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Anatomy and Neurochemistry of the Pair Bond

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ABSTRACT

Studies in monogamous rodents have begun to elucidate the neural circuitry underlying the formation and maintenance of selective pair bonds between mates. This research suggests that at least three distinct, yet interconnected, neural pathways interact in the establishment of the pair bond. These include circuits involved in conveying somatosensory information from the genitalia to the brain during sexual activity, the mesolimbic dopamine circuits of reward and reinforcement, and neuropeptidergic circuits involved specifically in the processing of socially salient cues. Here we present an integrated description of the interaction of these circuits in a model of pair bond formation in rodents with a discussion of the implications of these findings for evolution, individual variation, and human bonding. J. Comp. Neurol. 493:51–57, 2005.

Indexing terms: vasopressin; oxytocin; nucleus accumbens; ventral pallidum; dopamine

The emotional bonds between sexual partners are among the most powerful driving forces of human behavior, motivating some of the most notable examples of art, literature, and architecture. Furthermore, disruption of established pair bonds can have devastating consequences for mental health. Thus, the formation of a pair bond is one of the most profound events in the human experience. The monogamous prairie vole has proven to be a useful model for elucidating the neural substrates of pair bond formation (Carter et al., 1995; Young and Wang, 2004). This research has suggested that at least three separate, yet interconnected neural circuits converge to yield the development of the pair bond. Circuits involved in the processing of social cues and formation of social memory are tightly coupled with the brain's reward and reinforcement circuitry. These two circuits are modulated by ascending circuits conveying somatosensory information from the genitalia during sexual interactions. The interaction of these pathways during sex culminate in the development of a powerful association between the conditioned stimulus (sex) and the unconditioned stimulus (the partner) to form the conditioned "partner" preference, or pair bond (Young and Wang, 2004). Dissociation of these circuits in nonmonogamous species results in the failure to form pair bonds between mates. Here we discuss the integration of these circuits through the interactions of peptide and dopamine (DA) systems and propose a holistic model of pair bond formation. While these studies are based exclusively in rodents, some of these principles, if not the specific neurotransmitters and circuitry, are likely relevant to pair bond formation in humans.

VOLE MODEL OF PAIR BONDING

Prairie voles are hamster-sized rodents that form enduring pair bonds with their mates (Getz and Carter, 1996). Males and females nest together and both contribute to the rearing of their offspring. Pair bonds typically last a lifetime and field studies suggest that if one partner

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disappears, more than 70% of the surviving partners do not take on a new partner (Getz and Carter, 1996). While prairie voles are considered "monogamous" because of their social organization, extrapair copulations do occur (Wolff et al., 2002). Therefore, prairie voles are useful as a model of social bond formation, but not sexual fidelity. In the laboratory, the neural substrates underlying pair bond formation have been assessed using a "partner preference" test, in which the time spent with a partner versus a novel, opposite-sex individual is quantified (Williams et al., 1992). Early behavioral studies revealed two important observations. First, pair bonds are formed in both male and female partners (Williams et al., 1992; Winslow et al., 1993). Second, while pair bonds can form independently from sexual activity, mating greatly facilitates the formation of this bond (Williams et al., 1992; Winslow et al., 1993).

Early studies of the pair bond revealed that the neuropeptides oxytocin (OT) and arginine vasopressin (AVP) play critical roles in pair bond formation (Winslow et al., 1993; Williams et al., 1994). While there is now clear evidence that both peptides play a role in pair bonding in both sexes (Cho et al., 1999; Liu et al., 2001), most studies have focused on the role of OT in the female and AVP in the male pair bond. Central infusions of OT stimulate partner preference formation in females in the absence of mating, while a selective OT receptor antagonist blocks mating-induced partner preference formation (Williams et al., 1994). Similar effects have been reported with AVP and the AVP V1a receptor subtype (V1aR) antagonists in male prairie voles (Winslow et al., 1993).

