Effects of Neurotropin on Regional Brain Noradrenaline Metabolism in Rats

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Abstract—By measuring levels of noradrenaline (NA) and its major metabolite, 3-methoxy-4-hydroxyphenylethynlethylene glycol sulfate (MHPG-SO₄), in various rat brain regions, we investigated the effects of an extract isolated from vaccinia virus-inoculated and inflamed skin or tissue of rabbits (Neurotropin, NSP), administered acutely or chronically, on regional NA metabolism in stressed and nonstressed rats. An acute administration of NSP at 50 mg/kg significantly elevated MHPG-SO₄ levels in the amygdala and cerebral cortex; and 100 mg/kg of the drug significantly increased the metabolite levels in the hypothalamus, amygdala, thalamus, midbrain, cerebral cortex and pons plus medulla oblongata without affecting NA levels. This suggests that acutely injected NSP slightly increases NA release in these brain regions. One hour immobilization stress caused significant increases in MHPG-SO₄ levels, which were not affected by pretreatment with either 50 mg/kg or 100 mg/kg of NSP. Chronic injection with NSP daily at either 50 mg/kg or 100 mg/kg for 7 days was without effect on NA metabolism in all brain regions examined. However, increases in MHPG-SO₄ levels caused by stress were significantly attenuated in some regions including the hypothalamus, amygdala and midbrain in chronic NSP-treated rats. This indicates that although an acute administration of NSP slightly increases brain NA release, a chronic treatment with NSP rather attenuates increases in NA release caused by immobilization stress in brain regions such as the hypothalamus, amygdala and midbrain. This suggests a possibility that these attenuating effects on stress-induced increases in brain NA release caused by chronic administration of NSP might be related to the stress-reducing or anti-stress properties of NSP.

A non-protein extract isolated from vaccinia virus-inoculated and inflamed skin or tissue of rabbits (Neurotropin, NSP for short) has been considered to contain biologically active substances (1). NSP has been demonstrated to possess a variety of anti-stress actions: improvement in various physiological changes including those in organ weights (2, 3), hypotension (4), reduced response to acetylcholine of the isolated duodenum (5), and decreases in gastric blood flow and increases in dermal blood flow (6), caused by a specific stress situation, SART stress (specific alternation of rhythm in temperature) which involves both central and peripheral mechanisms (7, 8). Moreover, this drug has also been reported to possess anti-ulcer (9), analgesic (10, 11) and anti-allergic actions (12) in animal studies. Clinically, NSP is strongly effective in patients suffering from abnormalities in the autonomic nervous system (13). These findings suggest that NSP could protect an organism from various pathological changes caused by a variety of stressful stimuli.

By measuring levels of noradrenaline (NA) and its major metabolite in the rat brain, 3-methoxy-4-hydroxyphenylethynlethylene glycol sulfate (MHPG-SO₄), we have reported that immobilization stress causes marked in-
creases in NA release in an extended number of brain regions in rats (14–16).

Together with the findings that these stress-induced increases in NA release in brain regions such as the hypothalamus, amygdala and hippocampus are significantly attenuated by the potent opiate morphine (16), the opioid peptide Met-enkephalin (17), and the typical benzodiazepine anxiolytic diazepam (18), we proposed the hypothesis that regional brain increases in NA release caused by stress might be related to the provocation of “negative emotions” in animals exposed to stress and that the attenuation of increases in NA release by these drugs might be correlated with their anxiolytic action (19).

This hypothesis raises the possibility that if NSP possesses anti-stress actions which are very potent and which could affect a variety of bodily changes caused by stress, then NSP might also affect brain NA activity so as to attenuate stress-induced increases in NA metabolism in various brain regions. In order to investigate this hypothesis, we examined the effects of NSP given i.p. (intraperitoneally) on regional brain NA metabolism in rats in two different situations, i.e., stressed and nonstressed rats.

Materials and Methods

**Animals:** Male Wistar rats, weighing 170–190 g (Kyudo, K.K., Kumamoto), were housed 4 per cage containing wood shavings at constant room temperature (24±1°C) and humidity (50±10%) and allowed free access to standard chow (solid diet CE-2, Clea, Japan) and water. The animal colony was maintained on a 12-hr alternating light-dark cycle with light on at 07.00 hr. All experiments were carried out between 10.00 and 14.00 hr, since we found no diurnal variations of either NA or MHPG-SO₄ contents during this period (20).

