groups were compared. When three groups were compared, a Kruskal–Wallis nonparametric analysis of the variance (ANOVA) was performed with a post-hoc Dunnet's *t*-test. A value of $P < 0.05$ was considered significant.

3. Results

3.1. Wistar rats

High-frequency stimulation induced long-term potentiation of the slope of field EPSPs in the control injected group (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 99.4 ± 2.4 S.E.M. of % of baseline slope average to 172 ± 10 S.E.M. of % of baseline values, $P < 0.01$ in a two-tailed Wilcoxon test). Injection of 7-nitro-indazole (30 mg/kg ip) blocked the induction of long-term potentiation (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 99.4 ± 2.4 to 117 ± 5 S.E.M. of % of baseline values, $P < 0.4$ in a two-tailed Wilcoxon test). The drug had no effect on baseline transmission. Injection of TRIM (150 nmol/5μl icv) impaired the induction of long-term potentiation as compared to controls (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 100 ± 2 to 117 ± 5 S.E.M. of % of baseline values, $P < 0.01$ in a two-tailed Wilcoxon test). The difference between slopes after high-frequency stimulation

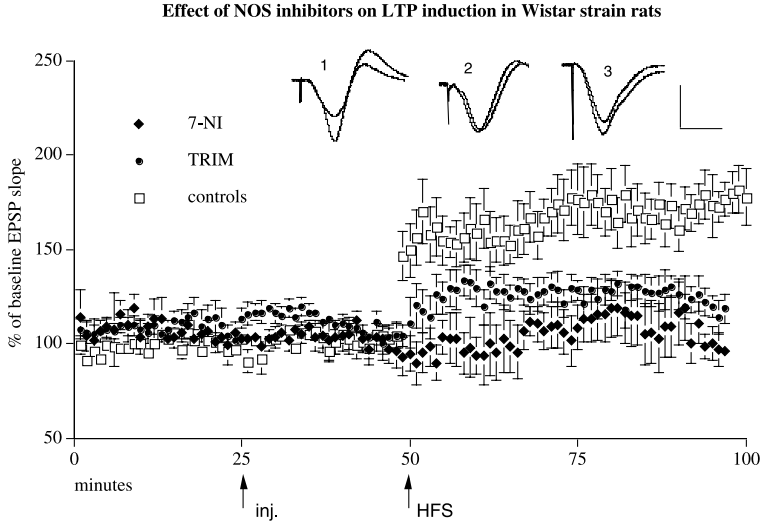

Fig. 1. High-frequency stimulation induced long-term potentiation of the slope of field EPSPs in the control Wistar group (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; $P < 0.01$ in a two-tailed Wilcoxon test). The NOS inhibitor 7-nitro-indazole (30 mg/kg ip) blocked the induction of long-term potentiation (no difference between pre- and post-high-frequency stimulation slopes). TRIM (150 nmol/5μl icv) impaired the induction of long-term potentiation as compared to controls ($P < 0.01$ in a Wilcoxon test when comparing pre- with post-high-frequency stimulation slopes of EPSPs). The difference between slopes after high-frequency stimulation in the control group and in the TRIM group was significant (measured 25 min after high-frequency stimulation; $P < 0.01$). The drug had no effect on baseline transmission. $n = 6$ for each group. inj. = time point of drug injection, HFS = time point of stimulation. Shown are typical EPSPs before and after HFS. 1 = control, 2 = 7-nitro-indazole group, 3 = TRIM group. Calibration bars: *x*-axis = 10 ms, *y*-axis = 1 mV.