OT and AVP are synthesized in the paraventricular (PVN) and supraoptic nuclei of the hypothalamus, where they are transported to the posterior pituitary and released into the general circulation (Gainer and Wray, 1994). Separate, centrally projecting OT and AVP systems are involved in the regulation of a number of social behaviors in addition to pair bonding, including parental care (Pedersen and Prange, 1979; Kendrick et al., 1987; Wang et al., 1994; Kendrick et al., 1997), aggression (Ferris et al., 1997), and anxiety-like behavior (Bielsky et al., 2004). Central OT projections most likely arise from neurons in the PVN, while AVP projections arise from the PVN, medial amygdala (MeA), and bed nucleus of the stria terminalis (BnST) (De Vries and Buijs, 1983).

In addition to OT and AVP, more recent studies have suggested that corticotrophin-releasing factor (CRF) also modulates pair bond formation (DeVries et al., 2002). Initial studies examining the interaction of stress and pair bond formation found that both stress and corticosterone facilitated pair bond formation in male prairie voles, while inhibiting pair bond formation in females (DeVries et al., 1995, 1996). Further examination of this relationship demonstrated that central infusions of CRF facilitated pair bond formation directly (Devries et al., 2002).

NEUROANATOMY OF PAIR BOND FORMATION

The initial insights into the neuroanatomical sites of action of all three neuropeptides in pair bond formation were gleaned from studies comparing the distribution of the peptide receptors in the monogamous and nonmonogamous vole species. Montane and meadow voles are much less social than prairie voles and do not typically form pair bonds after mating (Jannett, 1980; Shapiro and Dewsbury, 1990; Lim et al., 2004b). Interestingly, the distribution of OT, AVP, and CRF receptors in the brain are quite distinct in monogamous and nonmonogamous voles (Insel and Shapiro, 1992; Insel et al., 1994; Lim et al., 2005). The striking differences in receptor densities in the nucleus accumbens (NAcc) and ventral pallidum inspired early hypotheses of an involvement of reward systems in pair bond formation (Insel, 2003) (Fig. 1).

Prairie voles have high densities of OT receptors in the striatum compared to montane voles (Fig. 1A,B), and site-specific infusions of OT antagonist into NAcc, as well as the prefrontal cortex, block pair bond formation in the female (Insel and Shapiro, 1992; Young et al., 2001). Similarly, prairie voles have higher densities of V1aR in the ventral pallidum (Fig. 1C,D), and V1aR antagonist infusion into the ventral pallidum prevents pair bond formation in males (Insel and Shapiro, 1992; Lim and Young, 2004). In addition, V1aR antagonist into the lateral septum prevents partner preference formation in males (Liu et al., 2001). Finally, prairie voles have higher levels of CRF-R2 binding in the septal pole of the NAcc (Fig. 1E,F), and infusion of CRF into this region facilitates pair bond formation in males, while a selective CRF-R2 receptor antagonist, but not CRF-R1, blocks the facilitatory effect of CRF (Lim et al., 2005, submitted). Interestingly, nonmonogamous vole species have higher levels of CRF-R1 in the shell of the NAcc than prairie voles, and there is a significant inverse correlation between the strength of the pair bond and CRF-R1 density among individual prairie voles (Lim et al., submitted).

In addition to the respective receptors, the neuropeptides themselves have been localized in the NAcc and ventral pallidum (Lim et al., 2004a). Large-diameter OT-immunoreactive fibers in the NAcc of both male and female prairie voles are likely of hypothalamic origin since this is the major location of OT-producing neurons in rodents. Smaller-diameter, punctate AVP-immunoreactive fibers which course through the ventral pallidum and terminate in the lateral septum (Lim et al., 2004a) likely originate in the MeA and BnST (De Vries and Buijs, 1983). Finally, CRF mRNA-producing cells and immunoreactive fibers are concentrated in the septal pole of the NAcc (Lim et al., submitted).

While release of OT and CRF in these structures with mating has only been inferred from the effects of antagonist infusions, AVP has been shown to be released in the ventral pallidum concomitantly with ejaculation in the male prairie vole using in vivo microdialysis (Morales et al., 2004). Vaginocervical stimulation has been found to potently stimulate central release of OT (Kendrick et al., 1986; Sansone et al., 2002), suggesting that multiple mating bouts may also stimulate OT release in female prairie voles.