**Stress procedure:** Immobilization-stress was employed by enclosing rats in a flexible wire mesh (3x3 mm) initially formed into a cone and then bent to conform to the size of the individual animals (14–18).

**Drugs:** An injection preparation of Neurotropin® (Nippon Zoki Pharmaceutical Co., Ltd.) containing 10 mg of NSP in 1 ml of solution was used. NSP at the dose of either 50 mg/kg or 100 mg/kg or physiological saline was injected i.p. Injection volume was 1 ml/100 g of body weight.

**Experimental procedure:** Two studies were performed separately. In the first study, the effects of acutely administered NSP on regional NA and MHPG-SO₄ levels were examined in non-stressed and stressed rats. Rats in the 3 non-stressed groups were injected with either NSP at 50 mg/kg or 100 mg/kg or saline 70 min before sacrifice. The remaining 3 stress-groups received identical injections; however, 10 min after the injections, these animals were exposed to immobilization stress for 1 hr.

In the second study, rats in the 3 non-stressed groups were injected with daily doses of either NSP at 50 mg/kg or 100 mg/kg or saline for 7 consecutive days and sacrificed 24 hr after the final injections without stress exposure. Animals in the remaining 3 stress groups received identical injections for 7 days; however, 24 hr after the final injections, these rats were stressed by immobilization for 1 hr.

**Tissue preparation and biochemical determination:** Immediately after each treatment, rats were sacrificed by decapitation. The brain was rapidly removed and dissected into discrete regions according to the method of Gispen et al. (21) and frozen on solid CO₂. Brain regions dissected were: the hypothalamus, amygdala, thalamus, hippocampus, midbrain, cerebral cortex and pons plus medulla oblongata (pons+med. obl.). Blood was collected from the cervical wound into heparinized tubes. Dissected brain tissues and separated plasma were stored at −45°C until assayed.

Levels of NA and MHPG-SO₄, which is the major metabolite of rat brain NA and indicative of brain NA release (22–25), were determined simultaneously by our fluorometric method (26). Plasma corticosterone levels were determined fluorometrically by the method of Van der Vies (27).

**Statistical analyses:** All statistical analyses for the two neurochemical studies were performed by means of the two-tailed Student's t-test.
The effects of an acute administration of NSP on levels of NA and MHPG-SO₄ in discrete brain regions and plasma corticosterone levels in non-stressed and stressed rats are indicated in Figs. 1-3. Acute administration of NSP at a dose of 50 mg/kg to non-stressed rats significantly increased MHPG-SO₄ levels in the amygdala, midbrain and cerebral cortex, while NSP at a dose of 100 mg/kg also significantly elevated the metabolite levels in six out of the seven brain regions examined excluding the hippocampus (Fig. 1). Although NSP at a dose of 100 mg/kg significantly decreased NA levels in the hypothalamus, the drug at both doses did not significantly affect NA levels in the other brain regions of non-stressed rats (Fig. 2). Neither dose of the drug significantly affected plasma corticosterone levels in non-stressed rats (Fig. 3).

One hour immobilization stress significantly increased MHPG-SO₄ levels in all brain regions examined (Fig. 1), which were accompanied by significant reductions of NA levels in the hypothalamus and thalamus (Fig. 2). Pretreatment with NSP either at 50 mg/kg or 100 mg/kg did not affect these increases in the metabolite levels or the reductions of NA levels caused by stress in any brain region examined (Figs. 1 and 2). Immobilization stress significantly elevated the plasma corticosterone levels, and these increases were significantly attenuated by pretreatment with NSP at 50 mg/kg (Fig. 3).

Fig. 1. Effects of an acute administration of Neurotropin (NSP) on 3-methoxy-4-hydroxyphenylethanolamine-N-oxide (MHPG-SO₄) levels in 7 brain regions in non-stressed and stressed rats. NSP either at 50 mg/kg or 100 mg/kg or saline was injected 10 min before 1-hr stress in the stressed rats and 70 min before sacrifice in the non-stressed rats. Each value indicates the mean±S.E.M. of 8 rats. Abbreviations: SAL, saline; NSP, Neurotropin. The horizontal bar indicates the 2 groups that are compared statistically; Levels of statistical significance are: *P<0.05, **P<0.01, ***P<0.001.
Fig. 2. Effects of an acute administration of Neurotropin (NSP) on noradrenaline (NA) levels in 7 brain regions in non-stressed and stressed rats. NSP either at 50 mg/kg or 100 mg/kg or saline was injected 10 min before 1-hr stress in the stressed rats and 70 min before sacrifice in the non-stressed rats. Each value indicates the mean±S.E.M. of 8 rats. Abbreviations: SAL, saline; NSP, Neurotropin. The horizontal bar indicates the 2 groups that are compared statistically; Levels of statistical significance are: *P<0.05, **P<0.01.