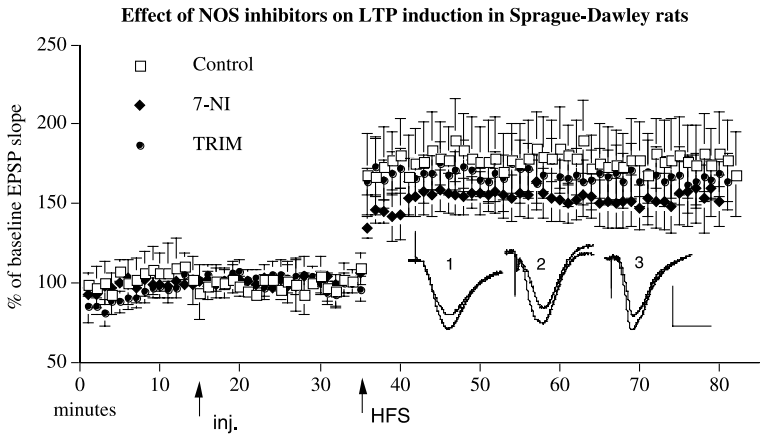

Fig. 2. High-frequency stimulation induced long-term potentiation of the slope of field EPSPs in the control Sprague–Dawley group (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; $P<0.01$ in a two-tailed Wilcoxon test, $n=6$). 7-Nitro-indazole (30 mg/kg ip) had no effect on the induction of long-term potentiation (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; $P<0.01$, $n=5$). The drug had no effect on baseline transmission. Injection of TRIM (150 nmol/5μl icv) did not affect the induction of long-term potentiation as compared to controls (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; $P<0.01$). The difference between slopes after high-frequency stimulation in the control group and in the TRIM group was not significant ($n=6$). The drug had no effect on baseline transmission. inj. = time point of drug injection, HFS = time point of stimulation. Shown are typical EPSPs before and after high-frequency stimulation. 1 = control, 2 = 7-nitro-indazole group, 3 = TRIM group. Calibration bars: *x*-axis = 10 ms, *y*-axis = 1 mV.

in the control group and in the TRIM group was significant ($172 \pm 10/117 \pm 5$ S.E.M. of slope after high-frequency stimulation as measured 25 min after high-frequency stimulation; $P<0.01$). The drug had no effect on baseline transmission, $n=6$ for each group (see Fig. 1).

3.2. Sprague–Dawley rats

High-frequency stimulation induced long-term potentiation of the slope of field EPSPs in the control injected group (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 96 ± 2.9 S.E.M. % of baseline slope average to 180 ± 24 S.E.M. of % of baseline values, $P<0.01$ in a two-tailed Wilcoxon test, $n=6$). Injection of 7-nitro-indazole (30 mg/kg ip) had no effect on the induction of long-term potentiation (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 108 ± 1.4 to 152 ± 12 S.E.M. of % of baseline values, $P<0.01$ in a two-tailed Wilcoxon test, $n=5$). The drug had no effect on baseline transmission. Injection of TRIM (150 nmol/5 μl icv) did not affect the induction of long-term potentiation as compared to controls (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 101 ± 7 to 166 ± 17 S.E.M. of % of baseline values, $P<0.01$ in a two-tailed Wilcoxon test). The difference between slopes after high-frequency stimulation in the control group and in the TRIM group was not significant

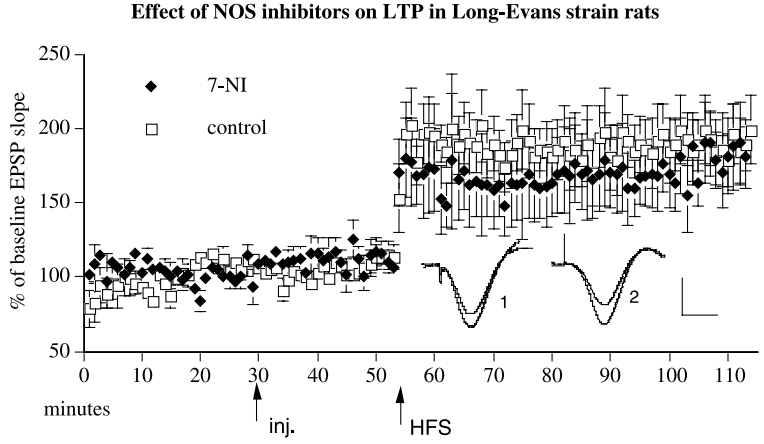

Fig. 3. High-frequency stimulation induced long-term potentiation of the slope of field EPSPs in the control Long–Evans group (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; $P<0.01$ in a two-tailed Wilcoxon test, $n=6$). 7-Nitro-indazole (30 mg/kg ip) had no effect on the induction of long-term potentiation ($P<0.01$, $n=6$). The drug had no effect on baseline transmission. inj. = time point of drug injection, HFS = time point of stimulation. Shown are typical EPSPs before and after high-frequency stimulation. 1 = 7-nitro-indazole group, 2 = control group. Calibration bars: *x*-axis = 10 ms, *y*-axis = 1 mV.