REWARD, REINFORCEMENT, AND BONDING

The critical role of the peptide receptors in the NAcc, prefrontal cortex, and ventral pallidum suggest that the mesolimbic reward pathway plays a critical role in pair bond formation. The NAcc and prefrontal cortex receive dopaminergic (DAergic) projections from the ventral tegmental area (VTA). The ventral pallidum is a major output of the NAcc and relays information to other nuclei

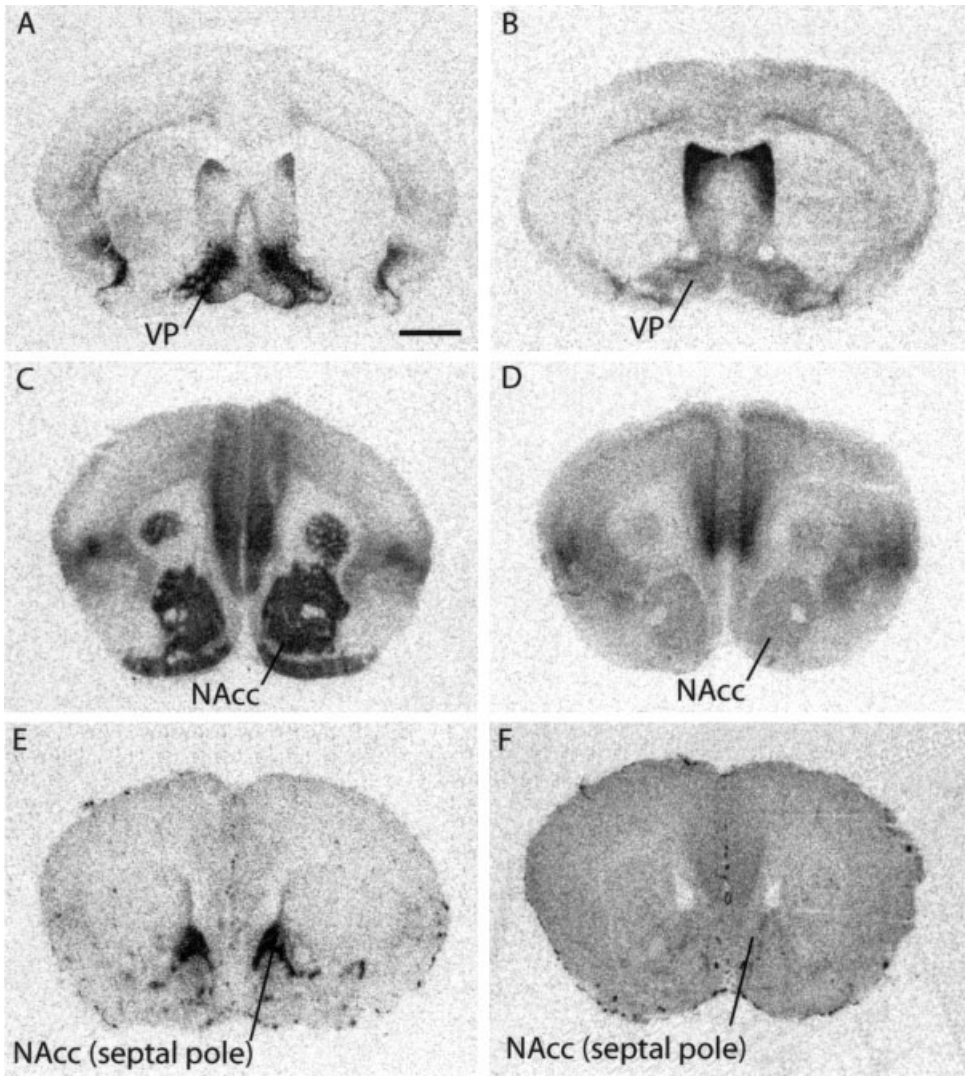

Fig. 1. Social organization and neuropeptide receptor distribution in forebrain reward circuitry. Autoradiographs of V1aR (**A,B**), OT receptor (**C,D**), and CRF-R2 receptor (**E,F**) reveal that monogamous prairie voles (left column) have higher densities of neuropeptide receptor than promiscuous montane voles (right column) in the nucleus accumbens (NAcc) and the ventral pallidum (VP). Panels E and F are courtesy of Miranda M. Lim. Scale bar = 1 mm in A (applies to A–F).