The effects of chronic administration of NSP on levels of NA and MHPG-SO₄ in discrete brain regions and plasma corticosterone levels in non-stressed and stressed rats are indicated in Figs. 4–6. Chronic administration of either dose of NSP did not affect MHPG-SO₄ levels in most brain regions examined; however, 100 mg/kg of NSP significantly increased the metabolite levels only in the thalamus and cerebral cortex (Fig. 4). NA levels in most brain regions were unaffected by chronic injections with both doses of NSP as compared to chronically saline injected rats, excluding only the cerebral cortex where NA levels were significantly increased by chronic administration of NSP at 50 mg/kg (Fig. 5).

In rats chronically injected with saline, immobilization stress caused significant increases in MHPG-SO₄ levels in all brain regions examined as it did in acutely injected animals. These increases were accompanied by significant reductions of NA levels in the hypothalamus, amygdala, thalamus and pons+med. obl. (Figs. 4 and 5).

The increases in metabolite levels induced by stress were significantly attenuated by chronic administration of NSP at 50 mg/kg or at 100 mg/kg in the hypothalamus, amygdala and midbrain and such a tendency was also observed in the hippocampus and pons+med. obl. (P<0.10, Fig. 4). However, chronic administration of NSP did not affect the stress-induced increases in the metabolite levels either in the thalamus or in the cerebral cortex. The reductions of NA levels caused by stress in the hypothalamus, amygdala, thalamus and pons+med. obl. were not affected by
Plasma corticosterone levels were also significantly elevated in the chronic saline-treated rats; however, chronic administration of NSP did not significantly affect these increases (Fig. 6).

Plasma corticosterone levels were elevated slightly but not significantly by NSP; however, marked and significant increases were caused by stress. Interestingly, NSP at 50 mg/kg, but not NSP at 100 mg/kg, significantly attenuated elevations of plasma corticosterone levels caused by stress. This suggests that a very limited dose of NSP could attenuate the elevated corticosterone levels by stress. The results on plasma corticosterone levels suggest that NSP could possess anti-stress action when rats were exposed to stress; however, this effect was not accompanied by attenuation of increases in brain NA release caused by stress, and the dose of NSP is limited for appearance of this effect. In contrast, diazepam, given before stress exposure, significantly attenuates not only increases in NA release in the same brain regions including the hypothalamus and amygdala but also elevations of plasma corticosterone levels caused by stress (18). However, morphine also significantly attenuates stress-induced increases in NA release but not the elevation of plasma corticosterone levels (16). Together with the findings that a variety of stressful situations cause increases in NA release in rat brain regions (14–18, 28–32), it is indicated that an acute injection of NSP...

Discussion

Immobilization stress for 1 hr significantly and markedly increased MHPG-SO₄ levels in all brain regions examined; and in some brain regions, these increases were accompanied by significant reductions in NA levels as previously reported (14–18). This indicates that immobilization stress causes marked increases in NA release in extended brain regions.

Neither 50 mg/kg nor 100 mg/kg of NSP, injected i.p. 10 min before stress exposure, affected these increases in the metabolite levels caused by stress. This indicates that an acute pretreatment with NSP does not affect stress-induced increases in NA release in rat brain regions.

However, in non-stressed rats, NSP significantly increased MHPG-SO₄ levels in six out of seven brain regions examined with virtually no effect on NA levels in these regions. This finding suggests that NSP increases NA release in extended brain regions; however, these actions did not always occur in a dose-dependent manner depending upon the brain region examined. Moreover, NA release caused by NSP is likely to be minimal, since increases in MHPG-SO₄ levels induced by NSP were not as marked as those caused by stress and were not accompanied by reductions in NA levels as was the case with stress in several brain regions. This suggests that NSP might affect not only brain cholinergic systems (7, 8) but also affects the noradrenergic system in such a manner that the drug causes a slight NA release.