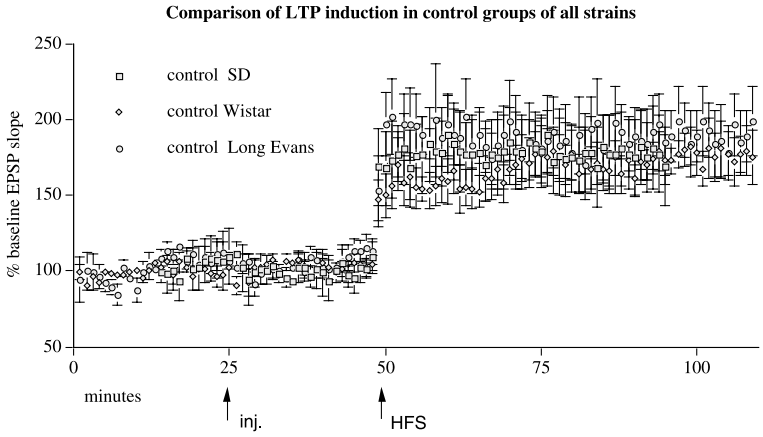

Fig. 4. The difference in the inducibility of long-term potentiation between strains was compared. Slopes measured 25 min after high-frequency stimulation were compared in a nonparametric Kruskal–Wallis ANOVA. There was no significant difference between groups ($P = 0.39$). inj. = time point of drug injection, HFS = time point of stimulation.

(180 ± 24/166 ± 17 S.E.M. of slope after high-frequency stimulation as measured 25 min after high-frequency stimulation; $n = 6$). The drug had no effect on baseline transmission (see Fig. 2).

3.3. Long–Evans rats

High-frequency stimulation induced long-term potentiation of the slope of field EPSPs in the control injected group (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 106 ± 5 S.E.M. % of baseline slope average to 182 ± 15 S.E.M. of % of baseline values, $P < 0.01$ in a two-tailed Wilcoxon test, $n = 6$). Injection of 7-nitro-indazole (30 mg/kg ip) had no effect on the induction of long-term potentiation (time points measured 10 min before high-frequency stimulation and 25 min after high-frequency stimulation; 99 ± 6 to 173 ± 24 S.E.M. of % of baseline values, $P < 0.01$ in a two-tailed Wilcoxon test, $n = 6$). The drug had no effect on baseline transmission (see Fig. 3).

3.4. Comparison between long-term potentiation induced in all groups

To investigate whether there is a difference in the inducibility of long-term potentiation between strains, all controls were compared. Slopes measured 25 min after high-frequency stimulation were compared in a nonparametric Kruskal–Wallis ANOVA (Wistar: 172 ± 10 S.E.M. of % of baseline values, Sprague–Dawley: 180 ± 24 S.E.M. of % of baseline values, Long–Evans: 182 ± 15 S.E.M. of % of baseline values). There was no significant difference between groups ($P = 0.39$) (see Fig. 4).

3.5. Comparison between groups for the effect of 7-nitro-indazole on long-term potentiation induction

To investigate whether there is a difference in the effect of 7-nitro-indazole on the inducibility of long-term potentiation between strains, all 7-nitro-indazole groups were compared. Slopes measured 25 min after high-frequency

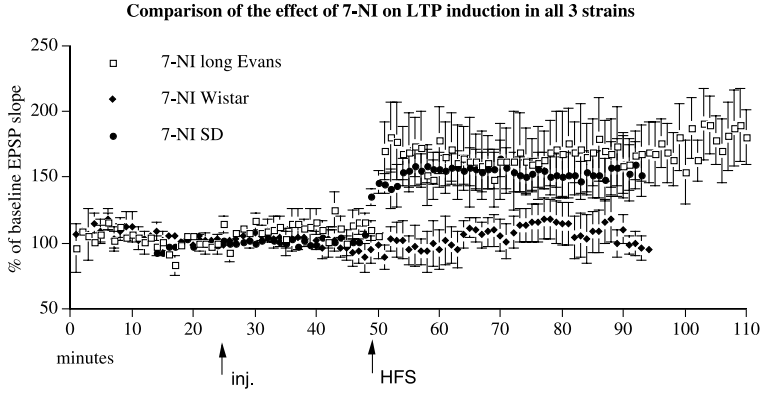

Fig. 5. All 7-nitro-indazole groups were compared. Slopes measured 25 min after high-frequency stimulation were compared in a nonparametric Kruskal–Wallis ANOVA with a post hoc Dunnet's *t*-test. There was a difference between the Wistar and the Sprague–Dawley group and between the Wistar and the Long–Evans group ($P < 0.01$ ANOVA, post-hoc *t*-test difference Wistar–Sprague–Dawley $P < 0.05$, Wistar–Long–Evans $P < 0.05$). inj. = time point of drug injection, HFS = time point of stimulation.

stimulation were compared in a nonparametric Kruskal–Wallis ANOVA with a post hoc Dunnet's *t*-test. There was a difference between the Wistar and the Sprague–Dawley group and between the Wistar and the Long–Evans group (Wistar: 117 ± 5 S.E.M. of % of baseline values, Sprague–Dawley: 152 ± 12 S.E.M. of % of baseline values, Long–Evans: 173 ± 24 S.E.M. of % of baseline values, $P < 0.01$ ANOVA, post-hoc *t*-test difference Wistar–Sprague–Dawley $P < 0.05$, Wistar–Long–Evans $P < 0.05$). See Fig. 5.