involved in reward processing (Zahm and Heimer, 1990; Heimer et al., 1991; Klitenick et al., 1992; Zahm et al., 1996). In female prairie voles, mating is associated with an increase in extracellular DA in the NAcc, and there is evidence of DAergic activity in males during mating (Gingrich et al., 2000; Aragona et al., 2003). Dopamine D2 receptor activation in the NAcc facilitates pair bond formation in both male and female prairie voles (Gingrich et al., 2000; Aragona et al., 2003). In addition, blockade of D2 receptors, but not DA D1 receptors, inhibits pair bond formation in both sexes. In female prairie voles, activation of both D2 and OT receptors is necessary for pair bonding, since blocking either receptor disrupts pair bond formation (Liu and Wang, 2003).

OT, AVP, AND SOCIAL RECOGNITION PATHWAYS

In addition to their role in pair bonding, OT and AVP play critical roles in the neural processing of social stimuli necessary for individual recognition, which is a critical component of pair bond formation. Rodents recognize previously encountered individuals, presumably via olfactory signatures, and display a decrease in olfactory investigation during subsequent encounters. Brattleboro rats, which have a natural mutation in the AVP gene, and V1aR knockout mice display social amnesia (Englemann and Landgraf, 1994; Bielsky et al., 2004). V1aR activation in the lateral septum appears to mediate social recognition since infusion of AVP into this area enhances the duration of the social memory (Engelmann et al., 1996), and infusion of V1aR antagonist or antisense oligonucleotides into the lateral septum disrupts social recognition (Englemann and Landgraf, 1994; Landgraf et al., 1995). As noted earlier, infusion of V1aR antagonist into the lateral septum blocks pair bond formation in male prairie voles, possibly by blocking social recognition. With its projections to the hippocampus and NAcc (Jakab and Leranth, 1995), the lateral septum represents a potential link between the social memory and reward circuitries involved in pair bond formation.

OT knockout mice also display social amnesia (Ferguson et al., 2000). In contrast to AVP, OT appears to be acting in the medial amygdala (MeA) to facilitate social

recognition, since infusions of OT into this area of OT knockout mice rescues social recognition (Ferguson et al., 2001). The MeA receives direct and indirect input from the accessory and main olfactory bulbs and is involved in processing socially relevant olfactory stimuli (Meredith and Westberry, 2004). Lesions of the vomeronasal organ inhibits pair bond formation in female prairie voles (Curtis et al., 2001) and the MeA is dramatically activated during a heterosexual social encounter or mating in prairie voles as measured by c-Fos immunoreactivity (Cushing et al., 2003; Lim and Young, 2004). Since the MeA is one of the major sources of the AVP projection to the ventral pallidum, this region likely serves an important role in linking sexual activity, social sensory stimuli and the reward pathway during pair bond formation.

SOMATOSENSORY MODULATION OF NEUROPEPTIDE AND REWARD CIRCUITS

Peptidergic and DAergic pathways are modulated by sexual activity through ascending somatosensory pathways. In males, sensory information from the penis is relayed primarily within the dorsal penile nerve, a branch of the pudendal nerve (Nunez et al., 1986). In females, sensory input from the vagina and clitoris is relayed centrally via the clitoral sensory nerve and vaginocervical afferent fibers traveling within the pelvic and pudendal nerves (Ueyama et al., 1987; Yucel et al., 2004). In both males and females sensory afferents from the external genitalia terminate bilaterally within the dorsal horn of the lumbosacral spinal cord and these neuronal populations are activated during vaginocervical stimulation (either artificially or via mating; Lee and Erskine, 1996, 2000) or copulation (Truitt et al., 2003).