Plasma corticosterone levels were elevated slightly but not significantly by NSP; however, marked and significant increases were caused by stress. Interestingly, NSP at 50 mg/kg, but not NSP at 100 mg/kg, significantly attenuated elevations of plasma corticosterone levels caused by stress. This suggests that a very limited dose of NSP could attenuate the elevated corticosterone levels by stress. The results on plasma corticosterone levels suggest that NSP could possess anti-stress action when rats were exposed to stress; however, this effect was not accompanied by attenuation of increases in brain NA release caused by stress, and the dose of NSP is limited for appearance of this effect. In contrast, diazepam, given before stress exposure, significantly attenuates not only increases in NA release in the same brain regions including the hypothalamus and amygdala but also elevations of plasma corticosterone levels caused by stress (18). However, morphine also significantly attenuates stress-induced increases in NA release but not the elevation of plasma corticosterone levels (16). Together with the findings that a variety of stressful situations cause increases in NA release in rat brain regions (14–18, 28–32), it is indicated that an acute injection of NSP...
shows the same directional changes as various stresses do.

Chronic administration of NSP caused significant increases in MHPG-SO₄ levels only in the thalamus and cerebral cortex and caused significant increases in NA levels in the cerebral cortex. The mechanism of increases in NA levels in the cerebral cortex is uncertain, but there seems to be a possibility that synthesis of NA is increased by repeated administrations of NSP in this region. However, these changes were limited in terms of the number of brain regions involved and the dosage used. This result indicates that chronic administration of NSP by itself does not significantly affect NA metabolism in most brain regions in non-stressed rats.

When rats were pretreated with NSP for 7 consecutive days, the increases in metabolite levels induced by stress were significantly attenuated in brain regions such as the hypothalamus, amygdala and midbrain. A similar tendency was observed in the thalamus, hippocampus and pons+med. obl. but not in the cerebral cortex. This finding suggests that chronic administration of NSP has attenuating effects against stress-induced increases in NA release in these regions.

Plasma corticosterone levels were significantly elevated by stress in the rats chronically treated with both saline and NSP. This indicates that NSP, when injected chronically, did not attenuate stress-induced elevations of plasma corticosterone levels; however, the degree of elevation in these animals was not as large as observed in the stressed rats acutely injected with saline. This might be due to the handling effects accompanied by
chronic treatment such as injection, measuring body weight, etc. Although acute administration of NSP at 50 mg/kg attenuated the stress-induced elevation of plasma corticosterone levels, this effect was not observed in the rats treated chronically with the same dose of the drug. This is partly due to differences in the number of injections of the drug and differences in injection time between the acute and chronic studies, i.e., immediately before and 24 hr before stress exposure (the final injection), respectively.

Various stresses including immobilization (14-18), immobilization with tail-shock (28), psychological stress (29), activity stress (30, 31) and preshock experience (32) have been reported to cause increases in NA release in the rat brain regions. As shown in these reports, it has been generally accepted that stress increases NA release in many brain regions of rodents (33). In contrast, these stress-induced increases in NA release have been reported to be attenuated by diazepam (18), morphine (16), opioid peptides (17, 19) and ethanol (34), which possess stress-reducing properties. The findings that an acute administration of NSP causes increases in brain NA release are consistent with those caused by various stresses with differences in their degrees; however, the mechanism of increased NA release by NSP is uncertain. In contrast, a chronic administration of NSP attenuated increases in brain NA release caused by immobilization stress as did the drugs possessing stress-reducing properties (16-19, 34). This suggests that the attenuating effect of NSP administered chronically on stress-induced increases in

![Graphs showing effects of chronic administration of Neurotropin on NA levels in 7 brain regions](image)
NA release in the brain regions such as the hypothalamus, amygdala and midbrain might be related to the stress-reducing or anti-stress properties of NSP. However, in order to confirm this hypothesis, further studies would be needed.

The present study suggests that brain noradrenergic systems, in addition to central cholinergic systems, might be involved in the anti-stress action of NSP. NSP may attenuate stress-induced increases in NA release in specific brain regions, in particular, in the hypothalamus, amygdala and midbrain, which play an important role in regulating the autonomic, endocrine, and immune systems and their functions under stressful situations.

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