4. Discussion

The results show that there are considerable differences between strains of rats in regards to the sensitivity of long-term potentiation to inhibitors of NOS. Wistar rats showed the greatest sensitivity in this study. Both 7-nitro-indazole and trim blocked or reduced the induction of long-term potentiation. Long-term potentiation in Sprague–Dawley rats was not impaired though there was a trend towards an impairment of long-term potentiation development after 7-nitro-indazole injection. Long-term potentiation in Long–Evans rats was not impaired by 7-nitro-indazole at a dose that completely obliterated long-term potentiation in Wistar rats. Interestingly enough, the inducibility of long-term potentiation when using the present protocol did not differ between strains, suggesting that at least under the present condition there is no inherent difference in the development of synaptic plasticity between the strains tested.

These findings are comparable to the results presented previously by other researchers. The studies that showed a block of long-term potentiation induction in the hippocampus in vivo or the impairment of spatial memory by NOS inhibitors used Wistar rats (Böhme et al., 1993; Doyle et al., 1996; Hölscher, 1994, 1999b), while studies that showed no effect of NOS inhibitors used Hooded Lister rats (Bannerman et al., 1994a,b). Lister rats are very similar to Long–Evans rats in the way that they are still partly pigmented and are closer to the wild type. Furthermore, other groups have consistently found a partial impairment of long-term potentiation (around 50%) after application of NOS inhibitors used Sprague–Dawley rats (Chapman et al., 1993; Haley et al., 1993) which also showed some sensitivity to NOS blockers in the study presented here. It is possible that the rat strains that were employed in those studies represent an intermediate stage of expression of NOS where long-term potentiation is dependent on NO production to some degree only. The strain differences in their sensitivity to impairment of long-term potentiation induction after application of NOS blockers could explain at least in part why there are such large differences in the results of studies that investigate the role of NO in synaptic plasticity. However, one cannot exclude that additional differences exist within rat strains supplied from different breeders. In addition, as mentioned in the introduction, there are several other reasons for such discrepancy, too. Strain differences only can explain some of the discrepancies observed in the literature.

How could these differences come about? Nitric oxide synthase is an enzyme that plays many roles in cellular communication (Akira et al., 1994; Harbrecht et al., 1994; Hölscher, 1997). Its expression and activity is highly controlled and can be modulated by a number of factors, such as phosphorylation by kinases or the expression of endogenous inhibitors (Bredt and Snyder, 1990; Corbett et al., 1992; Hu and El-Fakahany, 1996; Jaffrey and Snyder, 1996). It is known that an inducible Ca^{2+}-dependent isoform of NO synthase can be expressed in neurons (Kato et al., 1994; Minc-Golomb and Schwartz, 1994; Saxon and Beitz, 1994). It is therefore quite conceivable that the actual level of expression of the enzyme or the modulating factors for the enzyme differs widely between strains. It has been shown that the expression of inducible isoform of NOS in pancreatic islets differs between rat strains (Johannesen et al., 2001). Therefore, the induction of neuronal NOS and that of other NOS isoforms that are expressed in neurons (Dinerman et al., 1994; Doyle and Slater, 1997) might be variable also. If NOS is expressed less in a particular strain, the lack of this transmitter and modulator could be compensated for by the increased production of other transmitters (Hölscher, 1995a,b; Hölscher et al., 1995). Another possibility is that rat strains that are relatively close to the wild type (Hooded Lister or Long–Evans rats) express a more robust long-term potentiation that is activated by several different transmitter systems. If that is the case these systems can compensate for a block of NOS because of redundancy in synaptic signaling. If the redundancy is reduced in some strains that have been inbred perhaps by the accumulation of faulty genes, NO would become more important in the induction of long-term potentiation, and a block of NOS should be more potent in reducing long-term potentiation.

These results obtained in the research of the role of NO in neuronal transmission are comparable with the results obtained with agonists and antagonists of subtypes of metabotropic glutamate receptors. In this research area, similar discrepancies in results of experiments have been published as in the area of NOS research (see Hölscher et al., 1999, for a review). In a striking parallel, it was shown that different strains of rats showed quite different sensitivities to the metabotropic glutamate receptors-selective drugs used (Manahan-Vaughan, 2000). Such differences could explain at least in part why metabotropic glutamate receptors-selective drugs have shown such a range of contradictory effects on the induction of long-term potentiation or long-term depression in the same type of preparation.

In conclusion, it appears that the biochemical and neuronal differences in various rat strain are quite considerable and should be taken into account when generalising the results of particular experiments that only used one type of rat strain.

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