While a number of ascending pathways have been shown to relay information from the genitalia to the brain, spinal projections from the lumbosacral spinal cord to the nucleus tractus solitarius (NTS) and midbrain periaqueductal gray (PAG) are two likely candidates for modulating the OT, AVP, and DAergic systems involved in pair bond formation. The NTS receives direct input from the spinal cord (Menetrey and Basbaum, 1987) and electrophysiological studies have shown that the majority of NTS neurons respond to vaginocervical stimulation (VCS) in an estrogen-dependent manner (Hubscher and Berkley, 1994, 1995). The NTS projects heavily to the PVN (Sawchenko and Swanson, 1981; Cunningham and Sawchenko, 1988; Sim and Joseph, 1994), providing excitatory input to OT and AVP parvocellular neurons (Kannan and Yamashita, 1985). The PAG also receives dense input from the lumbosacral spinal cord (Mouton and Holstege, 1998; Mouton et al., 2001) and this region has been intimately linked to both male (Murphy and Marson, 2000; Murphy and Hoffman, 2001; Beall and Murphy, 2002) and female (Schwartz-Giblin and McCarthy, 1995; Holstege et al., 1997; Vanderhorst et al., 2000) reproductive behavior. The PAG sends direct projections to the PVN that preferentially terminate on neurons transneuronally labeled from the penis (Murphy and Marson, 2000) and vagina/clitoris (Murphy and Marson, 2001). Interestingly, a subpopulation of oxytocinergic PVN neurons, perhaps those receiving input from the PAG, project to the intermediolateral cell column (Swanson and McKellar, 1979) and may provide sympathetic control over erection and ejaculatory responses. In addition to the PAG and the NTS, the parvocellular subparafascicular thalamic nucleus (SPFp) is an interesting candidate for conveying sexual somatosensory information to the forebrain. The role of the SPFp in processing sexual stimuli is reviewed in detail elsewhere in this issue (Coolen, 2005).

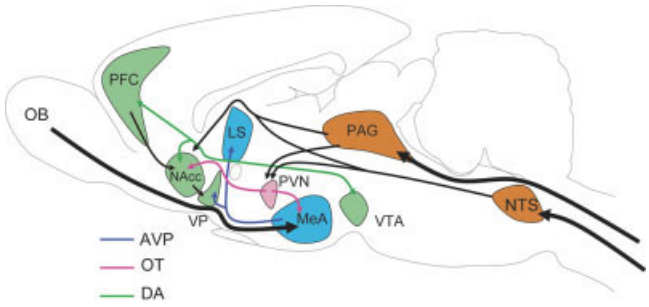

Fig. 2. Proposed neural circuitry of social bonding in monogamous prairie voles. Somatosensory input from the penis or vagina impinge on the nucleus tractus solitarius (NTS) and midbrain periaqueductal gray (PAG), which then project to the nucleus accumbens (NAcc) and paraventricular nucleus (PVN). Olfactory information is conveyed via the olfactory bulb to the medial amygdala (MeA), where oxytocin facilitates social recognition. The MeA sends vasopressinergic projections to the ventral pallidum (VP) and lateral septum (LS), which is also involved in the formation of social memory. Activation of the ventral tegmental area (VTA) results in dopamine release within the prefrontal cortex (PFC) and NAcc. The simultaneous activation of the dopaminergic and peptidergic pathways results in the formation of the selective pair bond.

Sex is one of the most pleasurable activities that humans engage in, and evolution has enlisted the reward centers of the brain to make sure that individuals have sex to ensure reproductive success. Yet little is known about the neurobiological mechanisms that create the pleasurable feeling associated with sex. Surprisingly, a direct pathway by which somatosensory stimulation during sex activates the reward circuitry has not been established. As discussed, the VTA, along with its connections with the NAcc and prefrontal cortex, is an essential neural substrate for producing natural reward, including sex. In male rhesus monkeys, stimulation of the VTA elicits touching and mounting of a receptive female (Okada et al., 1991), and recent studies have reported that the firing rate of VTA neurons increases with the pursuit of a receptive female and during mating (Hernandez-Gonzalez et al., 1997). There are no direct projections to the VTA from the lumbosacral spinal cord; however, there are direct noradrenergic projections from the NTS to the NAcc (Delfs et al., 1998). Since the NAcc is reciprocally connected to the VTA, activation of the NTS during sex may activate the NAcc-VTA pathway.

SYNTHESIS OF THE MODEL

Based on the pharmacological and anatomical data presented here, a working model of pair bond formation can be formulated (Fig. 2). First, ascending sensory stimulation from the genitalia during mating simultaneously activates the DAergic reward circuitry and the OT and AVP pathways involved in social recognition, presumably via activation of the NTS, PAG, and ultimately the VTA. Social olfactory information is conveyed via the olfactory bulbs to the MeA and lateral septum. Other factors medi-

ating reward, such as glutamate and opioids may also be involved, but their role in pair bonding has yet to be investigated. In monogamous species the interaction of the reward and olfactory recognition systems during mating stimulates the formation of a conditioned association between the reward of the sexual interactions and the olfactory signature of the partner. The precise neural and cellular mechanisms underlying this association are unknown. It may be useful to consider the NAcc and ventral pallidum as coincidence detectors, such that simultaneous activation of peptide and DA receptors in these regions leads to the development of the association.

Remarkable plasticity in the neuropeptide receptor distributions within the circuits involved in pair bonding suggests a model for evolution of social behavior. The differential expression of OT, AVP, and CRF receptors in the NAcc and ventral pallidum in monogamous and promiscuous vole species alters the coupling of the social recognition and reward circuits involved in pair bonding. Each of the circuits discussed here exist in all species, yet in the monogamous prairie vole they merge due to the particular expression pattern of the receptors. This idea is supported by a study in which overexpressing the V1aR in the ventral pallidum of the nonmonogamous meadow vole using a viral vector resulted in their developing partner preferences (Lim et al., 2004B). In that regard, it is interesting to note that nonmonogamous rats will display a conditioned partner preference, provided the female partner is scented with a nonsocial scent (Pfaus et al., 2001).

The molecular mechanisms resulting in the diversity of receptor expression patterns have been studied in detail for the V1aR. The prairie vole V1aR gene has a polymorphic repetitive microsatellite sequence in the promoter that is not present in the nonmonogamous montane and meadow vole genes (Young et al., 1999). This microsatellite may be responsible for the species differences in expression pattern, since it has been shown to alter gene expression in a cell-type-specific manner (Hammock and Young, 2004). Considerable individual variation in the length of this microsatellite element (>40 basepairs) also exists within the prairie vole species (Hammock and Young, 2002). A recent selective breeding experiment revealed that male prairie voles with a long microsatellite in the V1aR gene promoter had higher levels of V1aR binding in the olfactory bulb and lateral septum than males with a short microsatellite (Hammock and Young, 2005). These long males also displayed higher levels of paternal behavior and were more likely to form pair bonds after abbreviated cohabitation with a female. Therefore, even individual differences in the expression of the neuropeptide receptor within the circuits of pair bonding may partially explain individual differences in the likelihood of forming a pair bond. The human V1aR also has polymorphic microsatellite sequences in the promoter, and one microsatellite has been associated with autism in two independent studies (Kim et al., 2001; Wassink et al., 2004). This raises the possibility that variations in V1aR gene may alter expression patterns and potentially behaviors related to social bonding in humans.

IMPLICATIONS FOR HUMAN BONDING

There are few data to support the idea that common neural pathways are involved in pair bonding in voles and love in humans. Most certainly, higher-level cortical structures play a significantly greater role in pair bond formation in humans and other primates than in rodents; nonetheless, the pathways discussed here could modulate human bond formation. A recent study has suggested that in human females fidelity in relationships has a strong genetic component (Cherkas et al., 2004). Imaging studies reveal that the brain activation patterns in people while viewing pictures of their romantic partners are similar to that observed after infusion of cocaine or heroin (i.e., heavy activation in the VTA and striatum), and the activation pattern partially overlaps DAergic regions known to express OT receptors (Bartels and Zeki, 2000). Obviously, pair bonding in humans can occur in the absence of sex, but intimate sexual interactions may facilitate emotional bonding in mates. The lack of a strict relationship between ovarian cycle and sexual receptivity in human females permits frequent sexual activity that may serve to maintain the pair bond. Furthermore, nipple stimulation is an important component of human sexuality, unlike any other species, and in lactating females this stimulation is a potent stimulus of OT secretion (Christensson et al., 1989). OT and AVP are released into the blood during sexual arousal and orgasm in humans (Carmichael et al., 1987; Murphy et al., 1987). While in rodents OT and AVP primarily have been associated with the processing of olfactory social cues, the possibility remains that in primates these same peptides may modulate the processing of social cues from other modalities, including visual and auditory. Thus, in humans ascending somatosensory circuits activated during sexual intercourse, coincident with the heightened activation of visual, tactile, and auditory social pathways, may also modulate DA, OT, and AVP circuits, potentially promoting the formation and maintenance of the emotional bonds between partners.

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